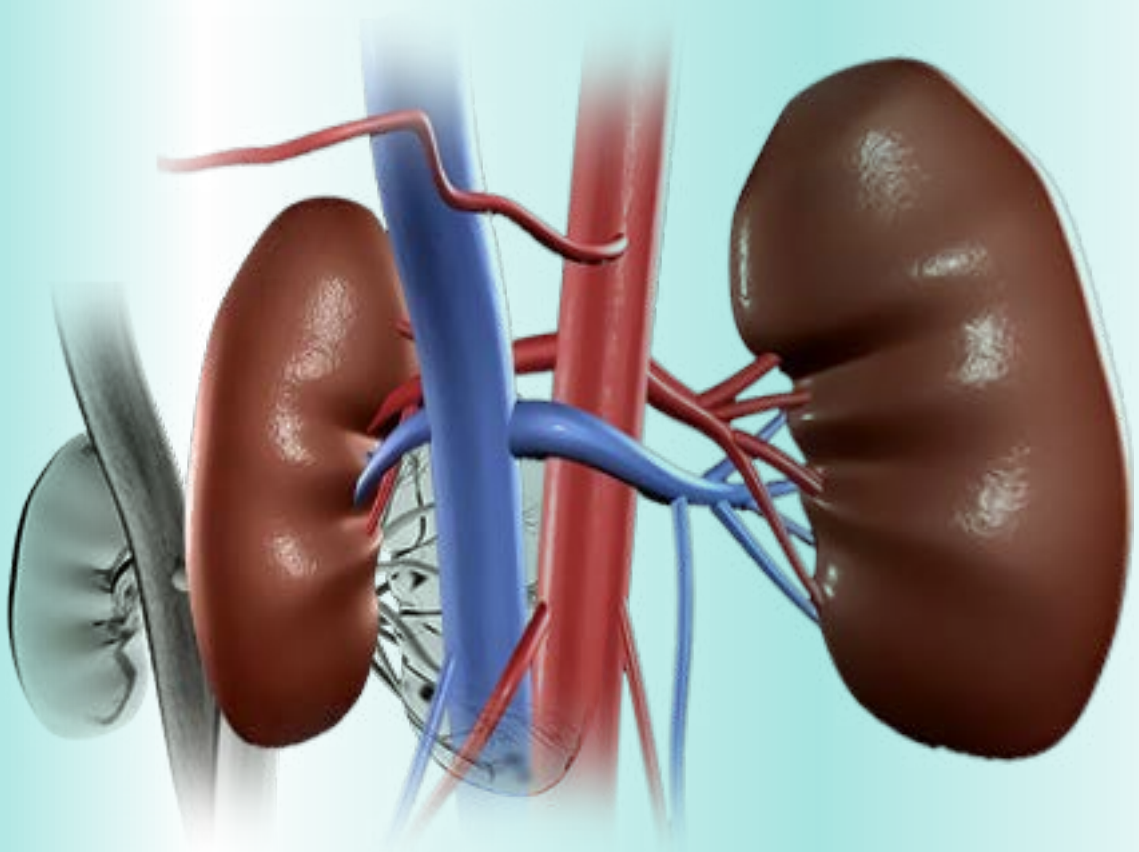
Openventio PUBLISHERS

ISSN 2380-0445

NEPHROLOGY

Open Journal



| April 2016 | Volume 1 | Issue 3 |

www.openventio.org

NEPHROLOGY

Openventio PUBLISHERS

ISSN 2380-0445

Open Journal

TABLE OF CONTENTS

NEPHROLOGY

Openventio PUBLISHERS

ISSN 2380-0445 Open Journal http://dx.doi.org/10.17140/NPOJ-1-e004

Editorial

*Corresponding author
Florian Simon, PD Dr. med
Department of Vascular and Endovascular Surgery
Heinrich-Heine-University of Düsseldorf
Moorenstr. 5 D-40225 Düsseldorf
Germany
Tel. 49 211 81 7168
Fax: 49 211 81 19091
E-mail: florian.simon@med.uni-duesseldorf.de

Volume 1 : Issue 3
Article Ref. #: 1000NPOJ1e004

Article History
Received: February 4th, 2016
Accepted: February 4th, 2016
Published: February 4th, 2016

Citation
Simon F, Schelzig H, Oberhuber A. Kidney ischemia and reperfusion injury – field of glory or warterloo for erythropoietin? *Nephrol Open J.* 2016; 1(3): e9-e12. doi: 10.17140/NPOJ-1-e004

Kidney Ischemia and Reperfusion Injury – Field of Glory or Warterloo for Erythropoietin?

Florian Simon*, Hubert Schelzig and Alexander Oberhuber

Department of Vascular and Endovascular Surgery, Heinrich-Heine-University of Düsseldorf, Germany

KEYWORDS: Ischemia; Reperfusion; Hypoxia; Kidney; Animal model; Erythropoietin.

When asking clinicians about their knowledge about Erythropoietin (EPO) most of them would say that it increases Red Blood Cell (RBC) count and can therefore be used to treat anemia, is produced in the kidneys and can be misused as doping agent in sports. The way to reach this today's common knowledge was long and hard. In the year 1667 by giving a lambs blood to an anemic patient and the lucky outcome that the patient felt better afterwards, it became clear that blood could heal.[1] Over two centuries later in a rabbit experimental set-up where plasma was transduced between an anemic and a healthy animal it could be seen that the red blood cell count increased in the anemic one. This gave birth to the thesis that a humeral factor is responsible and was named hemopoietin.[2] Seventy years later this mysterious substance was found by Goldwasser in patients´ urine[3] and was later on cloned by a colleague of him[4] what marked the beginning of EPOs therapeutic career in treating anemia that lasts on until today.

But meanwhile it became clear that there is more to EPO than just to increase red blood cell count. It was found that it also has antiapoptotic, antioxidative and angiogenetic effects that can be used to avoid and treat tissue damage in general.[5,6] This is possible, because of the widespread distribution of the EPO receptor that can mediate non-hematopoietic effects.[7] This is also true for renal tissue where the EPO receptor can be found in the cortex, medulla, papilla, mesangial proximal tubular and medullary collecting duct cells.[8] This means that the kidney tissue might also profit from the antiapoptotic effect of EPO when the kidney is confronted with an Ischemia and Reperfusion (I/R) injury. This scenario might appear during kidney transplantation or during aortic cross clamping as used in aneurysm repair surgery. And indeed experimental data suggest that EPO might protect kidneys in varying species when facing ischemia and reperfusion. In a rat model the animals were subjected to renal ischemia for 45 minutes and received EPO prior to I/R. The renal dysfunction and injury was measured by serum biochemical markers and after death of the animals by histologic evaluation using TUNEL assay and morphological criteria. The authors found that the EPO group had significantly lower serum creatinine levels and that morphological changes of the renal tissue especially of the tubular cells was much less than in the placebo group. Also apoptotic markers like BAX were reduced and the TUNEL assay showed only some positive cells.[9] This effect of renal tissue protection by EPO application was also seen in other rodent models.[10-12] Not only small animal models, but also experimental set-up with large animals that are much closer to clinical reality showed these positive effects. Maio et al.[13] demonstrated that organs obtained subsequent to cardiac death, but treated with EPO, showed improved organ function compared to organs without special treatment. In this context the kidneys were challenged with 30 minutes of warm ischemia and then transplanted after 24 hours of cold storage. Four hours after transplantation organ function was asset and showed significantly attenuated renal/glomerular dysfunction as well as an improved tubular function of the kidneys measured by N-acetyl-beta-D-glucosaminidase (NAG), Aspartate aminotransferase (AST), Glutathione S-transferase (GST), urea and fractional excretion of sodium. Along with improved parameters of inflammation, oxidative

ISSN 2380-0445 Open Journal http://dx.doi.org/10.17140/NPOJ-1-e004

stress etc. histologic evaluation showed explicit a reduction of the severe acute tubular damage including nuclear condensation, loss of nuclei, cytoplasmic swelling and cellular debris in the tubular lumen.[13] Other working groups could also prove these positive effects of EPO during renal ischemia in large animal models.[14,15] It is recognizable that there was also effort to test EPO in a non-human primate model what shows that EPO is of high interest in protecting kidneys against ischemia and reperfusion. These primates underwent 90 minutes of renal warm ischemia and were observed for further 7 days. EPO was given 5 minutes before clamping and additionally 5 minutes before blood flow was restored. The main findings were that EPO protected the renal tissue and therefore organ function measured by creatinine and blood urea nitrogen, additionally cystatin c and Interleukin-6 (IL-6) levels were improved. The number of apoptotic cells was also lower in the EPO group showing that medical treatment can protect renal cells from programmed cell death caused by ischemia and reperfusion.[16] These findings indicated that EPO might hold the promise many scientists and clinicians were waiting for.

The next step was to use EPO in real life meaning clinical settings of patients suffering from renal ischemia and reperfusion injury. A typical example for this clinical scenario is the transplantation of a kidney. Aydin et al. showed in the PROTECT study, a 12-month single center kidney transplantation study with high-dose EPO (3.3×10^4 International Units (IU) on 3 consecutive days, starting 3-4 h before the transplantation and 24 h and 48 h after reperfusion) that there was no beneficial effect to be seen. The group examined incidence of primary non-function and delayed graft function as well as duration of delayed function, renal function and proteinuria up to 1 year and thrombotic adverse events. EPO did not only show no beneficial effects but it also increased thrombotic risk events at 1 month and 1 year.[17] Another study dealing with high-dose EPO (3 doses of 40,000 IU) in kidney transplantation documented also no beneficial EPO effects but no increase in negative side effects. Endpoints were kidney function after 6 weeks after transplantation as well as incidence of delayed graft function and kidney function after 12 months. The authors conclude that the treatment with high-dose EPO after kidney transplantation was well tolerated, but had no effect on long-term graft function.[18] Results that were also seen in other studies dealing with high-dose EPO in renal transplantation.[19,20] Another interesting field of clinical use would be the protection of renal organ function after cardiac surgery. Two studies examined EPO effects in this setting. The first one evaluated the effectiveness of EPO (300 IU/kg before surgery) in the prevention of AKI after Coronary Artery Bypass Grafting (CABG). In the EPO group only 8% developed postoperative acute kidney failure compared to 29% in the placebo group. Both serum creatinine and estimated glomerular filtration rate were significantly improved in the EPO group indicating positive effects on organ function in the treatment group. The author's state by themselves that their study is only of small size that should be seen as a pilot trial that needs confirmation in a larger clinical trial.[21] The second study tested two different doses of EPO (40,000 IU *vs.* 20,000 IU) on kidney function after cardiac surgery. The end-points were the change in urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL) concentration from baseline, creatinine and cystatine C levels as well as acute inflammatory response (Interleukin 6 (IL-6) and Interleukin 8 (IL-8)). EPO treatment did not significantly modify the levels of the above mentioned parameters. The incidence of acute kidney injury and inflammatory cytokines levels did not differ between groups. Therefore one must say that, although safe, EPO demonstrated neither nephroprotective nor anti-inflammatory properties.[22]

A possible explanation for the ineffectiveness of EPO in clinical trials in comparison to experimental data might be that not enough effort was undertaken to examine side effects arising in older individuals. The authors own working group examined therefore in a large animal model the influence of atherosclerosis on EPO function in kidneys. We could not find any positive effect of EPO after an ischemia/reperfusion period. The reason for that controversal outcome was that the absolute number of EPO receptors in atherosclerotic renal tissue was up to 20 times lower as in the tissue of young and healthy animals.[23]

Regarding all this results, both experimental and clinical, one must say that EPO might not have the effect that everyone desired. When looking at EPO and its effects on renal tissue, future experimental set-ups should take in account that most of the clinical problems are in patients of older age. Therefore we must surely define better experimental set-ups when planning animal models. But EPO is not out of interest only because of its inability to work in atherosclerotic tissue, because there is much to investigate how EPO can help to improve renal function in younger patients e.g. undergoing kidney transplantation or having an ischemic injury after accident. Therefore it is still worth to take a closer look on EPO function and not to give up research on its clinical abilities.

Funding

All authors declare that there was no funding.

Author's contribution

Simon wrote article. Schelzig and Oberhuber critically reviewed.

ISSN 2380-0445 Open Journal http://dx.doi.org/10.17140/NPOJ-1-e004

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. Denis, JB. Concerning a new way of curing. *Philosophical Transactions.* 1667; 489-504.

2. Carnot P, Deflandre, C. On the hemopoietic activity of serum during the regeneration of blood. [French] *C. R. Acad. Sci.* 1906; 143: 348-387.

3. Goldwasser E. Erythropoietin: a somewhat personal history. *Perspect Biol Med.* 1996; 40(1): 18-32. doi: 10.1353/pbm.1996.0005

4. Lin F-K, Suggs S, Lin C-H, et al. Cloning and expression of the human erythropoietin gene. *Proc Natl Acad Sci.* 1985; 82: 7580-7584.

5. Maiese K, Li F, Chung Z. Erythropoietin in the brain: can the promise to protect be fulfilled? *Trends Pharmacol Sci.* 2004; 25: 577-583. doi: 10.1016/j.tips.2004.09.006

6. Nakano M, Satoh K, Fukumoto Y, et al. Important role of erythropoietin receptor to promote VEGF expression and angiogenesis in peripheral ischemia in mice. *Circ Res*. 2007; 100: 662-669. doi: 10.1161/01.RES.0000260179.43672.fe

7. Maiese K, Li F, Chong ZZ. New avenues of exploration for erythropoietin. *JAMA.* 2005; 293: 90-95. doi: 10.1001/jama.293.1.90

8. Westenfelder C, Biddle DL, Baranowski RL. Human, rat, and mouse kidney cells express functional erythropoietin receptors. *Kidney Int.* 1999; 55: 808-820.

9. Spandou E, Tsouchnikas I, Karkavelas G, et al. Erythropoietin attenuates renal injury in experimental acute renal failure ischaemic/reperfusion model. *Nephrol Dial Transplant.* 2006; 21: 330-336. doi: 10.1093/ndt/gfi177

10. Sharples EJ, Patel N, Brown P, et al. Erythropoietin protects the kidney against injury and dysfunction caused by ischemia-reperfusion. *J Am Soc Nephrol.* 2004; 15: 2115-2124. doi: 10.1097/01.ASN.0000135059.67385.5D

11. Ates E, Yalcin AU, Yilmaz S, Koken T, Tokyol C. Protective effect of erythropoietin on renal ischemia and reperfusion injury. *ANZ J Surg.* 2005; 75: 1100-1105. doi: 10.1111/j.1445-2197.2005.03612.x

12. Johnson DW, Pat B, Vesey DA, Guan Z, Endre Z, Gobe GC. Delayed administration of darbepoetin or erythropoietin protects against ischemic acute renal injury and failure. *Kidney Int.* 2006; 69: 1806-1813.

13. Maio R, Sepodes B, Patel NS, Thiemermann C, Mota-Filipe H, Costa P. Erythropoietin preserves the integrity and quality of organs for transplantation after cardiac death. *Shock.* 2011; 35: 126-133. doi: 10.1097/SHK.0b013e3181e83236

14. Forman CJ, Johnson DW, Nicol DL. Erythropoietin administration protects against functional impairment and cell death after ischaemic renal injury in pigs. *BJU Int.* 2007; 99: 162-165. doi: 10.1111/j.1464-410X.2006.06505.x

15. Sølling C, Christensen AT, Krag S, et al. Erythropoietin administration is associated with short term improvement in glomerular filtration rate after ischemia-reperfusion injury. *Acta Anaesthesiol Scand*. 2011; 55: 185-195. doi: 10.1111/j.1399-6576.2010.02369.x

16. Ishii Y, Sawada T, Murakami T, et al. Renoprotective effect of erythropoietin against ischaemia reperfusion injury in a non-human primate model. *Nephrol Dial Transplant.* 2011; 26: 1157-1162. doi: 10.1093/ndt/gfq601

17. Aydin Z, Mallat MJ, Schaapherder AF, et al. Randomized trial of short course high-dose erythropoietin in donation after cardiac death kidney transplant recipients. *Am J Transplant*. 2012; 12: 1793-1800. . doi: 10.1111/j.1600-6143.2012.04019.x

18. Hafer C, Becker T, Kielstein JT, et al. High-dose erythropoietin has no effect on short- or long-term graft function following

ISSN 2380-0445 Open Journal http://dx.doi.org/10.17140/NPOJ-1-e004

deceased donor kidney transplantation. *Kidney Int.* 2012; 81: 314-320. doi: 10.1038/ki.2011.349

19. Martinez F, Kamar N, Pallet N, et al. High dose epoetin beta in the first weeks following renal transplantation and delayed graft function: results of the Neo-PDGF Study. *Am J Transplant.* 2010; 10: 1695-1700. doi: 10.1111/j.1600-6143.2010.03142.x

20. Sureshkumar KK, Hussain SM, Ko TY, Thai NL, Marcus RJ. Effect of high-dose erythropoietin on graft function after kidney transplantation: a randomized, double-blind clinical trial. *Clin J Am Soc Nephrol.* 2012; 7: 1498-1506.

21. Song YR, Lee T, You SJ, et al. Prevention of acute kidney injury by erythropoietin in patients undergoing coronary artery by pass grafting: a pilot study. *Am J Nephrol.* 2009; 30: 253-260. doi: 10.1159/000223229

22. deSeigneux S, Ponte B, Weiss L, et al. Epoetin administrated after cardiac surgery: effects on renal function and inflammation in a randomized controlled study. *BMC Nephrol*. 2012; 13: 132. doi: 10.1186/1471-2369-13-132

23. Matejkova S, Scheuerle A, Wagner F, et al. Carbamylated erythropoietin-FC fusion protein and recombinant human erythropoietin during porcine kidney ischemia/reperfusion injury. *Intensive Care Med.* 2013; 39(3): 497-510. doi: 10.1007/s00134-012-2766-y

NEPHROLOGY

Openventio PUBLISHERS

ISSN 2380-0445 Open Journal http://dx.doi.org/10.17140/NPOJ-1-e005

Editorial

WORLD KIDNEY DAY 2016

Correspondence to
World Kidney Day
International Society of Nephrology
in collaboration with International
Federation of Kidney Foundation
Rues de Fabriques 1B
1000, Brussels, Belgium
E-mail: myriam@worldkidneyday.org

Volume 1 : Issue 3
Article Ref. #: 1000NPOJ1e005

Article History
Received: October 14th, 2015
Accepted: October 15th, 2015
Published: March 10th, 2016

Citation
World Kidney Day Steering Committee. Averting the legacy of kidney disease – focus on childhood. *Nephrol Open J*. 2016; 1(3): e13-e20. doi: 10.17140/NPOJ-1-e005

Averting the Legacy of Kidney Disease – Focus on Childhood

Julie R. Ingelfinger, Kamyar Kalantar-Zadeh and Franz Schaefer on behalf of the World Kidney Day Steering Committee*

World Kidney Day, International Society of Nephrology in collaboration with International Federation of Kidney Foundation, Rues de Fabriques 1B 1000, Brussels, Belgium

*Members of the World Kidney Day Steering Committee are: Philip Kam Tao Li, Guillermo Garcia-Garcia, William G. Couser, Timur Erk, Julie R. Ingelfinger, Kamyar Kalantar-Zadeh, Charles Kernahan, Charlotte Osafo, Miguel C. Riella, Luca Segantini, Elena Zakharova

ABSTRACT

World Kidney Day 2016 focuses on kidney disease in childhood and the antecedents of Adult Kidney Disease (AKD) that can begin in earliest childhood. Chronic Kidney Disease (CKD) in childhood differs from that in adults, as the largest diagnostic group among children includes congenital anomalies and inherited disorders, with glomerulopathies and kidney disease in the setting of diabetes being relatively uncommon. In addition, many children with acute kidney injury will ultimately develop sequelae that may lead to hypertension and CKD in later childhood or in adult life. Children born early or who are small-for date newborns have relatively increased risk for the development of CKD later in life. Persons with a high-risk birth and early childhood history should be watched closely in order to help detect early signs of kidney disease in time to provide effective prevention or treatment. Successful therapy is feasible for advanced CKD in childhood; there is evidence that children fare better than adults, if they receive kidney replacement therapy including dialysis and transplantation, while only a minority of children may require this ultimate intervention. Because there are disparities in access to care, effort is needed so that those children with kidney disease, wherever they live, may be treated effectively, irrespective of their geographic or economic circumstances. Our hope is that World Kidney Day will inform the general public, policy makers and caregivers about the needs and possibilities surrounding kidney disease in childhood.

"For in every adult there dwells the child that was, and in every child there lies the adult that will be." – John Connolly, *The Book of Lost Things*

INTRODUCTION AND OVERVIEW

The 11th World Kidney Day will be celebrated on March 10, 2016, around the globe. This annual event, sponsored jointly by the International Society of Nephrology (ISN) and the International Federation of Kidney Foundations (IFKF), has become a highly successful effort to inform the general public and policymakers about the importance and ramifications of kidney disease. In 2016, World Kidney Day will be dedicated to kidney disease in childhood and the antecedents of adult kidney disease, which can begin in earliest childhood.

Children who endure Acute Kidney Injury (AKI) from a wide variety of conditions may have long-term sequelae that can lead to chronic kidney disease (CKD) many years later.[1-4] Further, CKD in childhood, much of it congenital, and complications from the many non-renal diseases that can affect the kidneys secondarily, not only lead to substantial morbidity and mortality during childhood but also result in medical issues beyond childhood. Indeed, childhood deaths from a long list of communicable diseases are inextricably linked to kidney involvement. For example, children who succumb to cholera and other diarrheal infections often die,

ISSN 2380-0445 Open Journal http://dx.doi.org/10.17140/NPOJ-1-e005

not from the infection, but because of AKI induced by volume depletion and shock. In addition, a substantial body of data indicates that hypertension, proteinuria and CKD in adulthood have childhood antecedents – from as early as in utero and perinatal life (see Table 1 for definitions of childhood). World Kidney Day 2016 aims to heighten general awareness that much adult renal disease is actually initiated in childhood. Understanding high risk diagnoses and events that occur in childhood have the potential to identify and intervene preemptively in those people at higher risk for CKD during their lifetimes.

Perinatal Period	22 completed weeks of gestation to Day 7 of postnatal life
Neonatal Period	Birth to Day 28 of postnatal life
Infancy	Birth to 1 year of age
Childhood	1 year of age to 10 years of age
Adolescence	10 years of age to 19 years of age

Notes: The data in this table are as defined by the World Health Organization. The perinatal period is defined as 22 completed weeks of gestation to Day 7 of life; the neonatal period, as up to 28 days of life; infancy as up to one year of age; childhood as year 1 to 10; and adolescence from 10 years to age 19.
There is variation worldwide in how these stages of early life are defined. Some would define "young people" as those age 24 or less. In the United States, childhood is as a whole defined as going to age 21.

Table 1: Definitions of stages of early life.

Worldwide epidemiologic data on the spectrum of both CKD and AKI in children are currently limited, though increasing in scope. The prevalence of CKD in childhood is rare – and has been variously reported at 15-74.7 per million children.[3] Such variation is likely because data on CKD are influenced by regional and cultural factors, as well as by the methodology used to generate them. The World Health Organization (WHO) has recently added kidney and urologic disease to mortality information tracked worldwide, and should be a valuable source of such data over time – yet WHO does not post the information by age group.[5] Databases such as the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS)[6] the US Renal Data System (USRDS)[7] and the EDTA registry[8] include data on pediatric ESRD, and some on CKD. Projects such as the ItalKid[9] and Chronic Kidney Disease in Children (CKiD)[10] studies, the Global Burden of Disease Study 2013, as well as registries that now exist in many countries provide important information, and more is required.[11]

AKI may lead to CKD, according to selected adult population studies.[12] The incidence of AKI among children admitted to an intensive care unit varies widely – from 8% to 89%.[1] The outcome depends on the available resources. The results from projects such as the AWARE study, a five-nation study of AKI in children are awaited.[13] Single center studies, as well as meta-analyses indicate that both AKI and CKD in children account for a minority of CKD worldwide.[2,3] However, it is increasingly evident that kidney disease in adulthood often springs from a childhood legacy.

Spectrum of Pediatric Kidney Diseases

The conditions that account for CKD in childhood, with a predominance of congenital and hereditary disorders, differ substantially from those in adults. To date, mutations in more than 150 genes have been found to alter kidney development or specific glomerular or tubular functions.[14] Most of these genetic disorders present during childhood, and many lead to progressive CKD. Congenital Anomalies of the Kidney and Urinary Tract (CAKUT) account for the largest category of CKD in children (see Table 2) and include renal hypoplasia/dysplasia and obstructive uropathy. Important subgroups among the renal dysplasia's are the cystic kidney diseases, which originate from genetic defects of the tubuloepithelial cells' primary cilia. Many pediatric glomerulopathies are caused by genetic or acquired defects of the podocytes, the unique cell type lining the glomerular capillaries. Less common but important causes of childhood CKD are inherited metabolic disorders such as hyperoxaluria and cystinosis, and atypical hemolytic uremic syndrome, a thrombotic microangiopathy related to genetic abnormalities of complement, coagulation or metabolic pathways.

In various classifications it is not clear how to categorize children who have suffered AKI and apparently recovered, or how and whether to include those children who have had perinatal challenges, likely resulting in a relatively low nephron number (Figure 1).

Among children with childhood-onset End-stage renal disease (ESRD) glomerulopathies are slightly more and congenital anomalies less common (Table 2), due to the typically more rapid nephron loss in glomerular disease. However, recent evidence

ISSN 2380-0445 Open Journal http://dx.doi.org/10.17140/NPOJ-1-e005

suggests that many patients with milder forms of CAKUT may progress to ESRD during adulthood, peaking in the fourth decade of life.[15]

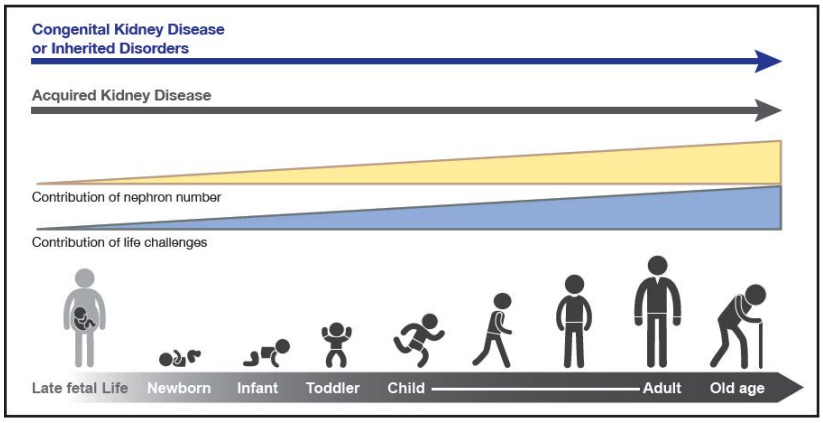


Figure 1: The types and risks of kidney disease change across the lifecycle. The contribution of nephron number increases over the life cycle, in concert with events that provide direct insults and challenges to kidney health.

CKD		ESRD	
Etiology	**Percentage (Range)**	**Etiology**	**Percentage (Range)**
CAKUT	48-59%	CAKUT	34-43%
GN	5-14%	GN	15-29%
HN	10-19%	HN	12-22%
HUS	2-6%	HUS	2-6%
Cystic	5-9%	Cystic	6-12%
Ischemic	2-4%	Ischemic	2%

Rare causes include congenital NS, metabolic diseases, cystinosis/Miscellaneous causes depend on how such entities are classified.
CAKUT: Congenital anomalies of the kidney and urinary tract; GN: Glomerulonephritis; HN: Hereditary Nephropathy; HUS: Hemolytic uremic syndrome.
*from Harambat, et al.[2] CKD data are from NAPRTCS, the Italian Registry and the Belgian Registry. ESRD data are from ANZDATA, ESPN/ERA-EDTA, UK Renal Registry and the Japanese Registry.

Table 2: Etiology of chronic kidney disease in children.

There are national and regional differences in the types and course of both AKI and CKD during childhood and beyond. Death from kidney disease is higher in developing nations, and national and regional disparities in care and outcome must be addressed. Further, access to care is variable, depending on the region, the country and its infrastructure. By focusing on kidney disease in childhood, cost-effective solutions may be reached, as treating disease early and preemptively may prevent later, more advanced CKD. Expectations depend on the availability of care and management. Treating children, even from infancy, who have AKI and CKD that requires renal replacement therapy can be effective in mitigating the burden of kidney disease in adulthood. Doing so requires resources that focus on the most expeditious and cost-effective ways to deliver acute RRT in childhood.

Congenital Kidney Disease and Developmental Origins of Health and Disease, Renal Endowment and Implications

In regions where antenatal fetal ultrasounds are routine, many children with urologic abnormalities are identified antenatally, which permits early intervention. However, in much of the world, children with structural abnormalities are not identified until much later, when symptoms develop. While generalized screening for proteinuria, hematuria and urinary tract infections are carried out in some countries and regions, there is a lack of consensus as to its effectiveness. However, there is general agreement that children with antenatal ultrasound studies that indicate possible genitourinary anomalies, children with a family history of kidney disease, and children with signs such as failure to thrive or a history of urinary tract infection, voiding dysfunction or an abnormal appearing urine should be examined. Initial screening would include a focused physical examination and a urine dipstick, formal urinalysis and a basic chemistry panel, followed by a more focused evaluation if indicated.

Depending on the diagnosis, definitive therapy may be indicated. However, the evidence that therapy will slow progression of CKD in childhood remains limited. Angiotensin converting enzyme inhibitors, angiotensin receptor blockers, antioxidants and,

ISSN 2380-0445 Open Journal http://dx.doi.org/10.17140/NPOJ-1-e005

possibly, dietary changes may be indicated, depending on the diagnosis. However, dietary changes need to permit adequate growth and development. The ESCAPE trial provided evidence that strict blood pressure control retards progression of CKD in children irrespective of the type of underlying kidney disease.[16]

Some very young children may require renal replacement therapy in early infancy. Recent data pooled from registries worldwide indicate good survival, even when dialysis is required from neonatal age.[2,17] Kidney transplantation, the preferred renal replacement therapy in children, is generally suitable after 12 months of age, with excellent patient and allograft survival, growth and development.

Evidence is accumulating that childhood-onset CKD leads to accelerated cardiovascular morbidity and shortened life expectancy. Ongoing large prospective studies such as the (Cardiovascular Comorbidity in Children with CKD) – (4C) study, are expected to inform about the causes and consequences of early cardiovascular disease in children with CKD.[18]

In addition to those children with congenital kidney disease, it is now known that perinatal events may affect future health in the absence of evident kidney disease in early life.[19] Premature infants appear to be particularly at risk for kidney disease long after they are born, based both on observational cohort studies, as well as on case reports. Increasingly premature infants survive, including many born well before nephrogenesis is complete.[20] The limited data available indicate that in the process of neonatal ICU care, such babies receive many nephrotoxins, and that those dying prior to discharge from the nursery have fewer and larger glomeruli.[21] Additionally, those surviving have evidence of renal impairment that may be subtle.[22] Even more concerning, abundant epidemiologic data indicate that persons born at term but with relatively low birth weights may be at high risk for hypertension, albuminuria and CKD in later life.[23] When direct measurements are pursued, such persons, as adults, may have fewer nephrons, thus a low cardiorenal endowment.

In focusing on children for World Kidney Day, we would note that it is key to follow kidney function and blood pressure throughout life in those persons born early or small-for-dates. By doing so, and avoiding nephrotoxic medications throughout life, it may be possible to avert CKD in many people.

Resources and Therapeutics for Children – Differences from Therapeutics in Adults

Disparities exist in the availability of resources to treat AKI in children and young people; consequently, too many children and young adults in developing nations succumb if AKI occurs. To address the problem the ISN has initiated the Saving Young Lives (SYL) Project, which aims both to prevent AKI with prompt treatment of infection and/or delivery of appropriate fluid and electrolyte therapy, and to treat AKI when it occurs. This ongoing project in Sub Saharan Africa and South East Asia, in which four kidney foundations participate equally (IPNA, ISN, ISPD and SKCF)*, focuses on establishing and maintaining centers for the care of AKI, including the provision of acute peritoneal dialysis. It links with the ISN's 0 by 25 project, which calls on members to ensure by 2025 that nobody dies from preventable and acute kidney injury.

In view of the preponderance of congenital and hereditary disorders, therapeutic resources for children with CKD have historically been limited to a few immunological conditions. Very recently, progress in drug development in concert with advances in genetic knowledge and diagnostic capabilities has begun to overcome the long-standing 'therapeutic nihilism' in pediatric kidney disease. Atypical Hemolytic Uremic Syndrome (aHUS), long considered ominous, with a high likelihood of progression to ESRD and post-transplantation recurrence, has turned into a treatable condition – with the advent of a monoclonal antibody that specifically blocks C5 activation.[24] Another example is the use of vasopressin receptor antagonists to retard cyst growth and preserve kidney function in polycystic kidney disease.[25] First proven efficacious in adults with autosomal dominant polycystic kidney disease, therapy with vaptans holds promise also for the recessive form of the disease, which presents and often progresses to ESRD during childhood.

However, patient benefit from pharmacological research breakthroughs is jeopardized on a global scale by the enormous cost of some of the new therapeutic agents. The quest for affordable innovative therapies for rare diseases will be a key issue in pediatric nephrology in the years to come.

The identification of children likely to benefit from novel therapeutic approaches will be greatly facilitated by the development of clinical registries that inform about the natural disease course, including genotype-phenotype correlations. Apart from

*The four partners are (in alphabetical order): IPNA (International Pediatric Nephrology Association), ISN (International Society of Nephrology), ISPD (International Society for Peritoneal Dialysis), SKCF (Sustainable Kidney Care Foundation).

ISSN 2380-0445 Open Journal http://dx.doi.org/10.17140/NPOJ-1-e005

disease-specific databases, there is also a need for treatment-specific registries. These are particularly relevant in areas where clinical trials are difficult to perform due to small patient numbers and lacking industry interest, as well as for therapies in need of global development or improvement. For instance, there is currently a large international gradient in the penetration and performance of pediatric dialysis and transplantation. Whereas pediatric patient and technique survival rates are excellent and even superior to those of adults in many industrialized countries, it is estimated that almost half of the world's childhood population is not offered chronic Renal Replacement Therapy (RRT) at all. Providing access to RRT for all children will be a tremendous future challenge. To obtain reliable information on the demographics and outcomes of pediatric RRT, the International Pediatric Nephrology Association (IPNA) is about to launch a global population-based registry. If successful, the IPNA RRT registry might become a role model for global data collection.

Transition from Pediatric to Adult Care

Transition of care for adolescents with kidney disease into an adult setting is critical both for patients and their caregivers. Non-adherence is a too-frequent hallmark of transition from pediatric to adult care for young patients with chronic disease states.[26-28] Hence, considered steps combined with systematically defined procedures supported by validated pathways and credible guidelines must be in place to ensure successful outcomes.

In the process of change from pediatric to adult care "transition," which should occur gradually, must be distinguished from "transfer," which is often an abrupt and mechanistic change in provider setting. Introducing the concept of transition should be preemptive, starting months to years prior to the targeted time, as children move into adolescence and adulthood. The ultimate goal is to foster a strong relationship and individualized plan in the new setting that allows the patient to feel comfortable enough to report non-adherence and other lapses in care.

A transition plan must recognize that the emotional maturity of children with kidney disease may differ widely. Assessment of the caregiver and the family structure as well as cultural, social, and financial factors at the time of transition are key, including a realistic assessment of caregiver burden.[4] The appropriate timing and format of transition may vary widely among different patients and in different settings; therefore, a flexible process without a set date and even without a delineated format may be preferred.

Importantly, transition may need to be slowed, paused or even reversed temporarily during crises such as disease flares or progression, or if family or societal instability occurs. A recent joint consensus statement by the International Society of Nephrology (ISN) and International Pediatric Nephrology Association (IPNA) proposed steps consistent with the points just outlined, aiming to enhance the transition of care in kidney disease in clinical practice.[29,30]

Call for Generating further Information and Action

Given vulnerabilities of children with kidney disease including impact on growth and development and future life as an adult, and given the much greater proportion of children in developing nations facing resource constraints educating everyone involved is imperative in order to realign communications and actions.[31,32] These efforts should foster regional and international collaborations and exchange of ideas between local kidney foundations, professional societies, other not-for-profit organisations, and states and governments, so as to help empower all stakeholders to improve the health, well-being and quality of life of children with kidney diseases and to ensure their longevity into adulthood.

Until recently, however, the WHO consensus statement on Non-communicable diseases (NCD) included cardiovascular disease, cancer, diabetes and chronic respiratory disease, but not kidney disease.[33,34] Fortunately, due, in part, to a global campaign led by the ISN, the Political Declaration on NCDs from the *United Nations* Summit in 2011 mentioned kidney disease under Item 19.[35]

Increasing education and awareness about renal diseases in general and kidney disease in childhood in particular is consistent with the objectives of the WHO to reduce mortality from NCD with a 10 year target population level initiatives focusing on changes in life style (including tobacco use reduction, salt intake control, dietary energy control, and alcohol intake reduction) and effective interventions (including blood pressure, cholesterol and glycemic control). Heightened efforts are needed to realign and expand these multidisciplinary collaborations with more effective focus on early detection and management of kidney disease in children. Whereas the issues related to kidney disease may be overshadowed by other NCDs with apparently larger public health implications such as diabetes, cancer, and cardiovascular diseases, our efforts should also increase education and awareness on such overlapping conditions as cardiorenal connections, the global nature of the CKD and ESRD as major NCDs, and the role of kidney

ISSN 2380-0445 Open Journal http://dx.doi.org/10.17140/NPOJ-1-e005

disease as the multiplier disease and confounder for other NCDs. White papers including consensus articles and blueprint reviews by world class experts can serve to enhance these goals.[36]

REFERENCES

1. Goldstein SL. Acute kidney injury in children and its potential consequences in adulthood. *Blood Purif.* 2012; 33: 131-137. doi: 10.1159/000334143

2. Harambat J, van Stralen KJ, Kim JJ, Tizard EJ. Epidemiology of chronic kidney disease in children. *Pediatr Nephrol.* 2012; 27: 363-373. doi: 10.1007/s00467-011-1939-1

3. Warady BA, Chadha V. Chronic kidney disease in children: the global perspective. *Pediatr Nephrol.* 2007; 22: 1999-2009. doi: 10.1007/s00467-006-0410-1

4. Furth SL, Cole SR, Moxey-Mims M, et al. Design and methods of the chronic kidney disease in children (CKiD) prospective cohort study. *Clin J Am Soc Nephrol.* 2006; 1: 1006-1015. doi: 10.2215/CJN.01941205

5. Health statistics and information systems. Estimates for 2000-2012. Website: http://www.who.int/healthinfo/global_burden_disease/estimates/en/index1.html 2000; Accessed 2015.

6. NAPRTCS ANNUAL Reports. Website: https://web.emmes.com/study/ped/annlrept/annlrept.html 2013; Accessed 2015.

7. Saran R, Li Y, Robinson B, et al. US Renal Data System 2014 Annual Data Report: Epidemiology of Kidney Disease in the United States. *Am J Kidney Dis.* 2015; 65: A7.

8. ESPN/ERA-EDTA Registry. European registry for children on renal replacement therapy. Website: http://www.espn-reg.org/index.jsp 2015; Accessed 2015.

9. Ardissino G, Dacco V, Testa S, et al. Epidemiology of chronic renal failure in children: data from the ItalKid project. *Pediatrics.* 2003; 111: e382-e387.

10. Wong CJ, Moxey-Mims M, Jerry-Fluker J, Warady BA, Furth SL. CKiD (CKD in children) prospective cohort study: a review of current findings. *Am J Kidney Dis.* 2012; 60: 1002-1011. doi: 10.1053/j.ajkd.2012.07.018

11. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet.* 2013; 386: 743-800. doi: 10.1016/S0140-6736(15)60692-4

12. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. *Kidney Int.* 2012; 81: 442-448. doi: 10.1038/ki.2011.379

13. Basu RK, Kaddourah A, Terrell T, et al. Assessment of Worldwide Acute Kidney Injury, Renal Angina and Epidemiology in critically ill children (AWARE): study protocol for a prospective observational study. *BMC Nephrol.* 2015; 16: 24. doi: 10.1186/s12882-015-0016-6

14. Eckardt KU, Coresh J, Devuyst O, et al. Evolving importance of kidney disease: from subspecialty to global health burden. *Lancet.* 2013; 382: 158-169. doi: 10.1016/S0140-6736(13)60439-0

15. Wuhl E, van Stralen KJ, Verrina E, et al. Timing and outcome of renal replacement therapy in patients with congenital malformations of the kidney and urinary tract. *Clin J Am Soc Nephrol.* 2013; 8: 67-74. doi: 10.2215/CJN.03310412

16. The ESCAPE Trial Group. Strict blood-pressure control and progression of renal failure in children. *N Engl J Med.* 2009; 361: 1639-1650. doi: 10.1056/NEJMoa0902066

17. van Stralen KJ, Borzych-Dużalka D, Hataya H, et al. Survival and clinical outcomes of children starting renal replacement therapy in the neonatal period. *Kidney Int.* 2014; 86(1): 168-174. doi: 10.1038/ki.2013.561

18. Querfeld U, Anarat A, Bayazit AK, et al. The cardiovascular comorbidity in children with chronic kidney disease (4C) study: objectives, design, and methodology. *Clin J Am Soc Nephrol.* 2010; 5: 1642-1648. doi: 10.2215/CJN.08791209

19. Hoy WE Ingelfinger JR, Hallan S, Hughson MD, Mott SA, Bertram JF. The early development of the kidney and implications for future health. *Journal of developmental origins of health and disease.* 2010; 1: 216-233. doi: 10.1017/S204017441000022X

20. Flynn JT, Ng DK, Chan GJ, et al. The effect of abnormal birth history on ambulatory blood pressure and disease progression in children with chronic kidney disease. *J Pediatr.* 2014; 165: 154-162e151. doi: 10.1016/j.jpeds.2014.02.051

21. Rodriguez MM, Gómez AH, Abitbol CL, Chandar JJ, Duara S, Zilleruelo GE. Histomorphometric analysis of postnatal glomerulogenesis in extremely preterm infants. *Pediatric and developmental pathology: the official journal of the Society for Pediatric Pathology and the Paediatric Pathology Society.* 2004; 7: 17-25. doi: 10.1007/s10024-003-3029-2

22. Abitbol CL, Bauer CR, Montané B, Chandar J, Duara S, Zilleruelo G. Long-term follow-up of extremely low birth weight infants with neonatal renal failure. *Pediatr Nephrol.* 2003; 18: 887-893. doi: 10.1007/s00467-003-1186-1

23. Hodgin JB, Rasoulpour M, Markowitz GS, D'Agati VD. Very low birth weight is a risk factor for secondary focal segmental glomerulosclerosis. *Clin J Am Soc Nephrol.* 2009; 4: 71-76. doi: 10.2215/CJN.01700408

24. Verhave JC, Wetzels JF, van de Kar NC. Novel aspects of atypical haemolytic uraemic syndrome and the role of eculizumab. *Nephrol Dial Transplant.* 2014; 29(Suppl 4): iv131-iv141. doi: 10.1093/ndt/gfu235

25. Torres VE. Vasopressin receptor antagonists, heart failure, and polycystic kidney disease. *Annu Rev Med.* 2015; 66: 195-121. doi: 10.1146/annurev-med-050913-022838

26. Jarzembowski T, John E, Panaro F, et al. Impact of non-compliance on outcome after pediatric kidney transplantation: an analysis in racial subgroups. *Pediatr Transplant.* 2004; 8: 367-371. doi: 10.1111/j.1399-3046.2004.00158.x

27. Watson AR. Non-compliance and transfer from paediatric to adult transplant unit. *Pediatr Nephrol.* 2000; 14: 469-472.

28. Aujoulat I, Deccache A, Charles AS, et al. Non-adherence in adolescent transplant recipients: the role of uncertainty in health care providers. *Pediatr Transplant.* 2011; 15: 148-156. doi: 10.1111/j.1399-3046.2010.01429.x

29. Watson AR, Harden PN, Ferris ME, et al. Transition from pediatric to adult renal services: a consensus statement by the International Society of Nephrology (ISN) and the International Pediatric Nephrology Association (IPNA). *Kidney Int.* 2011; 80: 704-707. doi: 10.1038/ki.2011.209

30. Watson AR, Harden P, Ferris M, Kerr PG, Mahan J, Ramzy MF. Transition from pediatric to adult renal services: a consensus statement by the International Society of Nephrology (ISN) and the International Pediatric Nephrology Association (IPNA). *Pediatr Nephrol.* 2011; 26: 1753-1757. doi: 10.1007/s00467-011-1981-z

31. Gallieni M, Aiello A, Tucci B, et al. The burden of hypertension and kidney disease in Northeast India: the Institute for Indian Mother and Child noncommunicable diseases project. *The Scientific World Journal.* 2014; 2014: 320869. doi: 10.1155/2014/320869

32. White A, Wong W, Sureshkumur P, Singh G. The burden of kidney disease in indigenous children of Australia and New Zealand, epidemiology, antecedent factors and progression to chronic kidney disease. *Journal of paediatrics and child health.* 2010; 46: 504-509. doi: 10.1111/j.1440-1754.2010.01851.x

33. Zarocostas J. Need to increase focus on non-communicable diseases in global health, says WHO. *BMJ.* 2010; 341: c7065. doi: 10.1136/bmj.c7065

ISSN 2380-0445 Open Journal http://dx.doi.org/10.17140/NPOJ-1-e005

34. Gulland A. WHO agrees to set up body to act on non-communicable diseases. *BMJ.* 2013; 346: f3483. doi: 10.1136/bmj.f3483

35. Feehally J. Chronic kidney disease: health burden of kidney disease recognized by UN. *Nat Rev Nephrol*. 2011; 8: 12-13.

36. Couser WG, Remuzzi G, Mendis S, Tonelli M. The contribution of chronic kidney disease to the global burden of major noncommunicable diseases. *Kidney Int.* 2011; 80: 1258-1270. doi: 10.1038/ki.2011.368

NEPHROLOGY

Openventio PUBLISHERS

ISSN 2380-0445 Open Journal http://dx.doi.org/10.17140/NPOJ-1-108

Research

*Corresponding author
Gite Vandana, MD
Associate Consultant
Department of Lab Services
Apollo Hospitals
Bilaspur, Chhattisgarh, India
Tel. 09755040727; 09893542691
E-mail: vandanagite@gmail.com

Volume 1 : Issue 3
Article Ref. #: 1000NPOJ1108

Article History
Received: October 14th, 2015
Accepted: November 5th, 2015
Published: November 6th, 2015

Citation
Vandana G, Maruti D. Pediatric Genitourinary tumors-Clinicopathological experience. *Nephrol Open J*. 2015; 1(3): 44-48. doi: 10.17140/NPOJ-1-108

Pediatric Genitourinary Tumors-Clinico-pathological Experience

Gite Vandana[1*] and Dhakane Maruti[2]

[1]Department of Lab Services, Apollo Hospitals, Bilaspur, Chhattisgarh, India
[2]Seth GS Medical College and KEMH Parel, Mumbai, India

ABSTRACT

Objective: To document general baseline data on the patterns of childhood genitourinary tumors.
Design, Setting and Participants: This is a retrospective analysis of 28 cases of pediatric genitourinary tumors (Age group 0-12 years) in surgical pathology in a tertiary care hospital encountered over a period of 5 years.
Results: In the genitourinary system tumors of the kidney, bladder, prostate, testis, and adrenal were included. A total of 3149 pediatric surgical specimen presented over a five years. Of this, 28 were diagnosed with genitourinary tumors. In the renal tumors only Wilm's tumors (WTs) (9 cases) was seen, with classical triphasic tumors were more common. The mean age of presentation is 3 year with commonest age group of presentation (8 cases out of 9) in the age group 1-5 years. Three of them had showed unfavorable histology. Among the gonadal germ cell tumors, there were noted four mature teratoma, one immature teratoma, two yolk sac tumors of ovary & one yolk sac tumour in testis was seen. In the adrenal gland, adrenal medullary tumors were more common than adrenal cortex with neuroblastoma (4 of 10 cases) as common individual tumor.
Conclusion: Different types of genitourinary tumors seen in the childhood. A high index of suspicion should be maintained with an aim of surgical treatment to avoid the poor management. Histological type is important for understanding etiology and progression of disease. The likelihood of a given type of tumor being present in a particular age or sex group or particular site may heighten the index of suspicion and ultimately influences etiology, biology, and natural history, relative incidence and distribution frequency, clinical presentation and manifestations, and response to therapy and outcome."

KEYWORDS: Genitourinary; Childhood tumors; Wilm's tumor; Neuroblastoma; Germ cell tumor.

ABBREVIATIONS: H & E: Hematoxylin and Eosin; WTs: Wilm's tumors.

INTRODUCTION

The natural history and management of genitourinary tumors in the pediatric age is different from that of the adults. Among the primary pediatric kidney tumors, the most frequent is the Wilm's tumor, followed by the mesoblastic nephroma.[1,2] Wilm's tumor is the most common pediatric abdominal malignancy and the fifth most common childhood malignancy. Many histological variants of non-Wilms primary renal tumors are recognized, with prognosis and management varying by age and histology. Congenital mesoblastic nephroma is the primary diagnostic consideration for a renal mass in the neonate, although its incidence decreases with increasing age during infancy.[3] Adrenal tumors occur rarely in childhood. Most antenatally detected suprarenal tumors are attributed to neurobalstoma. Neuroblastoma along with ganglioneuroblastoma and ganglioneuroma constitute a group of ganglion cell origin tumors that originate from primordial neural crest cells, which are the precursors of the sympathetic nervous system.

ISSN 2380-0445 Open Journal http://dx.doi.org/10.17140/NPOJ-1-108

Ovarian malignancies in children may represent an array of unique problems for the clinician who is more accustomed to diagnosing and treating ovarian neoplasia in adults. Although ovarian malignancies in children are rare, their recognition and diagnosis are vital because they can be fulminant if treated inadequately. Tumors of germ cell origin (e.g., mature teratoma, malignant teratoma, endodermal sinus tumor (yolk sac tumor), embryonal carcinoma, dysgerminoma, primary choriocarcinoma) constitute approximately 70% of ovarian tumors in children.[4] In addition to benign lesions, the differential diagnosis for a painless scrotal mass in a child includes leukemia, rhabdomyosarcoma, and a primary testicular tumor (germ or non-germ cell). Yolk sac tumors (endodermal sinus tumors) and teratomas are the most common primary pre-pubertal testicular tumors.[5] All tumors of the bladder and urethra is rare in children; benign tumors are even more infrequent. Benign tumors in children described in case reports include polyps, papilloma, hemangioma etc. The most common carcinoma to involve the bladder is transitional cell carcinoma.

MATERIALS AND METHODS

This was a retrospective analysis of 28 cases of pediatric genitourinary tumors in surgical pathology department encountered over a period of 5 years. Surgical specimens and biopsy tissues received were fixed overnight in 10% buffered formalin and submitted for processing. Paraffin sections were cut at 4-6 microns thickness and routine Hematoxylin and Eosin (H & E) staining were performed. All cases were re-evaluated histologically on sections from routinely processed formalin fixed, paraffin embedded blocks. Special stains & Immunohistochemistry were studied wherever necessary. The clinical, radiological and therapeutic data were obtained from patients case paper records. Pattern of childhood malignancies were studied with a focus on tumor incidence, age and sex distribution, environmental and other etiological factors, demographic pattern, and histological type.

RESULTS

A total of 3149 pediatric surgical specimen obtained over a period of five years was analyzed. Of this, 28 were diagnosed with genitourinary tumors. Average incidence of genitourinary tumors pediatric tumors was 0.89%. The commonest individual tumor was wilm's tumor followed by neuroblastoma. In the renal tumors only wilms tumors was seen, with classical triphasic tumors were more common. The mean age of presentation is 3 year with commonest age group of presentation in the age group 1-5 years (Table 1). Three of them had showed unfavorable histology. Among the gonadal germ cell tumors, we noted four mature teratoma, one immature teratoma, two yolk sac tumors of ovary & one yolk sac tumour in testis was seen. In the adrenal gland, adrenal medullary tumors were more common than adrenal cortex with neuroblastoma (4 of 10 cases) as common individual tumor (Tables 2 and 3). One case of squamous cell carcimoma of urinary bladder at the age of 10 years was documented and no any predisposing factor was elicited.

Tumor	0-1 yr	1-5 yrs	5-10 yrs	10-12 yrs	Total
Mature teratoma		1	2	1	4
Immature teratoma				1	1
Yolk sac tumour		1		2	3
Wilms tumour	1	8			9
Bladder carcinoma			1		1
Adrenocortical adenoma			1		1
Adrenocortical carcinoma			1		1
Pheochromocytoma			2		2
Ganglioneuroma		1			1
Ganglioneuroblastoma		1			1
Neuroblastoma	1	3			4
Total	02	15	07	4	28

Table 1: Age distribution of individual tumor.

Tumour	Male (M)	Female (F)	Total	M:F
Wilms tumour	7	2	9	3.5:1
Bladder carcinoma	1		1	1(M)
Mature teratoma		4	4	4(F)
Immature teratoma		1	1	1(F)
Yolk sac tumour	1	2	3	1:02
Adrenocortical adenoma	1		1	1(M)
Adrenocortical carcinoma		1	1	1(F)
Pheochromocytoma	1	1	2	1:01
Ganglioneuroma		1	1	1(F)
Ganglio-neuroblastoma	1		1	1(M)
Neuroblastoma	2	2	4	1:1
Total	14	14	28	1:1

Table 2: Gender distribution of individual tumor.

Tumour	Total No.(n=28)	Percentage (%)
Benign	08	28.57%
Malignant	20	71.53%

Table 3: Incidence of benign *vs.* malignant tumors.

DISCUSSION

Childhood malignant tumors account for no more than 2% of all cancers.[6] Tumors of the kidney, adrenal, ovary, testis and bladder represent a large part of the adult urologic practice, but are relatively infrequent in children. Among the primary pediatric kidney tumors, the most frequent is the wilm's tumor (WT), followed by the mesoblastic nephroma. In the present study, wilm's tumour with 9 cases was the largest group. All pediatric renal tumors were Wilms tumor i.e. 100% as compared to the 78.4% by Louisa Paul, et al.[7] This difference may be due to small sample size in the present study. All the cases in this study presented with abdominal mass. Eight out of 09 cases were presented in an age group 1-5 years & 01 case was seen in an age group 0-1 year, which was comparable to the study done by

ISSN 2380-0445 Open Journal http://dx.doi.org/10.17140/NPOJ-1-108

Louisa Paul, et al.[7] The median age of presentation was 3 years. Thus, the age distribution was consistent with other studies.[7-9] Wilms tumor presenting in infancy when treated appropriately has a good outcome. Age 4 years at first diagnosis is clearly an adverse prognostic factor probably that due to adverse biologic features. There were seven cases in males & two in females giving a ratio of male to female ratio of 3.5:1. This was slightly on higher side as compared to study done by Louisa Paul, et al.[7] Patel A. A., et al.[10] in their study of 11 infantile Wilm's tumour found the male to female ratio was 2.3:1. Husain A. N., et al.[8] found Wilm's tumour slightly more common in girls in whom it tends to present at an older age. Pathologically the mean tumour size in present study was 8 cm with a range of 4 cm to 15 cm (Figures 1 and 2). One of the poles of kidney was commonly affected. This was in accordance to the study done in the literature.[7] Eight cases (88.89%) were classical (Triphasic) composed of epithelial, blastemal, and stromal elements and one case was monophasic type with predominantly epithelial component. Four other types of renal tumors can occur in childhood with sufficient frequencies are mesoblastic nephroma, clear cell sarcoma of the kidney, rhabdoid tumor, and renal cell carcinoma. Congenital mesoblastic nephroma is the most common renal tumor in infants.[8] We have not observed these tumours in our present study.

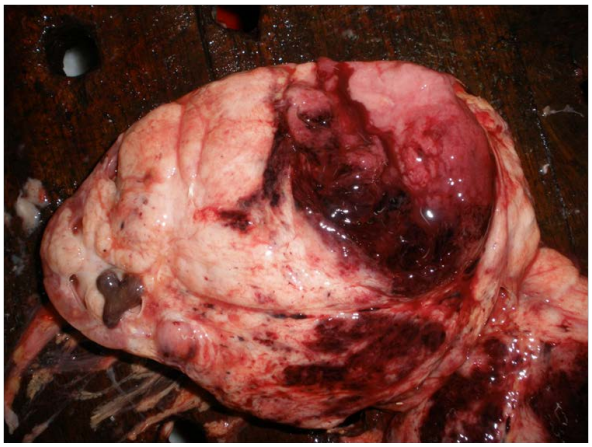


Figure 1: Wilms tumour gross pathology.

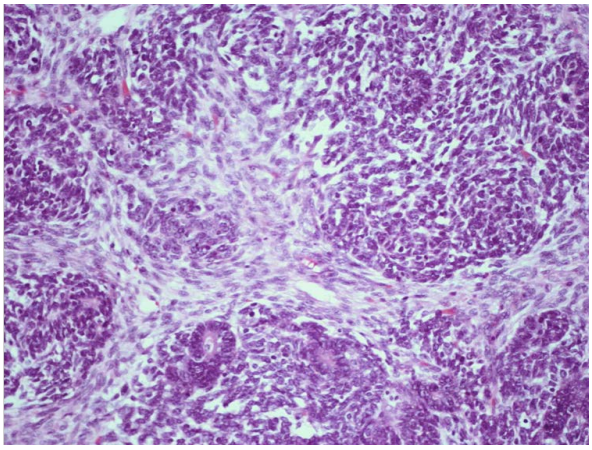


Figure 2: Wilms-tumor-triphasic histology.

It has observed that, infants with neuroblastoma seemed to have better prognosis than older children even after minimal therapy.[11] About 37% are diagnosed as infants, and 90% are younger than 5 years at diagnosis, with a median age at diagnosis of 19 months.[11] In the present study, four of neuroblastoma cases were presented at the age of 11 months, 18 months, 3 years & 5 years with male & female ratio of 1:1. No overall sex predominance has been reported.[12] All were presented with suprarenal or retroperitoneal mass & pain. Uncommon manifestations of NB related to unusual clinical behavior or to paraneoplastic syndromes were not seen in any case. Pathologically tumor cells forming the typical Homer-Wright rosettes arranged around the central fibrillary material without a central lumen or canal also seen (Figures 3 and 4). Mitotic activity was low in two of surgically resected neuroblastic tumors and absent in two of biopsy material. Calcification was noticed in all cases. The bone marrow biopsy record was not available in any case, which is also important in the monitoring of the disease activity.

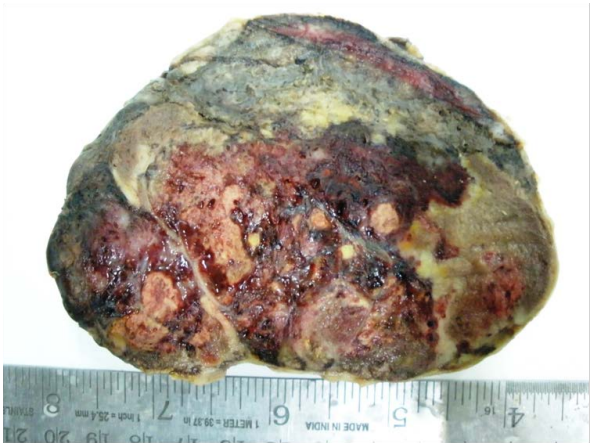


Figure 3: Neuroblastoma gross pathology.

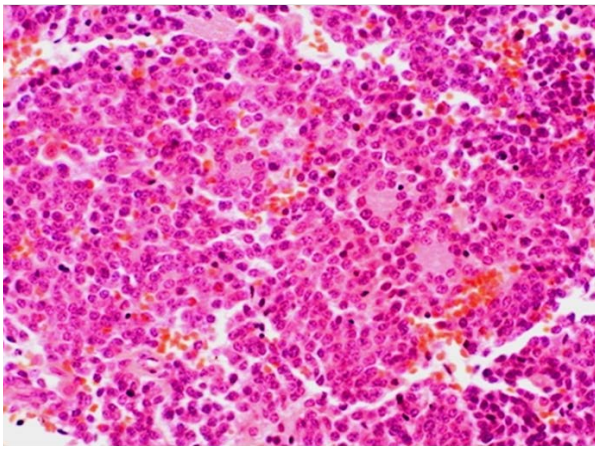


Figure 4: Neuroblastoma histology.

Some neuroblastomas have substantial internal morphologic variability about the degree of neuroblastic differentiation, ganglion cell maturation and Schwannian stroma. Differentiation in neuroblastic cells is recognized as neuropil formation and the acquisition of gangliocytic features. The phenomenon of

differentiation has been codified by use of the term Ganglioneuroblastoma to denote intermediate differentiation and Ganglioneuroma to denote the fully mature neuroblastic neoplasm. One case of ganglioneuroblastoma at the age of 4 years in females was documented presenting as suprarenal mass.

Adrenocortical carcinoma are rare tumors that have a bimodal distribution, the first peak is in children less than five years and the second around the fifth decade.[13] In our study, a single case of Adrenocortical carcinoma at an age of 7 years in a female child was observed and grossly have shown size of 15*12 cm, weight 650 gm, nodular mass with solid, cystic & necrotic areas. Microscopically the growth pattern was diffuse sheets of tumour cells with bright pink cytoplasm & broad mitotically active pleomorphic cells separated by broad fibrous bands and capsular invasion. Cagle, et al. specifically studied the adrenal cortical neoplasms in children; they found that only size (expressed as weight) was a reliable predictor of malignancy, with a weight greater than 500 g indicative of a carcinoma.[8] The macroscopic features, presence or absence of necrosis and microscopic features, such as broad fibrous bands in the tumor, increased mitotic activity, capsular invasion, and a diffuse growth pattern helped to differentiate between adenoma & carcinoma.

Malignant germ cell tumors in the ovaries of very young children are exceedingly rare. In the present study one case was of immature teratoma, two cases of yolk sac tumour in ovary and one case of yolk sac tumour in the testis was documented. All three cases of the ovary presented at the age of 11 years & showed elevated levels of AFP. Yolk sac tumors are the second most common histological subtype (22%) of malignant ovarian germ cell tumor in children. Yolk sac tumors are the most common testicular germ cell tumor in childhood, representing in excess of 60% of cases and almost 50% of all testicular tumors in children.[7] An asymptomatic scrotal mass in a child younger than 3 years of age are the common presentation. The histology and cytology of yolk sac tumors vary widely, often causing difficulty in diagnosis. The prototypic Schiller-Duvall bodies of endodermal sinus tumors are present in 50-75% of tumors.[8] Yolk sac tumors are commonly associated with highly elevated serum AFP levels, which may be monitored clinically for recurrence and/or metastasis. In the present study, two of the yolk sac tumour was located at ovary & one at testis. All three had showed elevated levels of AFP. Both ovarian yolk sac tumors presented at the age of 11 years & one case of testicular yolk sac tumour at the age of 5 years. Grossly they have solid, yellow appearance. Microscopically polygonal tumour cells in reticular, trabecular & papillary pattern seen with Schiller-Duvall bodies. Microcystic change is seen in one ovarian yolk sac tumour.

All tumors of the bladder and urethra are rare in children. In the present study, one case of squamous cell carcimoma at the age of 10 years was documented and no any predisposing factor was eliciated. In contrast to adults, most pediatric bladder carcinomas are low grade, superficial, and have a good prognosis following transurethral resection. Rare cases of, leiomyosarcoma, and secondary involvement of leukemia, lymphoma, and Wilm's tumor has been reported.[8]

To conclude, different types of genitourinary tumors are seen in the childhood. A high index of suspicion should be maintained with an aim of surgical treatment. Histological type is important for understanding etiology and progression of disease. The likelihood of a given type of tumor being present in a particular age or sex group or particular site may heighten the index of suspicion and ultimately influences etiology, biology, and natural history, relative incidence and distribution frequency, clinical presentation and manifestations, and response to therapy and outcome.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

CONSENT

The Patient has provided written permission for publication of the case details.

REFERENCES

1. Lowe LH, Isuani BH, Heller RM, et al. Pediatric renal masses: Wilms tumor and beyond. *Radiographics*. 2000; 20(6): 1585. doi: 10.1148/radiographics.20.6.g00nv051585

2. Spreafico F, Bellani FF. Wilms' tumor: past, present and (possibly) future. *Expert Rev Anticancer Ther.* 2006; 6(2): 249. doi: 10.1586/14737140.6.2.249

3. van den Heuvel-Eibrink MM, Grundy P, Graf N. Characteristics and survival of 750 children diagnosed with a renal tumor in the first seven months of life: a collaborative study by the SIOP/GPOH/SFOP, NWTSG, and UKCCSG Wilms tumor study groups. *Pediatr Blood Cancer*. 2008; 50(6): 1130-1134. doi: 10.1002/pbc.21389

4. Breen J, Denehy T. Pediatric ovarian malignancies. *Glob libr women's med.* 2008. doi: 10.3843/GLOWM.10251

5. Taskinen S, Fagerholm R, Aronniemi J, et al. Testicular tumors in children and adolescents. *J Pediatr Urol.* 2008; 4(2): 134-137. doi: 10.1016/j.jpurol.2007.10.002

6. Steliarova-Foucher E, Hery C, Pisanim P. The burden of childhood cancer. *International Union against Cancer, UICC.* 2006.

7. Louisa P, Durrane T, Suhail M, Irshad N, Zafar N, Sheema H. Clinicopathological profile of Wilms' tumor. *Indian Journal of Pediatrics*. 2000; 67(10): 765-767.

8. Stocker JT, Dehner LP, Husain AN, Ovid Technologies, Inc. Stocker & Dehner's pediatric pathology. 3rd ed. Philadelphia:

ISSN 2380-0445 Open Journal http://dx.doi.org/10.17140/NPOJ-1-108

Lippincot Williams & Wilkins; 2001.

9. Breslow NE, Beckwith JB. Epidemiological features of Wilms tumor: results of the national wilms' tumor study. *Journal of the National Cancer Institute.* 1982; 68(3): 429-436.

10. Patel A, Patel K, Shah S, et al. Three years experience of infantile Wilms tumour at a single institute in a developing country. *Journal of Clinical Oncology.* 2007; 25(18S): 20028.

11. Audrey E, Giulio J. Age at diagnosis and prognosis in children with neuroblastoma. *Journal of Clinical Oncology.* 2005; 23(27): 6443-6444. doi: 10.1200/JCO.2005.05.005

12. London W, Castleberry R, Matthay K, et al. Evidence for an age cutoff greater than 365 days for neuroblastoma risk group stratification in the children's oncology group. *J ClinOncol.* 2005; 23(27): 6459-6465. doi: 10.1200/JCO.2005.05.571

13. Ng L, Libertino JM. Adrenocortical carcinoma: diagnosis, evaluation and treatment. *J Urol.* 2003; 169: 5-11. doi: 10.1016/S0022-5347(05)64023-2

NEPHROLOGY

Openventio PUBLISHERS

ISSN 2380-0445 Open Journal http://dx.doi.org/10.17140/NPOJ-1-109

Commentary

*Corresponding author
Rudolf Fluckiger, PhD
Instructor Harvard Medical School Boston
Brigham and Women's Hospital
Orthopaedic Research (Retired)
Novacule, LLC
2587 Albany Ave
West Hartford, CT 06617, USA
Tel. 860-519-1621
E-mail: Novacule@gmail.com
Website: http://novacule.com/

Volume 1 : Issue 3
Article Ref. #: 1000NPOJ1109

Article History
Received: February 4th, 2016
Accepted: February 25th, 2016
Published: February 25th, 2016

Citation
Flückiger R. Nephrology should trail blaze the end of chronic disease. *Nephrol Open J*. 2016; 1(3): 49-50. doi: 10.17140/NPOJ-1-109

Nephrology should Trail Blaze the End of Chronic Disease

Rudolf Fluckiger, PhD*

Instructor Harvard Medical School Boston, Brigham and Women's Hospital, Orthopaedic Research (Retired), West Hartford, CT 06617, USA

If history can serve as a guide quite some time can lapse between the inception of a concept and its proof. For instance, Einstein had described the special theory of relativity in 1905, but he published the general theory of relativity only after thinking about the problems for 10 years. On March 29, 1919, the opportunity to get proof came. British Astronomer Sir Arthur Eddington had traveled to Príncipe Island off the western coast of Africa. His team photographed star fields during the eclipse and compared the photos with those of the same star field taken when the sun was not present. Eddington found the apparent location of the stars had shifted, just as was predicted by Einstein's theory. That 15-year delay between conception and proof did not cause suffering or deaths as was the case with the germ theory of Semmelweis, who did not live to see his momentous insight being accepted. He was declined reappointment and admitted to an asylum where he died after only two weeks with the following on his mind "*When I look back upon the past, I can only dispel the sadness which falls upon me by gazing into that happy future when the infection will be banished . . . The conviction that such a time must inevitably sooner or later arrive will cheer my dying hour*".[1]

The author postulates based on his personal experience and strive with cancer that the end of chronic disease is near. He postulates that chronic disease arrises whenever the innate immune system turns on the body. He feels that he cannot justify to wait until the editor of a prestigious medical journal decides to allow his manuscript to get peer reviewed until he let his unified theory of the cause of chronic disease become known. Too much is at stake, patients suffer unnecessarily and great cost is added to our overburdened health care system. So he takes the occasion of the Einstein's anniversaries, 100 years relativity theory[2] and his 60th death anniversary together with the generous invitation of Nephrology open journal editor Ms. K. Jessie to publish his theory. He bases his theory on four facts (1) he had managed to suppress the pain of his chemotherapy-induced peripheral neuropathic pain by attenuating the activity of the complement system with the mega dosed antioxidants Pyrroloquinoline quinone (PQQ) and N-acetylcysteine (NAC). They create a reactive oxygen radical-free state that prevents the activation of Transient Potential Receptor ion channels which serve as pain receptors; (2) that the metabolic syndrome of his wife resolved when taking PQQ/NAC; there is an obvious explanation for this reversal of diabetes. In the absence of attack by the complement system on the insulin producing beta cells they can recover and repopulate from resident stem cells to respond to physiological stimuli again. We hypothesize that similar mechanisms may be at work in other chronic disease states like Multiple Sclerosis, Alzheimer's disease, Parkinson's, Macular Degeneration, and Amyotrophic Lateral Sclerosis; (3) that the severity and frequency of migraine attacks decreased with PQQ/NAC intake; (4) that the pathophysiology underlying diabetes and migraine both involve Transient Receptor Potential (TRP) ion channels. It appears that the use of PQQ/NAC in Nephrology will most quickly yield the results to support our hypothesis as a dysfunctional immune system has been shown to be involved in causing renal damage.[3] Based on this insight the highly potent complement inhibitor compstatin was designed.[4] However, the toxicity of this compound does not allow it to be administered to patients for prolonged periods of time. In contrast, PQQ/NAC are well tolerated, the author has used them to suppress his pain from peripheral neuropathy for over three years without experiencing any adverse side effects. According to the literature TRP ion channels have beneficial effects in some thirty medical conditions for many of which there currently exist no efficient therapies. Preventative long-term intake of PQQ/NAC is therefore a good way to swart off chronic dis-

ISSN 2380-0445 Open Journal http://dx.doi.org/10.17140/NPOJ-1-109

ease and correct non-life threatening medical inconveniences. The challenge is now to quickly make PQQ/NAC available to as many people as possible in order to see chronic disease disappear within our lifetime. It took over a year to reverse diabetes but complement activity following dialysis is quickly assessed. The benefits of PQQ/NAC on the outcome of hemodialysis should be apparent after a few rounds of hemodialysis. If it turns out that we are correct with our assumption, PQQ/NAC has to be made available to as many people as possible in the shortest time feasible. Enforcing the food supply with PQQ/NAC is one way to do so, introducing gut resident bacteria that are able to produce high enough quantities of PQQ and NAC is another. We are pursuing both options and will bring our product, Novapyrin™, which contains both PQQ and NAC on the market. We are pursuing this option vigorously as it obviously is the final fix for a problem that Nature could not satisfactorily solve. Nature has put in place the superoxide dismutases to protect from damage from the superoxide radicals but could not find a way to handle the hydroxyl radical efficiently through enzymatic deactivation, likely because it would be difficult to bind. The efficiency of small molecule hydroxyl radical scavengers like glutathione or polyphenols is not strong enough to deal with this reactive small radical.

Our manuscript stating just the facts was apparently not exiting enough to catch the fancy of editors.[5] The thought that we need a sexier title occurred to me when I picked up the Science issue celebrating the 100 year anniversary of the Theory of Relativity. A Unified Theory of Chronic Disease could be put forward without the conclusive evidence in hand and would imply that there is a single therapeutic solution which I already had found. I saw this solution to my problem and to a pressing health issue with great clarity. This is was my idol ETH-Zürich Organic Chemistry Professor Vladimir Prelog must have experienced when he had his insight about chirality that brought him the 1975 Nobel Prize in Chemistry which was divided equally between John Warcup Cornforth "*for his work on the stereochemistry of enzyme-catalyzed reactions*" and Vladimir Prelog "*for his research into the stereochemistry of organic molecules and reactions*".[6,7] There are other reasons why to publish this material. The birthday of genius author William Shakespeare falls on the 23th as does that of my wife who wondered why my neuropathy was relatively mild while a much severe condition was sketched in a television ad for a product promising relief from neuropathic pain. She noted that I had unintentionally been on a diet rich in PQQ (green vegetables, yogurt, milk, vinegar-based salads) in preparation and after the cell stem transplant. She had some 20 years ago helped me in the laboratory with performing pyrroloquinoline determinations and still remembered the samples with high readings. So I ordered PQQ gel caps and experienced some relief the first night after taking it. As the dose of 10 mg was certainly a mega dose I expected full relief and had to experiment for a while until I found the formulation giving full relief.

REFERENCES

1. Explorable. *Semmelweis' germ theory.* Available at: https://explorable.com/semmelweis-germ-theory 2010; Accessed 2016.

2. Moerchen M, Coontz R. Einstein's vision. *Science.* 2015; 347(6126): 1082-1083. doi: 10.1126/science.347.6226.1082

3. Sahu A, Morikis D, Lambris JD. Compstatin, a peptide inhibitor of complement, exhibits species-specific binding to complement component C. *Mol. Immunol.* 2003; 39(10): 557-566. doi: 10.1016/S0161-5890(02)00212-2

4. Ricklin D, Lambris JD. Compstatin: a complement inhibitor on its way to clinical application. *Current Topics In Complement II*. 2008; 262-281. doi: 10.1007/978-0-387-78952-1_20

5. Fluckiger R. Oxidative stress release with PQQ/NAC ameliorates peripheral neuropathic pain and lowers systolic blood pressure by preventing TRP activation: effects that establish pyrroloquinoline quinone as a vitamin. *Nature Communications*. submitted 2014.

6. Prelog V. Chirality in Chemistry. Nobel Lecture, Stockholm Sweden. *Science.* 1975;193:17. Available at: http://www.nobelprize.org/nobel_prizes/chemistry/laureates/1975/prelog-lecture.pdf

7. Comforth J, Prelog V. The Nobel Prize in Chemistry 1975. Nobelprize.org. Nobel Media AB 2014. Available at: http://www.nobelprize.org/nobel_prizes/chemistry/laureates/1975/ 2014; Accessed February 13, 2016.

NEPHROLOGY

Openventio PUBLISHERS

ISSN 2380-0445 Open Journal http://dx.doi.org/10.17140/NPOJ-1-110

Mini Review

*Corresponding author
Zhousheng Xiao, PhD
Associate Professor
Department of Nephrology
The University of Tennessee Health Science Center
Memphis, TN 38103, USA
Tel. 901-448-1489
Fax: 901-448-1188
E-mail: zxiao2@uthsc.edu

Volume 1 : Issue 3
Article Ref. #: 1000NPOJ1110

Article History
Received: March 10th, 2016
Accepted: March 21st, 2016
Published: April 4th, 2016

Citation
Nayani SS, Xiao Z. Recent advances in fibroblast growth factor-23 functions. *Nephrol Open J.* 2016; 1(3): 51-58. doi: 10.17140/NPOJ-1-110

Recent Advances in Fibro-blast Growth Factor-23 Functions

Shahzad Shoukat Nayani, MBBS; Zhousheng Xiao, PhD*

Division of Nephrology, Department of Medicine, The University of Tennessee Health Science Center, Memphis, TN 38165, USA

ABSTRACT

During the past decade a lot of work has been done to better understand the roles of fibroblast growth factor-23 (FGF-23); a relatively newly discovered endocrine hormone, in multiple organ systems in the body. This review focuses on expressions of FGF-23, co-expressions of α-Klotho and FGF receptors, and FGF-23 mediated end-organ effects in the physiological and pathological conditions. We also discuss the controversial reports regarding α-Klotho-dependent and α-Klotho-independent functions of FGF-23.

EXPRESSION OF FGF-23, α-KLOTHO, AND FGF RECEPTORS

FGF-23

FGF-23 is a family member of 22 fibroblast growth factors (FGFs) including FGF-1-FGF-23, all of which are not only structurally but also evolutionarily related proteins. These FGFs have been classified as being paracrine (15 FGFs), endocrine (3 FGFs), or intracrine (4 FGFs)[1] and using a mammalian (murine) model the endocrine FGFs, especially FGF-23 an approximately 32 kD protein,[2] have been thoroughly investigated in recent years.

FGF-23 is expressed in multiple cells in the body. It has been conclusively shown to be secreted in bone by cells of the osteoblast lineage and osteocytes, as a part of the lacuna-canalicular system, under the influence of phosphate.[3] Local factors derived from bone itself also regulate its expression as seen in cases of inactivating mutations of *PHEX* which results in increased transcription and circulating levels of FGF-23.[4] It is also expressed in the pericyte-like endothelial cells surrounding the venous sinusoids in bone marrow[5] and in the thymus.[2] FGF-23 also plays a part in the body's immune response since its expression is induced in activated dendritic cells and macrophages in response to inoculation with *E. coli* and *S. aureus via* nuclear factor-kappa B (NF-κB) signaling.[6] FGF-23 is found to be expressed in the ventero-lateral (VL) thalamic nucleus as well. In addition, FGF-23 is also expressed in heart by cardiac interstitial fibroblasts.[7,8] Apart from these tissues, there is also FGF-23 expression seen in the muscle, spleen, skin, lung, testes, kidney, and liver to a much lesser extent.[7]

α-Klotho

α-Klotho is a unique molecule that establishes a regulatory system of calcium homeostasis by affecting transepithelial transport of calcium, parathyroid hormone secretion, and FGF-23 signal transduction.[9] Evolutionarily the FGF-23-α-Klotho system is part of a major milestone in vertebrate evolution that started in the ocean when the early piscine ancestors acquired the bony endoskeleton.[10] α-Klotho has been demonstrated to enhance FGF-23 activity over 10-fold[11] and has also been identified as a necessary co-receptor for FGF-23 binding due to the phenotypic similarity observed in α-Klotho and FGF-23 knockout mice, i.e.; hyperphosphatemia and hypercalcemia.[11]

α-Klotho is expressed in high levels in kidney, parathyroidgland (PTG), testis, ovary, brain, pituitary, and apical plasma membrane of ependymal cells in the choroid plexus but

ISSN 2380-0445 Open Journal http://dx.doi.org/10.17140/NPOJ-1-110

not in bone, lung, liver, skin, spleen, small intestines, or adrenal glands.[12] The identification of these sites of expression is important because these must be compared to the sites of expression of FGFRs, since FGF-23 has the majority of its effects through the FGFRs α-Klotho complexes pathway.[13]

Expression of FGF Receptors

There are four single pass transmembrane proteins called the fibroblast growth factor receptors (FGFRs 1-4),[14] which are involved with important biological processes ranging from cell division and maturation to formation of blood vessels, wound healing, and embryonic development.[15] Local and systemic secreted FGFs bind FGFRs to dimerize them, followed by activation of intracellular FGF signaling pathways including RAS–RAF–MAPK, PI3K–AKT, STAT, and PLCγ pathways.[1]

FGFR has been shown to be highly expressed in the skin and heart with moderate expression in the ovary.[16] Some degree of expression has also been shown in the kidney and urinary bladder.[17] {Luqmani, 1992 #67}Other than these sites, FGFR-1 expression was noticed in low levels in the breast, lung spinal cord, adrenal, thyroid, ileum, colon, and stomach.[18] FGFR-2 expression has also been detected in these tissues except for the heart. A particularly high level of expression of FGFR-2 was noted in stomach and in the thyroid.[16,18] FGFR-3 shows very little expression, if any, throughout the human body. However, high expression levels have been noted in the skin.[19] FGFR-4 shows moderate levels of expression in the lung and low levels in the ovary, kidney, intestines, and the liver. Nonetheless, other than these tissues there is limited expression seen in the body.[20] Tissue specific FGFR expression and activation has been shown to be modulated by heparin, heparan sulfate, or other glycosaminoglycan chains.[21] FGFRs 1-3 show an alternative splicing pattern which leads to formation of 'b' and 'c' isoforms. The 'b' isoform is expressed preferentially in epithelial tissues while 'c' is found in mesenchymal tissues.[22] This, along with the different sites of expression of different FGFs, renders specificity to the FGF signaling system.[14]

Co-expression of FGFRS and α-klotho Utilized by FGF-23

As noted above, FGFR-1, FGFR-2, and FGFR-4 have some sites of expression in common with α-Klotho, particularly the kidneys and the ovary. FGF-23 was found to act preferentially via FGFR-1c, FGFR-3c, and FGFR-4 since α-Klotho forms complexes with them.[11,14] However, a single or double depletion of FGFR-3 and FGFR-4 does not lead to defects in phosphate homeostasis.[23] A deletion of FGFR-1 however, is embryonically lethal in mice[24] and FGF-23 expression is notably increased when FGFR-1 is activated in rats with normal kidney function and *in vitro* in osteo blast-like cells derived from bone.[25] This increased expression also occurs in cases of activating mutations of FGFR-1 as evident in osteoglophonic dysplasia.[3] At the same time a conditional deletion of FGFR-1 in the osteocytes of Hyp mice showed decreased FGF-23 expression.[5] This leads to the conclusion that FGFR-1c is the most significant binding site for FGF-23.

END-ORGAN EFFECTS OF FGF-23 IN THE PHYSIOLOGICAL AND PATHOLOGICAL CONDITIONS

Aside from the issues discussed above, there are also some gaping holes in the research regarding FGF-23 that have not been investigated yet and could possibly lead to answers that will not only link multiple effects and disorders caused by FGF-23 in the body but also provide more paradigm-shifting knowledge regarding the complex metabolic balance in our bodies and the hitherto unknown roles of multiple organs in this. These issues are briefly discussed here according to the organs that they concern most directly.

Kidney

FGF-23 acts *via* the α-Klotho:FGFR-1 complex in the renal tubules. The highest expression of these complexes has been seen in the distal tubule indicating that this is where the initial effect of FGF-23 takes place. However, FGF-23 was found to inhibit sodium-dependent phosphate reabsorption *via* decreased expression of NPT-2a and NPT-2c in the proximal tubule.[26,27] FGF-23 also promotes calcium reabsorption in the distal tubule *via* the TRPV-5 channel.[28] It is also linked to vitamin D3 levels since 1, 25(OH)2D administration stimulates FGF-23 expression.[29] Furthermore, FGF-23 inhibits 1 α-hydroxylase expression in the proximal tubule while simultaneously increasing 24-hydroxylase expression leading to formation of a less active form of vitamin D,[5,30] setting up an effective feedback loop. FGF-23 also decreases the expression of α-Klotho by the kidney, establishing a complete feedback loop regarding its effects in the kidney.[31] Meanwhile the serum levels of FGF-23 have also been established as biomarkers for renal failure.[32]

Gastrointestinal Tract

FGF-23 has been shown to inhibit expression of the intestinal phosphate transporter NTP-2b,[33] thus leading to a decrease in serum phosphate levels. As an indirect effect of FGF-23 we also see that due to decreased activation of 1, 25(OH)2D from the kidney, there is decreased absorption of calcium and phosphate from the intestine.[34]

Parathyroid Gland

α-Klotho and FGFR-1 are both expressed in high levels in the PTG.[35] However, many different studies have reached different conclusions regarding FGF-23 and its effects on the PTG. This has raised a lot of questions and will be discussed in the following section. The one undisputed fact is that PTH acts on bone to cause an increased expression of FGF-23[36] and FGF-23 decreases PTH expression,[37] setting up a feedback inhibition loop.

ISSN 2380-0445 Open Journal http://dx.doi.org/10.17140/NPOJ-1-110

Bone

The bone is the major origin of FGF-23. However, α-Klotho is not expressed in bone,[38] but all of FGF-23's receptors (FGFR-1c, FGFR-2c, and FGFR-3c) are expressed in osteoblasts.[39] FGF-23's importance as a vital hormone came to light when the FGF-23 gene was identified as the one linked to Autosomal Dominant Hypophosphatemic Rickets (ADHR).[40] This discovery prompted further research and FGF-23 was also found to be the causative agent behind human tumor-induced osteomalacia which is a disease linked to hypophosphatemia due to renal phosphate wasting,[41] thus leading to the discovery of its role as a part of a bone-kidney-parathyroid axis. Given FGF-23's obviously important role in bone-related pathologies, and the work already done on the indirect effects it has on the bone *via* its effects on the other endocrine organs, much more work needs to be done on the direct effects FGF-23 has on bones.

Thalamus, Choroid Plexus, and Pituitary Gland

The venterolateral (VL) thalamic nucleus is related to the motor system and is an important relay for deep cerebellar nuclei to the motor cortex which is in fact where, at the time of FGF-23's discovery, it was thought it might have its effects.[2] Despite that, not much research has been carried out to assess FGF-23's function there. The choroid plexus and pituitary gland both exhibit high levels of α-Klotho expression and thus are potential targets for FGF-23.[12] Following FGF-23 injections in mice in both of these organs, there is induction of early growth response-1 (EGR-1) expression as well as phosphorylation of the extracellular signal-regulated kinase (ERK).[42] The choroid plexus and the pituitary gland are both sites of α-Klotho expression [12] but FGF-23's function in these organs is still unknown. The choroid plexus is involved in the composition of the cerebrospinal fluid (CSF) and the pituitary gland is a major endocrine gland. As such, the knowledge of how FGF-23 is involved in the functioning of both these organs is of vital importance if we are to understand completely the diverse effects it can cause physiologically as well as in certain pathologies.

Heart

Cardiac tissue is one of the sites of FGF-23 expression,[8] but there is no α-Klotho expression in the heart tissues.[43] Single nucleotide polymorphisms (SNPs) in FGF-23 have been identified as potential risk factors for cardiac abnormalities in Kawasaki disease,[44] and the serum levels of FGF-23 have been recognized as biomarkers for cardiovascular failure.[45] FGF-23 had also been linked to greater risks of left ventricular hypertrophy in patients with CKD.[46] However, no conclusion has been reached whether this effect is *via* α-klotho independent pathways or indirectly due to the renal effects of FGF-23. This is also discussed in the next section.

Ear

FGF-23 is expressed throughout the cochlea and while α-Klotho also has receptors in the ear, FGF-23's specific effects were determined by the fact that functional assessments of hearing in FGF-23 null mice did not match the auditory phenotype of α-Klotho null mice. There is also an overlap of initiation of FGF-23 activity and the development of the eustachian tube during embryogenesis which could be the cause of middle ear malformations in FGF-23 deficiency. FGF-23 heterozygous knockout mice have been found to be deaf with close to normal morphology, while homozygous knockout mice have dysplastic bulla and ossicles.[47] There is a difference in auditory phenotype between the FGF-23 null mice and α-Klotho null mice.[47] Investigating this further can not only help us find out how FGF-23 might be carrying out α-Klotho independent functions in the ear, but also set a template for investigation into α-Klotho independent functions of FGF-23 in other organs.

Prostate

FGF-23 is heavily linked with prostate cancer. It has been shown that it is not only expressed as an autocrine factor in prostate cancer cells but also enhances proliferation, invasion and anchorage when given exogenously. FGF-23 knock down was shown to decrease *in vivo* tumor growth.[48] Single nucleotide polymorphisms in FGF-23 have also been linked to a risk of prostate cancer.[49]

Vasculature

The role of FGF-23 in causing vascular calcification has also been studied recently. Nevertheless, the scientific community has reached a consensus neither regarding the exact effect of FGF-23 on vasculature nor regarding the mechanism of such an effect. This issue is also outlined in the following sections. Meanwhile the serum levels of FGF-23 have been definitely established as biomarkers for stroke.[50] While previous studies have shown that ablation of FGF-23 leads to increased serum phosphate levels and thus vascular calcification and death,[51] a new study states that FGF-23 enhances phosphate induced calcification in the aortic rings of rats by promotion of osteoblastic differentiation involving the ERK1/2 pathway.[52] However, there are other studies which do not support α-Klotho mediated effects of FGF-23 in the vasculature.[53] Studies looking into this could not only help understand the link between FGF-23 and cardiovascular abnormalities in the body but also FGF-23's link with strokes.

Immune System (Macrophages)

FGFR-1c is expressed in macrophages and FGF-23 has been shown to not only increase the number of macrophages but also to induce TNF* expression in the macrophages.[6] FGF-23 might play a key role in inflammation *via* its effects on macrophages as discussed above.[6] However much more work needs to be done in this respect, since inflammation could also account for, or at least play a major role in, many different complications associated with disease states with elevated FGF-23 levels.

ISSN 2380-0445 Open Journal http://dx.doi.org/10.17140/NPOJ-1-110

Indirect Effects via The RAAS Pathway

FGF-23 has been shown to stimulate the rennin-angiotensin-aldosterone-system (RAAS) by suppression of ACE-2 expression in renal tissue, independent of other bone-mineral disorder abnormalities.[54] Renin expression in the kidney also increases indirectly due to the inhibition of 1, 25(OH)2D by FGF-23.[34] Through this stimulation of RAAS, FGF-23 leads to numerous adverse effects like hypertension, diabetic nephropathy, baroreceptor dysfunction, activation of sympathetic system, endothelial dysfunction, atherosclerotic progression, and fibrinolytic system inhibition.[55] This also helps link FGF-23 to many of its observed adverse effects.

KLOTHO-DEPENDENT AND KLOTHO-INDEPENDENT FUNCTIONS OF FGF-23

As discussed above, FGF-23 is linked deeply with many of the organ systems in the physiological conditions to contribute to the body's overall endocrine homeostasis and is also responsible for diseases linked to disturbances in the pathophysiological conditions. So far the new focus of research regarding FGF-23 is concerned with the identification of α-Klotho dependent and α-Klotho independent effects of FGF-23. It has been reported that besides acting as a co-receptor of FGF-23 binding to FGFRs, α-Klotho also acts as a molecular switch. Its presence or absence determines which intracellular signaling pathways will be recruited downstream of the FGFRs. Thus disease states with α-Klotho deficiency may not involve global FGF-23 resistance, but rather they may in fact promote a switch of the FGF-23-induced signaling towards different cellular responses and outcomes in cells which express FGFRs, but not α-Klotho.[56]

Previously FGF-23 functions on major organs, directly or indirectly, were considered only when α-Klotho was co-expressed along with FGFRs in the target tissue,[42] but with new studies that have been conducted exploring different mechanisms of action of FGF-23, researchers need to reassess the role FGF-23 plays in the organs and how that is achieved. There is clearly a delicate balance between FGF-23's α-Klotho dependent actions on the FGFRs and its α-Klotho independent actions on FGFR's throughout the body that need to be considered simultaneously and further studied. We discuss these issues here according to the target organ they impact.

Kidney

What needs to be clarified regarding FGF-23's role in the kidney by future studies is how exactly FGF-23 stimulation of the distal renal tubule leads to regulation of proximal tubule function, and which signaling pathways are involved in signal transduction from the distal to the proximal tubule. It has been shown that murine proximal tubular epithelium also expressed α-Klotho and that FGF-23 acts directly on these proximal tubular cells to down regulate membrane expression of NPT-2a via ERK-1/2 and SGK-1.[57] This suggests that FGF-23's actions in the kidney are all reliant on α-Klotho-dependent stimulation of FGFR's, in the proximal as well as the distal tubule, with no observable α-Klotho-independent actions. However the above observation can possibly be confounded by the use of FGF-23 amounts high enough to activate α-Klotho-independent receptors of FGF-23, and by the authenticity of the proximal tubular phenotype in the cell culture model which could have been either contaminated with distal tubular cells or have undergone dedifferentiation. Thus where we already know of the effects down-stream of α-Klotho-dependent stimulation by FGF-23 at the distal tubular cells, further research should focus on possible α-Klotho-independent receptor stimulation of FGF-23 at proximal tubular cells.

Bone

Despite being the site of greatest expression and production of the hormone, little is known about the direct effects of FGF-23 on the bone itself. Though the absence of α-Klotho indicates a greatly reduced affinity of FGF-23 for its receptors, studies have shown that FGF-23 might directly inhibit bone formation *via* weak activation of FGFR signaling.[39,58] This could be due to a α-Klotho-independent action of FGF-23 on bone cells. There have been defects in bone mineralization noted in FGF-23 null mice but these might be secondary to the elevated levels of 1, 25(OH)2D in these mice since the deletion of the vitamin D receptor rescues the phenotype of FGF-23 null mice.[59] Further research in this aspect would serve to further the understanding of the role that bone plays in the delicate endocrine axis and the role of α-Klotho, if any, in this regard.

Parathyroid Gland

In human disease conditions and in murine models, FGF-23 has been linked to increased levels of PTH,[60] while in more recent studies FGF-23 has been shown to decrease PTH expression and secretion from the PTG.[37] However due to lack of research into FGF-23's Klotho-independent signaling *via* FGFRs in the PTG, it is as of yet unknown whether FGF-23 directly causes an increase in PTH, or if the increase in PTH might be a misleading finding due to FGF-23 induced down regulation of α-Klotho in the PTG rendering FGF-23 unable to exert its suppressive effects on PTH *via* a α-Klotho-dependent mechanism. It is also possible, as discussed above, that the down regulation of α-Klotho in the PTG enables FGF-23 to activate different downstream signaling pathways that lead to different effects than those seen in the presence of α-Klotho. Another theory is that only the extremely elevated levels of FGF-23 in disease states, like chronic kidney disease (CKD), lead to a 1, 25(OH)2D level low enough to cause not only the release of PTG from the FGF-23 induced inhibition, but also to cause a subtle hypocalcemia which chronically stimulates the PTG to cause a secondary hyperparathyroidism.[61] This is supported by the fact that among the factors known as chronic kidney disease related mineral and bone disorders (CKD-MBD), FGF-23 has also been noted to be

ISSN 2380-0445 Open Journal http://dx.doi.org/10.17140/NPOJ-1-110

the first to increase in concentration before changes in levels of PTH, 1, 25, (OH)2D, or serum phosphate,[62,63] pointing to it having a causal role in this disease. It is also possible that the hypophosphatemia that results from elevated FGF-23 levels leads to a decreased PTH secretion, since phosphorus levels *in vitro* in rat PTGs have been linked directly to PTH secretion.[64] Further studies need to work specifically on this aspect of FGF-23's actions since knowledge of how exactly the FGF-23-PTG axis is set up and the role of α-Klotho-dependent and α-Klotho-independent receptors will help clarify the development and mechanism of many pathologies associated with variance in FGF-23 levels.

Heart

Left ventricular hypertrophy (LVH) is a serious mortality causing condition linked to chronic kidney disease (CKD) and the elevated FGF-23 levels that it is associated with. Since there is a scarcity of research into the α-Klotho-dependent and α-Klotho-independent actions of FGF-23 in the heart muscle, and since α-Klotho is absent in cardiomyocytes, the current thought is that LVH in CKD must be a complication due to the indirect effects of FGF-23 on the kidneys.

However, studies have demonstrated the role of FGF-23 in causing pathological hypertrophy in isolated rat cardiomyocytes *via* an α-Klotho independent, FGFR-4 dependent activation of calcineurin-NFAT pathway.[56,65] Activation of this FGFR-4/calcineurin/NFAT pathway has been shown to be enough to cause cardiac hypertrophy in mice while FGFR-4 blockade, even with high serum FGF-23 levels, attenuates cardiac hypertrophy in rats with CKD.[56] In another study FGF-23 has been shown to induce cardiomyocyte hypertrophy *via* PLC-γ signaling, upstream of calcineurin/NFAT, independent of Klotho.[43] These studies bring to light questions regarding α-Klotho independent functions of FGF-23 in the heart that must be further investigated. Another thing that needs to be clarified by future research is whether the FGF-23 of cardiac origin plays a role in causing LVH in a paracrine manner.

CONFLICTS OF INTEREST: None.

REFERENCES

1. Ornitz DM, Itoh N. The Fibroblast Growth Factor signaling pathway. *WIREs Dev Biol*. 2015; 4(3): 215-266. doi: 10.1002/wdev.176

2. Yamashita T, Yoshioka M, Itoh N. Identification of a novel fibroblast growth factor, FGF-23, preferentially expressed in the ventrolateral thalamic nucleus of the brain. *Biochem Biophys Res Commun*. 2000; 277(2): 494-498. doi: 10.1006/bbrc.2000.3696

3. ADHR Consortium. Autosomal dominant hypophosphataemic rickets is associated with mutations in FGF-23. *Nat Genet*. 2000; 26(3): 345-348. doi: 10.1038/81664

4. Liu S, Guo R, Simpson LG, Xiao Z-S, Burnham CE, Quarles LD. Regulation of fibroblastic growth factor 23 expression but not degradation by PHEX. *J Biol Chem*. 2003; 278(39): 37419-37426. doi: 10.1074/jbc.M304544200

5. Liu S, Zhou J, Tang W, Menard R, Feng JQ, Quarles LD. Pathogenic role of FGF-23 in Dmp1-null mice. *Am J Physiol Endocrinol Metab*. 2008; 295(2): E254-E261. doi: 10.1152/ajpendo.90201.2008

6. Masuda Y, Ohta H, Morita Y, et al. Expression of FGF-23 in activated dendritic cells and macrophages in response to immunological stimuli in mice. *Biol Pharm Bull*. 2015; 38(5): 687-693. doi: 10.1248/bpb.b14-00276

7. Liu S, Quarles LD. How fibroblast growth factor 23 works. *J of the Am Soc of Nephrology*. 2007; 18(6): 1637-1647. doi: 10.1681/ASN.2007010068

8. Bowman MH, Gardner B, Earley J, Rateri D, Daugherty A, Yan L. Abstract 478: FGF-23 expression in cardiac fibroblasts is augmented by S100/Calgranulins-Mediated Inflammation and Associated With Cardiac Hypertrophy, but Not in Angiotensin II-Induced Cardiac Hypertrophy. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2015; 35(Suppl 1):A478. Web site. http://atvb.ahajournals.org/content/35/Suppl_1/A478.abstract. Accessed March 9, 2016.

9. Nabeshima Y, Imura H. alpha-Klotho: a regulator that integrates calcium homeostasis. *Am J Nephrol*. 2008; 28(3): 455-464. doi: 10.1159/000112824

10. Hu MC, Shiizaki K, Kuro-o M, Moe OW. Fibroblast growth factor 23 and klotho: Physiology and pathophysiology of an endocrine network of mineral metabolism. *Annu Rev Physiol*. 2013; 75(1): 503-533. doi: 10.1146/annurev-physiol-030212-183727

11. Kurosu H, Ogawa Y, Miyoshi M, et al. Regulation of fibroblast growth factor-23 signaling by klotho. *J Biol Chem*. 2006; 281(10): 6120-6123. doi: 10.1074/jbc.C500457200

12. Quarles LD. Endocrine functions of bone in mineral metabolism regulation. *J Clin Invest*. 2008; 118(12): 3820-3828. doi: 10.1172/JCI36479

13. Nabeshima Y. The discovery of alpha-Klotho and FGF-23 unveiled new insight into calcium and phosphate homeostasis. *Cell Mol Life Sci*. 2008; 65(20): 3218-3230. doi: 10.1007/s00018-008-8177-0

14. Zhang X, Ibrahimi OA, Olsen SK, Umemori H, Mohammadi M, Ornitz M. Receptor specificity of the fibroblast growth factor family. The complete mammalian FGF family. *J Biol Chem*. 2006; 281(23): 15694-15700. doi: 10.1074/jbc.M601252200

15. U.S. National Library of Medicine. Genetics Home Reference: FGFR1 2015 [cited 2015 17 November]. Available from: http://ghr.nlm.nih.gov/gene/FGFR1. Accessed March 9, 2016.

16. Hughes SE. Differential expression of the fibroblast growth factor receptor (FGFR) multigene family in normal human adult tissues. *J Histochem Cytochem*. 1997; 45(7): 1005-1019. doi: 10.1177/002215549704500710

17. The Human Protein Atlas. FGFR1 [cited 2015 18 November]. Available from: http://www.proteinatlas.org/ENSG00000077782-FGFR1/tissue. Accessed March 9, 2016.

18. Luqmani YA, Graham M, Coombes RC. Expression of basic fibroblast growth factor, FGFR1 and FGFR2 in normal and malignant human breast, and comparison with other normal tissues. *Br J Cancer*. 1992; 66(2): 273-280. doi: 10.1177/002215549704500710

19. The Human Protein Atlas. FGFR3 [cited 2015 18 November]. Web site. http://www.proteinatlas.org/ENSG00000068078-FGFR3/tissue. Accessed March 9, 2016.

20. The Human Protein Atlas. FGFR4 [cited 2015 18 November]. Available from: http://www.proteinatlas.org/ENSG00000160867-FGFR4/tissue. Accessed March 9, 2016.

21. Taylor KR, Rudisill JA, Gallo RL. Structural and sequence motifs in dermatan sulfate for promoting fibroblast growth factor-2 (FGF-2) and FGF-7 activity. *J Biol Chem*. 2005; 280(7): 5300-5306. doi: 10.1074/jbc.M410412200

22. Beer HD, Vindevoghel L, Gait MJ, et al. Fibroblast growth factor (FGF) receptor 1-IIIb is a naturally occurring functional receptor for FGFs that is preferentially expressed in the skin and the brain. *J Biol Chem*. 2000; 275(21): 16091-16097. doi: 10.1074/jbc.275.21.16091

23. Liu S, Vierthaler L, Tang W, Zhou J, Quarles LD. FGFR3 and FGFR4 do not mediate renal effects of FGF-23. *J Am Soc Nephrol*. 2008; 19(12): 2342-2350. doi: 10.1681/ASN.2007121301

24. Yamaguchi TP, Harpal K, Henkemeyer M, Rossant J. fgfr-1 is required for embryonic growth and mesodermal patterning during mouse gastrulation. *Genes Dev*. 1994; 8(24): 3032-3044. doi: 10.1101/gad.8.24.3032

25. Wohrle S, Bonny O, Beluch N, et al. FGF receptors control vitamin D and phosphate homeostasis by mediating renal FGF-23 signaling and regulating FGF-23 expression in bone. *J Bone Miner Res*. 2011; 26(10): 2486-2497. doi: 10.1002/jbmr.478

26. Shimada T, Urakawa I, Yamazaki Y, et al. FGF-23 transgenic mice demonstrate hypophosphatemic rickets with reduced expression of sodium phosphate cotransporter type IIa. *Biochem Biophys Res Commun*. 2004; 314(2): 409-414. doi: 10.1016/j.bbrc.2003.12.102

27. Baum M, Schiavi S, Dwarakanath V, Quigley R. Effect of fibroblast growth factor-23 on phosphate transport in proximal tubules. *Kidney Int*. 2005; 68(3): 1148-1153. doi: 10.1111/j.1523-1755.2005.00506.x

28. Andrukhova O, Smorodchenko A, Egerbacher M, et al. FGF-23 promotes renal calcium reabsorption through the TRPV5 channel. *EMBO J*. 2014; 33(3): 229-246. doi: 10.1002/embj.201284188

29. Liu S, Tang W, Zhou J, et al. Fibroblast growth factor 23 is a counter-regulatory phosphaturic hormone for vitamin D. *J Am Soc Nephrol*. 2006; 17(5): 1305-1315. doi: 10.1681/ASN.2005111185

30. Shimada T, Hasegawa H, Yamazaki Y, et al. FGF-23 is a potent regulator of vitamin D metabolism and phosphate homeostasis. *J Bone Miner Res*. 2004; 19(3): 429-435. doi: 10.1359/JBMR.0301264

31. Marsell R, Krajisnik T, Goransson H, et al. Gene expression analysis of kidneys from transgenic mice expressing fibroblast growth factor-23. *Nephrol Dial Transplant*. 2008 ;23(3): 827-833 doi: 10.1093/ndt/gfm672

32. Ozeki M, Fujita S, Kizawa S, et al. Association of serum levels of FGF-23 and alpha-Klotho with glomerular filtration rate and proteinuria among cardiac patients. *BMC Nephrol*. 2014; 15: 147. doi: 10.1186/1471-2369-15-147

33. Saito H, Kusano K, Kinosaki M, et al. Human fibroblast growth factor-23 mutants suppress Na+-dependent phosphate co-transport activity and 1alpha,25-dihydroxyvitamin D3 production. *J Biol Chem*. 2003; 278(4): 2206-2211. doi: 10.1074/jbc.M207872200

34. Valdivielso JM, Cannata-Andia J, Coll B, Fernandez E. A new role for vitamin D receptor activation in chronic kidney disease. *Am J Physiol Renal Physiol*. 2009; 297(6): F1502-F1509. doi: 10.1152/ajprenal.00130.2009

35. Li SA, Watanabe M, Yamada H, Nagai A, Kinuta M, Takei K. Immunohistochemical localization of Klotho protein in brain, kidney, and reproductive organs of mice. *Cell Struct Funct*. 2004; 29(4): 91-99. doi: 10.1247/csf.29.91

36. Lavi-Moshayoff V, Wasserman G, Meir T, Silver J, Naveh-Many T. PTH increases FGF-23 gene expression and mediates the high-FGF-23 levels of experimental kidney failure: a bone parathyroid feedback loop. *Am J Physiol Renal Physiol*. 2010; 299(4): F882-F889. doi: 10.1152/ajprenal.00360.2010

37. Ben-Dov IZ, Galitzer H, Lavi-Moshayoff V, et al. The parathyroid is a target organ for FGF-23 in rats. *J Clin Invest*. 2007;

117(12): 4003-4008. doi: 10.1172/JCI32409

38. Kuro-o M, Matsumura Y, Aizawa H, et al. Mutation of the mouse klotho gene leads to a syndrome resembling ageing. *Nature*. 1997; 390: 45-51. doi: 10.1038/36285

39. Wang H, Yoshiko Y, Yamamoto R, et al. Overexpression of fibroblast growth factor 23 suppresses osteoblast differentiation and matrix mineralization in vitro. *J Bone Miner Res*. 2008; 23(6): 939-948. doi: 10.1359/jbmr.080220

40. White KE, Cabral JM, Davis SI, et al. Mutations that cause osteoglophonic dysplasia define novel roles for FGFR1 in bone elongation. *Am J Hum Genet*. 2005; 76(2): 361-367. doi: 10.1086/427956

41. Shimada T, Mizutani S, Muto T, et al. Cloning and characterization of FGF-23 as a causative factor of tumor-induced osteomalacia. *Proc Natl Acad Sci U S A*. 2001; 98(11): 6500-6505. doi: 10.1073/pnas.101545198

42. Urakawa I, Yamazaki Y, Shimada T, et al. Klotho converts canonical FGF receptor into a specific receptor for FGF-23. *Nature*. 2006; 444(7120): 770-7744. doi: 10.1038/nature05315

43. Jimbo R, Shimosawa T. Cardiovascular risk factors and chronic kidney disease-FGF-23: A key molecule in the cardiovascular disease. *Int J Hypertens*. 2014; 2014: 381082. doi: 10.1155/2014/381082

44. Falcini F, Rigante D, Masi L, et al. Fibroblast growth factor 23 (FGF-23) gene polymorphism in children with kawasaki syndrome (KS) and susceptibility to cardiac abnormalities. *Ital J Pediatr*. 2013; 39: 69. doi: 10.1186/1824-7288-39-69

45. di Giuseppe R, Buijsse B, Hirche F, et al. Plasma fibroblast growth factor 23, parathyroid hormone, 25-hydroxyvitamin D3, and risk of heart failure: a prospective, case-cohort study. *J Clin Endocrinol Metab*. 2014; 99(3): 947-955. doi: 10.1210/jc.2013-2963

46. Hu MC, Kuro-o M, Moe OW. Secreted klotho and chronic kidney disease. *Adv Exp Med Biol*. 2012; 728: 126-157. doi: 10.1007/978-1-4614-0887-1_9

47. Lysaght AC, Yuan Q, Fan Y, et al. FGF-23 deficiency leads to mixed hearing loss and middle ear malformation in mice. *PLoS One*. 2014; 9(9): e107681. doi: 10.1371/journal.pone.0107681

48. Feng S, Wang J, Zhang Y, Creighton CJ, Ittmann M. FGF-23 promotes prostate cancer progression. *Oncotarget*. 2015; 6(19): 17291-17301. doi: 10.18632/oncotarget.4174

49. Kim HJ, Kim KH, Lee J, et al. Single nucleotide polymorphisms in fibroblast growth factor 23 gene, FGF-23, are associated with prostate cancer risk. *BJU Int*. 2014; 114(2): 303-310. doi: 10.1111/bju.12396

50. Wright CB, Dong C, Stark M, et al. Plasma FGF-23 and the risk of stroke: The northern manhattan study (NOMAS). *Neurology*. 2014; 82(19): 1700-1706. doi: 10.1212/WNL.0000000000000410

51. Stubbs JR, Liu S, Tang W, et al. Role of hyperphosphatemia and 1,25-dihydroxyvitamin D in vascular calcification and mortality in fibroblastic growth factor 23 null mice. *J Am Soc Nephrol*. 2007; 18(7): 2116-2124. doi: 10.1681/ASN.2006121385

52. Jimbo R, Kawakami-Mori F, Mu S, et al. Fibroblast growth factor 23 accelerates phosphate-induced vascular calcification in the absence of Klotho deficiency. *Kidney Int*. 2014; 85(5): 1103-1111. doi: 10.1038/ki.2013.332

53. Lindberg K, Olauson H, Amin R, et al. Arterial klotho expression and FGF-23 effects on vascular calcification and function. *PLoS One*. 2013; 8(4): e60658. doi: 10.1371/journal.pone.0060658

54. Dai B, David V, Martin A, et al. A comparative transcriptome analysis identifying FGF-23 regulated genes in the kidney of a mouse CKD model. *PLoS One*. 2012; 7(9): e44161. doi: 10.1371/journal.pone.0044161

55. Perazella MA, Setaro JF. Renin-angiotensin-aldosterone system: fundamental aspects and clinical implications in renal and cardiovascular disorders. *J Nucl Cardiol*. 2003; 10(2): 184-196. doi: 10.1067/mnc.2003.392

56. Grabner A, Amaral AP, Schramm K, et al. Activation of cardiac fibroblast growth factor receptor 4 causes left ventricular hypertrophy. *Cell Metab*. 2015; 22(6): 1020-1032. doi: 10.1016/j.cmet.2015.09.002

57. Andrukhova O, Zeitz U, Goetz R, Mohammadi M, Lanske B, Erben R. FGF-23 acts directly on renal proximal tubules to induce phosphaturia through activation of the ERK1/2-SGK1 signaling pathway. *Bone*. 2012; 51(3): 621-628. doi: 10.1016/j.bone.2012.05.015

58. Sitara D, Kim S, Razzaque MS, et al. Genetic evidence of serum phosphate-independent functions of FGF-23 on bone. *PLoS Genet*. 2008; 4(8): e1000154. doi: 10.1371/journal.pgen.1000154

59. Sitara D, Razzaque MS, St-Arnaud R, et al. Genetic ablation of vitamin D activation pathway reverses biochemical and skeletal anomalies in Fgf-23-null animals. *Am J Pathol*. 2006; 169(6): 2161-2170. doi: 10.2353/ajpath.2006.060329

60. Bai X, Miao D, Li J, Goltzman D, Karaplis AC. Transgenic mice overexpressing human fibroblast growth factor 23 (R176Q) delineate a putative role for parathyroid hormone in renal phos-

ISSN 2380-0445 Open Journal http://dx.doi.org/10.17140/NPOJ-1-110

phate wasting disorders. *Endocrinology*. 2004; 145(11): 5269-5279. doi: 10.1210/en.2004-0233

61. Isakova T, Wolf MS. FGF-23 or PTH: which comes first in CKD? *Kidney Int*. 2010; 78(10): 947-949. doi: 10.1038/ki.2010.281

62. Isakova T, Wahl P, Vargas GS, et al. Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. *Kidney Int*. 2011; 79(12): 1370-1378. doi: 10.1038/ki.2011.47

63. Evenepoel P, Meijers B, Viaene L, et al. Fibroblast growth factor-23 in early chronic kidney disease: additional support in favor of a phosphate-centric paradigm for the pathogenesis of secondary hyperparathyroidism. *Clin J Am Soc Nephrol*. 2010; 5(7): 1268-1276. doi: 10.2215/CJN.08241109

64. Almaden Y, Canalejo A, Hernandez A, et al. Direct effect of phosphorus on PTH secretion from whole rat parathyroid glands in vitro. *J Bone Miner Res*. 1996; 11(7): 970-976. doi: 10.1002/jbmr.5650110714

65. Faul C, Amaral AP, Oskouei B, et al. FGF-23 induces left ventricular hypertrophy. *J Clin Invest*. 2011; 121(11): 4393-4408. doi: 10.1172/JCI46122