ISSN 2220-6124 (online)

World Journal of *Nephrology*

World J Nephrol 2015 September 6; 4(4): 444-479

Published by Baishideng Publishing Group Inc

WJN World Journal of Nephrology

A peer-reviewed, online, open-access journal of nephrology

Editorial Board

2011-2015

The *World Journal of Nephrology* Editorial Board consists of 295 members, representing a team of worldwide experts in nephrology. They are from 47 countries, including Algeria (1), Argentina (4), Australia (8), Belgium (2), Bosnia and Herzegovina (1), Brazil (11), Canada (3), Chile (1), China (21), Croatia (3), Czech Republic (2), Denmark (2), Egypt (7), Finland (1), France (1), Germany (5), Greece (13), Hungary (4), India (13), Iran (10), Ireland (1), Israel (2), Italy (22), Japan (14), Jordan (1), Malaysia (2), Mexico (1), Morocco (1), Netherlands (5), Nigeria (2), Pakistan (2), Palestine (1), Poland (6), Portugal (4), Qatar (1), Romania (1), Serbia (2), Singapore (3), South Africa (1), South Korea (4), Spain (10), Sweden (2), Thailand (6), Turkey (11), United Arab Emirates (2), United Kingdom (11), and United States (64).

Romania

Gheorghe Nechifor, *Bucharest*

Serbia

Amira Peco-Antic, *Belgrade*
Radojica V Stolic, *K.Mitrovica*

Singapore

Tan Ban Hock, *Singapore*
Anselm Mak, *Singapore*
Woo Keng Thye, *Singapore*

South Africa

Rajendra Bhimma, *Durban*

South Korea

Byoung Soo Cho, *Seoul*
Tae-Sun Ha, *Chungbuk*
Chan Kyo Kim, *Seoul*
Jae IL Shin, *Seoul*

Spain

Miguel A Arrabal-Polo, *Granada*
Ricardo J Bosch, *Alcalá de Henares*
Javier Fernandez de Canete, *Malaga*
Victor M Garcia-Nieto, *Santa Cruz de Tenerife*
Francisco J López Hernández, *Salamanca*
JF Navarro-González, *Santa Cruz de Tenerife*
Alberto Ortiz, *Madrid*
Katia Lopez Revuelta, *Madrid*
Fernando Santos, *Oviedo*

Sweden

Peter Bárány, *Stockholm*
Per Magnusson, *Linköping*

Thailand

Pornanong Aramwit, *Bangkok*
Sinee Distha-Banchong, *Bangkok*
Somchai Eiam-Ong, *Bangkok*
Prasit Futrakul, *Bangkok*
Weekitt Kittisupamongkol, *Bangkok*
Viroj Wiwanitkit, *Bangkok*

Turkey

Turgay Akgül, *Osmaniye*
Filiz Akyuz, *Istanbul*
Mustafa Arici, *Ankara*
Ozgu Aydogdu, *Nigde*
Esra Guzeldemir, *Kocaeli*
Mehmet Kanbay, *Istanbul*
Salih Kavukcu, *Izmir*
Ahmet Kiykim, *Mersin*
Aysel Kiyici, *Konya*
Habibe Şahin, *Kayseri*
Mahmut Ilker Yilmaz, *Ankara*

United Arab Emirates

Bassam Bernieh, *Al Ain*
Anil Kumar Saxena, *Abu Dhabi*

United Kingdom

Jacob A Akoh, *Plymouth*
Rodney D Gilbert, *Southampton*
Colin Andrew Hutchison, *Birmingham*
Jonathon Olsburgh, *London*
Dipen S Parikh, *Durham*
Adrian William Philbey, *Scotland*
Bhusana Premande, *High Wycombe*
Badri Man Shrestha, *Sheffield*
Nestor Velasco, *Kilmarnock,*
Alexander Woywodt, *Preston*
Qihe Xu, *London*

United States

Horacio J Adrogué, *Houston*
Anil K Agarwal, *Columbus*
Patrick D Brophy, *Iowa*
Yiqiang Cai, *New Haven*
Daniel J Canter, *Atlanta*
Oscar A Carretero, *Detroit*
James CM Chan, *Portland*
Brian S Decker, *Indianapolis*
James V Donadio, *Rochester*
Yong Du, *Dallas*
Amy C Dwyer, *Louisville*
Ewa Elenberg, *Houston*
Kevin Finkel, *Houston*
Eli A Friedman, *New York*
Crystal A Gadegbeku, *Ann Arbor*
Claudia Gragnoli, *Hershey*
Parta Hatamizadeh, *Ann Arbor*
Adriana M Hung, *Nashville*
Bernard G Jaar, *Baltimore*
Pedro A Jose, *Washington*
Theodoros Kelesidis, *Los Angeles*
Bruce C Kone, *Houston*
Dean Akira Kujubu, *Los Angeles*
Rajesh Kumar, *Temple*
Daniel L Landry, *Springfield*
Krista Lentine, *Missouti*
Yan Chun Li, *Chicago*
Julie Lin, *Boston*
Youhua Liu, *Pittsburgh*
John K Maesaka, *Mineola*
Robert Hon Kwong Mak, *La Jolla*
Joseph Keith Melancon, *Washington*
Tibor Nadasdy, *Columbus*
Ali Olyaei, *Portland*
Macaulay Amechi Onuigbo, *Eau Claire*
Isak Prohovnik, *New York*
Amanda C Raff, *New York*
Armin Rashidi, *Norfolk*
Anjay Rastogi, *Los Angeles*
Mohammed S Razzaque, *Boston*
Abdalla Rifai, *Providence*
Jeff M Sands, *Atlanta*
Martin J Schreiber, *Cleveland*
Maria-Luisa S Sequeira-Lopez, *Charlottesville*
James Alan Shayman, *Ann Arbor*
Andrey Sorokin, *Milwaukee*
Alison Leah Steiber, *Cleveland*
Theodore I Steinman, *Boston*
James D Stockand, *San Antonio*
Mingming Su, *Kannapolis*
Yunxia Tao, *Amarillo*
George Christos Tsokos, *Boston*
Jaime Uribarri, *New York*
Ulka Vaishampayan, *Detroit*
Volker Vallon, *San Diego*
Paul A Voziyan, *Nashville*
Bradford Lee West, *Springfield*
Mark Edward Williams, *Boston*
Anna Woodbury, *Atlanta*
Robert Peter Woroniecki, *Bronx*
J Ruth Wu-Wong, *Chicago*
Rubin Zhang, *New Orleans, Louisiana*
Xin-Jin Zhou, *Dallas*

World Journal of Nephrology

Contents

Bimonthly Volume 4 Number 4 September 6, 2015

World Journal of Nephrology
Volume 4 Number 4 September 6, 2015

Contents

NAME OF JOURNAL
World Journal of Nephrology

ISSN
ISSN 2220-6124 (online)

LAUNCH DATE
February 6, 2012

FREQUENCY
Bimonthly

EDITORIAL OFFICE
Jin-Lei Wang, Director
Xiu-Xia Song, Vice Director
World Journal of Nephrology
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

PUBLICATION DATE
September 6, 2015

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/2218-6220/g_info_20100722175812.htm.

ONLINE SUBMISSION
http://www.wjgnet.com/esps/

World Journal of Nephrology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5527/wjn.v4.i4.444

World J Nephrol 2015 September 6; 4(4): 444-454
ISSN 2220-6124 (online)

EDITORIAL

Pediatric primary urolithiasis: Symptoms, medical management and prevention strategies

Maria Goretti Moreira Guimarães Penido, Marcelo de Sousa Tavares

Maria Goretti Moreira Guimarães Penido, Marcelo de Sousa Tavares, Department of Pediatrics, Pediatric Nephrology Unit, School of Medicine, Federal University of Minas Gerais, Belo Horizonte 30130100, Brazil

Maria Goretti Moreira Guimarães Penido, Marcelo de Sousa Tavares, Pediatric Nephrology Unit, Center of Nephrology, Santa Casa de Belo Horizonte Hospital, Belo Horizonte 30150320, Brazil

Author contributions: Moreira Guimarães Penido MG and de Sousa Tavares M contributed equally to the conception and design of the study, the acquisition, analysis and interpretation of data, and the drafting and critical revision of the article.

Conflict-of-interest statement: The authors (Maria Goretti Moreira Guimarães Penido and Marcelo de Sousa Tavares) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Correspondence to: Maria Goretti Moreira Guimarães Penido, MD, PhD, Professor of Pediatrics and Pediatric Nephrology, Department of Pediatrics, Pediatric Nephrology Unit, School of Medicine, Federal University of Minas Gerais, Av Alfredo Balena 190 CEP, Belo Horizonte 30130100, Brazil. mariagorettipenido@yahoo.com.br
Telephone: +55-31-92991595
Fax: +55-31-32414466

Received: January 28, 2015
Peer-review started: January 29, 2015
First decision: April 10, 2015
Revised: June 30, 2015
Accepted: July 21, 2015
Article in press: July 23, 2015

Published online: September 6, 2015

Abstract

In the past few decades pediatric urolithiasis has become more frequent. The reason for this increase is not completely clear but has been attributed to changes in climate, nutritional habits and possibly other environmental factors. Although less frequent than adult stone disease, urolithiasis in the pediatric age group is also related to significant morbidity, particularly since stones tend to recur, and, thus, should not be underestimated. Most children with idiopathic stone disease have an underlying metabolic abnormality substantiating the importance of metabolic evaluation already following initial diagnosis of urolithiasis. Identification of the metabolic abnormality allows for more specific prescription of non pharmacological and pharmacological interventions aimed at preventing recurrent stone formation. A better understanding of the causes of kidney stone disease will provide better strategies for stone prevention in children.

Key words: Urolithiasis; Hypercalciuria; Cystinuria; Hyperoxaluria; Treatment; Prevention

Core tip: In the past few decades pediatric urolithiasis has become more frequent. The reason for this increase is not completely clear. Although less frequent than adult stone disease, pediatric urolithiasis is also related to significant morbidity, particularly since stones tend to recur. Most children with idiopathic stone disease have an underlying metabolic abnormality. Identification of the metabolic abnormality allows for more specific prescription of non pharmacological and pharmacological interventions aimed at preventing recurrent stone formation. A better understanding of the causes of kidney stone disease will provide better

strategies for stone prevention in children.

Moreira Guimarães Penido MG, de Sousa Tavares M. Pediatric primary urolithiasis: Symptoms, medical management and prevention strategies. *World J Nephrol* 2015; 4(4): 444-454 Available from: URL: http://www.wjgnet.com/2220-6124/full/v4/i4/444.htm DOI: http://dx.doi.org/10.5527/wjn.v4.i4.444

INTRODUCTION

Urolithiasis (UL) is a worldwide problem and is the end product of a multifactorial process. It affects children of all ages and recurrence is a striking feature. No technique of calculi removal diminishes or alters this recurrence morbidity that in pediatric patients is directly related to surgical interventions and morphological changes resulting from possible obstructions of the urinary tract as well as to their clinical manifestations.

The incidence, composition and clinical characteristics of urinary calculi in children vary in relation to geographical location and historical periods. This variation is related to climate, genetic and dietary factors and socio-economical factors[1-3].

Recent decades studies have shown an increased incidence of kidney stones in adults[4-8]. This same trend has also been observed in children[9-14], and possibly results from increased attention to the diagnosis of UL, the routine evaluation with ultrasonography (USG) in children with specific or nonspecific symptoms, and changes in socio-economic conditions and dietetic habits of the pediatric population. However, the true incidence of pediatric UL remains unknown due to the multiplicity of etiopathogenic factors, unspecific clinical picture and lack of studies with appropriate epidemiological design. Studies conducted in different areas of the globe showed variation regarding gender and age. Sas *et al*[11] in South Carolina, United States, showed that the incidence of UL in children under 18 years was 7.9/100000 in 1996 and 18.5/100000 in 2007, higher in girls *vs* boys, and more prevalent in adolescents. In Japan, Yasui *et al*[5] showed an incidence of 17.7/100000 in males and 12.4/100000 in females in children and adolescents between 10 and 19 years of age. In Iceland, Edvardsson *et al*[15] reported that the incidence in patients younger than 18 years was 5.6/100000 on the basis of 26 new diagnoses of UL during a 6-year period among a national population of approximately 78000 children. VanDervoort *et al*[9] demonstrated that pediatric UL increased almost five times over the last decade in United States. Dwyer *et al*[13] reported that the incidence of pediatric UL in Minnesota, United States, increased from 13/100000 between 1984-1990 to 36/100000 between 2003-2008. Even in the United States, 1/685 pediatric hospitalizations are motivated by urinary calculi and over 50% are under 13 years-old individuals[10]. In 2013, Penido *et al*[14] demonstrated that the annual incidence of primary pediatric UL *per* 1000 renal clinic visits tripled from 1999 to 2010 in a children's hospital in the Midwestern United States. Data from Croatia showed that UL was responsible for 2.5/1000 pediatric hospitalizations, and its overall incidence rate in children under 18 years in 2011 was 6.5/100000[16].

UL is multifactorial and different factors are involved in its genesis, working in an interrelated way: infectious, anatomical, epidemiological, climatic, socioeconomic, dietary, genetic and metabolic. Some medications are also associated with higher risk for stone formation and among them sulfadiazine, ceftriaxone, topiramate, indinavir, triamterene, furosemide, steroids and vitamin D[17]. These risk factors, along with the physical and physiological changes in urine alter the balance between promoter elements, aggregation inhibitors and growth of crystals, resulting in the formation of stones. The evaluation of risk factors and calcium oxalate calculi formation may be evaluated through methods such as the BONN-Risk Index. This index reflects an individual balance between the promoters and inhibitors of the crystallization processes ongoing in the whole native urine[18,19]. This method is simple, cost-effective and provides accurate results. Porowski *et al*[20] showed that an increased Bonn-RiskIndex reflects the risk of calcium oxalate crystallization and may indicate early metabolic disorders leading to urolithiasis in children and adolescents.

Although various aspects of the UL have not yet explained, it is known that hypersaturation of urine is indispensable for the formation of urinary stones. Therefore, crystallization starts when the urine is supersaturated for a particular solute. If the solution is unsaturated, crystals are not formed[3]. The supersaturation depends on the ionic strength, abnormalities of the urinary pH, decreased urine volume, inability of crystallization inhibitors (citrate, magnesium, pyrophosphate, nephrocalcin, glycosaminoglycans, *etc*.) and states of hyperexcretion of calcium, uric acid, phosphorus, oxalate and cystine[3].

At this point, is necessary to mention the Randall plaque. It initially forms at the basement membrane of the thin loops of Henle before expanding to the interstitium. Randall plaque's formation has been established as an integral part of idiopathic calcium oxalate stone disease[21]. Bouchireb *et al*[22] described 25 pediatric cases of urolithiasis and Randall plaques, pointing to a prevalence of approximately 3%.

UL in children and adolescents is associated with metabolic abnormalities identified in 30% to 84% of the cases[14,23-25]. Idiopathic hypercalciuria is the most prevalent metabolic disorder in pediatric patients[9-12,14,23-25]. Besides hypercalciuria, hypocitraturia is also common and is the second most prevalent metabolic disorder in childhood UL[9,26-29]. Idiopathic hypocitraturia may present as isolated or in association with hypercalciuria, secondary to chronic diarrhea, diuretic-induced hypokalemia, renal tubular acidosis and predisposes to UL[29,30]. Less often is hyperuricosuria,

absorptive hyperoxaluria, cystinuria, and hypomagnesiuria[14,23,24].

The association between idiopathic hypercalciuria and reduced bone mineral density has been described in adult patients[31-35] and in children[36-46]. The loss of bone mass or unsuitable gain can be harmful to growth of children, because the peak bone mass occurs in childhood and at a highest rate during adolescence[47,48]. This process should occur without interference for an individual to achieve his/her optimal bone mass. Anything affecting continually a child's bone metabolism could increase the possibility of osteoporosis and fractures during adulthood[49-51]. However, alterations in childhood bone mass acquisition may not affect bone mass many decades later in late adulthood because there is a homeostatic system that tends to return to a set point after any transient perturbation[52]. Thus, workup of idiopathic hypercalciuria necessarily involves the investigation of bone mineral metabolism and the characterization of the profile of bone changes, so the physician can act objectively in prevention and treatment[40,42,43,53].

Obesity associated with metabolic syndrome is a known risk factor for UL in adults, however, this association is not well established in pediatric patients. Kieran *et al*[54] collected obesity related data from 134 patients with urinary calculi. No difference regarding stone properties was observed when BMI was considered. Another study (by Dwyer *et al*[13]) confirmed that no tendency towards obesity was associated with stone formers. This tendency was also described by Routh *et al*[12], where no different pattern of nutritional status in both pediatric stone forming and the normal population was observed. A reasonable explanation for the different nutritional trends between lithiasic pediatric patients and adults rely probably on the distinct lithogenic profiles. Uric acid stones are more common in obese adults, whereas this etiology is relatively scarce in children[7]. Stones due to hypercalciuria are not linked to obesity and can therefore explain this particularity[13,14].

Epidemiological studies have shown that diet has a major role in the pathogenesis of UL[24,30]. Diets low in animal protein but rich in cereals contribute to formation of endemic bladder stones in children[30,55]. Moreover, a high intake of animal protein predisposes hyperexcretion of uric acid, calcium, oxalate, a hypoexcretion of citrate and reduces urinary pH, all favoring the formation of calcium oxalate calculi[30]. The association between urinary sodium concentration and the calcium excretion and, consequently, the relationship between the sodium content of the diet and hypercalciuria has been described[17,56-59]. In developed countries, high consumption of processed foods far exceeds the physiological sodium needs[57]. A study showed that chloride sodium intake induces mild metabolic acidosis and may impair bone mass, as could be a risk factor for the formation of calculi[60]. On the other hand, the high potassium intake has an inverse effect on urinary calcium, *i.e.*, reduces the excretion of urinary calcium[17,56].

The clinical and metabolic pattern of pediatric UL has changed in recent years. Thus, specific and detailed diagnostic tests are required for each child or adolescent presenting renal calculus, even if unique. Considering that every pediatric patient is metabolically active, diagnostic steps should be directed to elucidate the pathophysiology of UL in order to prevent recurrence and reduce morbidity.

SIGNS AND SYMPTOMS

A pediatric patient can be considered acute due to a stone in the ureter, or may be diagnosed as an incidental finding of an intrarenal or intravesical stone, during workup imaging in the abdomen for any other reason. In adult patients, the most frequent clinical presentation is the classical renal colic caused by displacement of calculi or clots in the urinary tract. This clinical presentation is also observed in adolescents, however, abdominal pain is the main complaint in school children[61]. Lack of specificity related to localized pain is typical of lithiasic infants and preschool children[61]. Gross or microscopic hematuria and uncharacteristic abdominal pain are much more prevalent than the classic renal colic, which appearing in only 10% to 14% of all pediatric cases[62]. General manifestations such as nausea, vomiting, anorexia and malaise may be present.

As aforementioned, hematuria, flank or abdominal pain as well as urinary tract infection (UTI) are the most common clinical presentations. Gross or microscopic hematuria appears in 30% to 55% of all pediatric UL[9,63,64] and may remain for some time before the stone appears. Recurrent UTI or unexplained sterile pyuria should raise the level of suspicion for UL and generally should lead to the suspicion of urolithiasis in younger children[64-66]. Some authors have reported that about 10% of pediatric UL have signs and symptoms of lower urinary tract dysfunction (nocturnal and/or diurnal enuresis, urgency and/or urinary incontinence, suprapubic or urethral pain)[9,67,68]. Although the pediatric UL could have many different signs and symptoms at clinical onset, long time intervals without urinary complaints may be observed in these patients. Authors refer that 15% to 25% of children with UL, specially the younger ones, are asymptomatic and require more attention[9,63].

Lower urinary tract symptoms, *i.e.*, dysuria, urine retention, enuresis, urinary incontinence and polakiuria may be associated with distal displacement of calculi. Excessive manipulation of genitalia in preschool children may be an early sign of urethral lithiasis. Urethral obstruction due to calculi migration may be even palpable in infants. This may not allow the urine flux, resulting in pain[64].

MANAGEMENT OF ACUTE PEDIATRIC UL

Laboratory and imaging tests are needed to confirm

the diagnosis. The tests performed in the acute phase are: urine routine, bacterioscopy of uncentrifuged urine, urine culture and antibiogram, plain abdominal radiography (Rx) and kidney and urinary tract USG. Usually, blood tests are not required, however, in cases with suspected acute pyelonephritis, a complete biochemical evaluation should be performed to appropriate patient monitoring and evaluation of the severity of this clinical condition.

USG of the urinary tract usually suffices regarding diagnosis. Its main advantages include lack of exposure to radiation and potential adverse effects of contrast media, *i.e.*, in computed tomography (CT) and intravenous pyelography. These, however, are indicated in specific cases in which USG was not sufficient for a clinical decision concerning the intervention. The need of sedation is another disadvantage of CT in pediatric patients[64,69]. Calculi migration may also be followed by sequential USG, which is another advantage of this method[64]. Although the noncontrast CT scanning is considered the gold standard test for the UL diagnostic, it is a costly procedure and not always available. When obstruction is a concern or if anatomic details are necessary, the use of contrast agents may be used.

Type and stone dimension are directly related to success in diagnosing urinary stones and their position within the urinary tract. Diagnosis of small calculi depends on operator experience, but even a lithos with a diameter of just 2 mm can be observed and its position correctly described by experienced professionals[64].

Urinary stones migrating within the renal collecting system can cause pain or infection in a partially or completely obstructed urinary tract. Pain is intense and requires immediate and effective care. It is due to stimulation of receptors during dilatation of the urinary system and release of pain mediators through to local irritation and swelling of the wall of the renal pelvis or ureter. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) may be indicated as first choice, due to their higher benefits in this situation. Ureteropelvic consequences of the acute attempt to eliminate stones, such as ureteral oedema, increased peristalsis and pelvic pressure, may be effectively alleviated by nonsteroidal anti-inflammatory drugs through inhibition of prostaglandin synthesis. Hospital readmissions and new pain episodes may be avoided through these drugs, but time until complete elimination or even the likelihood of stone passing appears to be unaffected[70]. During its use, renal function should be monitored due to the risk of nephrotoxicity. Other antispasmodic and/or analgesic drugs that could be used for this acute pain control are: n-scopolamine butylbromide, amitriptyline, calcium channel blockers, steroids, morphine and analogues used in cases of intractable pain and alpha-1 blockers (*e.g.*, tamsulosin). The direct effect of alpha-1 blockers on pain is still controversial, but it is probably related to relief of ureteral spasm and promotion of stone expulsion[71].

During the acute phase, hydration should be increased after the diagnosis of a migrating calculus, considering it may be eliminated. The increased urine flow will be guaranteed by oral or parenteral hydration in cases with severe vomiting, diarrhea or lack of oral acceptance.

Adequate urinary flow is essential to prevent supersaturation of calcium oxalate and phosphate as well as uric acid. Urine flow equal to or higher than 1 mL/kg was shown by Lande *et al*[72] to be efficacious as protector against kidney stone formation. This water intake should be distributed throughout the 24 h, and should not exceed two liters. Clinical, laboratory and imaging evaluation should be done systematically at the patient with a migrating calculus. This interval depends on the severity of the clinical picture. The patient should be instructed to observe the elimination of the stone, because it may occur even without pain. About 60%-70% of calculi will be spontaneously eliminated and the size and characteristics of the surface limit their passage. The waiting period for stone migration without affecting the kidney function is six weeks[73,74]. After this period, it is advisable the referral to an urologist.

UL's presence does not necessarily imply surgical removal and there are criteria that help the decision. A surgical approach may be considered in cases of intractable pain, obstruction or associated infection. Indications for calculi removal in the proximal ureter include: calculi with a diameter > 5 mm; calculi with diameter < 4 mm associated with complete obstruction, urosepsis, solitary kidney, renal function deterioration, intractable symptoms, and no migration of the calculus for six weeks. In cases with involvement of the distal ureter, the indications for surgical removal of the calculus are: calculi with diameter > 7 mm; calculi with diameter < 6 mm associated with complete obstruction, urosepsis, solitary kidney, renal function deterioration, intractable symptoms, and no migration for six weeks. Therefore, the management of the stone is related to its location and its effect on the kidneys. Therapeutic options for stones that do not progress include: extracorporeal shockwave lithotripsy (ESWL), endoscopic lithotripsy with ultrasound, and percutaneous nephrolithotomy and open pyelolithotomy. ESWL can be used for treatment of children with stones and is safe with minimal complications[75,76].

Recently, Long and Srinivasan showed a significant improvement in management of pediatric UL with the miniaturization of both ureteroscopes and percutaneous nephrolithotomy equipment. These new technology possibilities have facilitated the access to the entirety of the urinary tract and have made ureteroscopy a first-line therapy option along with shock-wave lithotripsy for kidney and ureteral pediatric stones[77]. Nevertheless, larger studies with long follow-up time are required.

MANAGEMENT OF NON-ACUTE PEDIATRIC UL

After resolution of the acute phase, considering stone

elimination or removal by any technique, the pediatric patient will be conducted to the metabolic evaluation. All pediatric patient is metabolically active and, as already mentioned, rates of metabolic abnormalities in pediatric stone formers have been quoted as 30% to 84% of all cases[14,23-25]. The high recurrence rate is considered a major issue in pediatric urolithiasis. Lack of treatment results in a 50% recurrence rate within 7 years after the first colic episode[71,78]. Milliner and Murphy reported that 221 children have developed one or more kidney stones in mean follow-up of 59 mo[79]. Schwarz *et al*[80] showed a recurrence rate of UL in children equal to adults. Whereas all pediatric patients are metabolically active and that the recurrence rate is high, the metabolic study is always indicated in the pediatric UL.

All evaluations should be performed at least one month after diagnosis of the stone(s) while participants were asymptomatic and on their usual diet, normal fluid intake and physical activities[14,64]. In order to preserve the 24-h urinary sample should be used[81,82]. Pediatric metabolic testing should consist of: two 24-h urine collections analyzed for total volume, creatinine, calcium, phosphate, citrate, sodium, potassium, uric acid, oxalate; one venous blood sample analyzed for creatinine, calcium, phosphorus, uric acid, magnesium, sodium, chlorine, potassium, bicarbonate and blood gases; one random urine for urinalysis and pH. This criterion is similar to "The American Urological Association Guideline for medical management of kidney stones in adults"[83].

An adequate 24-h urine collection may be impracticable in patients without sphincter control. Random urine quantification and its proportion per mg of urine creatinine may allow the identification of the metabolic abnormality[64]. The following analytes should be quantified: oxalate, sodium, potassium, magnesium, uric acid, phosphate, citrate and calcium[64]. Qualitative determination of cystine through the nitroprusside test is acceptable, since the sensibility of the test is near to the level accepted as the limit for cystinuria. Amino acids chromatography remains, however, the gold standard for the diagnosis. When a stone is available, clinicians should obtain a stone analysis at least once. Stone composition of a single element is the exception, leading to the need of determination of the multiple components of the calculus. Despite the possibility of quantification of small amounts of a constituent (less than 1 mg, *i.e.*,) through infrared spectroscopy or X-ray diffraction, the exact stone analysis is prone to errors[64].

The metabolic diagnosis will enable appropriate treatment. Therefore, this will result in preventing the formation of new and growth of existing stones, inducing the patient to metabolic inactivation. A small percentage of pediatric patients forming urinary stones presents no metabolic abnormality[14]. Table 1 shows abnormal values for the excretion of various substances[17,81]. Interruption of the growth process involving preexisting calculi as well as development of new ones should be the goal of the medical treatment. Identification of the underlying metabolic cause, adequate treatment with supplements (potassium citrate), drugs (thiazides) and dietary modification mean prevention, and all these measures together are assigned as metaphylaxis.

To date there is no known medical treatment to determine the healing of UL. Those existing are directed to restore the biochemical and urinary physical chemistry. The UL treatment consists of long-term general measures (hydration, nutrition, physical activity) and specific measures (pharmacological intervention). Free urinary flux and adequate hydric ingestion compose the mainstay of urine supersaturation avoidance. It must be ensured a urinary flow at least 1.0 mL/kg per hour to reduce the urinary concentration[72] but ideally 2.0 to 3.0 mL/kg per hour. If there are higher expenses (insensitive and sweating loss), there should be an increase of this intake. The amount of liquid intake should be distributed throughout the day for good and constant urinary flow maintenance. About half of net quantity must be water and the other half, can be chosen by the patient (juices, teas, *etc*.). Hydric ingestion is well bellow the desired range in the vast majority of children with urolithiasis[56]. Beverage constituents should be monitored, since they can act as pro-lithiasic beverages (apple and grapefruit juice)[84] or anti-lithiasic (coffee, tea and alcoholic beverages)[84,85]. The reason for those associations is unknown.

The use of soda based beverages and urolithiasis is controversial[84,85]. Studies in adult populations showed no relation, but the discontinuation of this kind of drink was described as protective against stone recurrence in others, particularly those containing phosphoric acid[86]. For children it would be appropriate to allow the use of soda drinks only in special occasions. Severe dietary restrictions are contraindicated. First because they can hinder adherence to treatment; second, because they can determine nutritional deficiencies that may be more significant than the UL *per se* (reduced bone mineral density, height and weight loss, multiple vitamin deficiency, other). The diet should be corrected and appropriate to the child or adolescent's needs and recommended normal diet for calcium, calories and proteins according to RDA.

The ideal daily intake of sodium varies according to age: 1.2 g for 4-8 years old children, 1.5 g for those aged 9-18 years. The corresponding upper limits are 1.9 g and 2.3 g, above which health risk may be attributable[87]. Potassium is mostly provided as dairy products, vegetables and fruits. Its optimal recommendations also vary according to age: 3.8 for 4-8 years old children and 4.5 g for those between 9 and 18 years[87]. This is roughly equivalent to 3 units a day.

Monitoring of adequate ingestion of these elements can be achieved through determination of urine Na/K ratio, which should be under 2.5[88]. Higher ingestion of sodium-containing food is associated with increased natriuria, which can determine hypercalciuria, a stone predisposing condition[88]. All patients with hypercalciuria should have the Na/K ratio checked and

Table 1 Normal values for random urine and 24-h urine factors for children and adolescents

	24-h urine	Random urine corrected by creatinine		Random urine factored for GFR
Volume	⩾ 1.0 mL/kg per hour			
Creatinine	2 to 3 yr: 6 to 22 mg/kg > 3 yr: 12 to 30 mg/kg			
Calcium	< 4.0 mg/kg (0.10 mmol/kg)	Age 0-6 mo 6-12 mo 1-2 yr 2-18 yr	mg/mg; mmol/mmol < 0.80; < 2.24 < 0.60; < 1.68 < 0.40; < 1.12 < 0.21; < 0.56	< 0.10
Citrate	⩾ 400 mg/g creatinine	⩾ 0.28 (mmol/L/mmol/L)		> 0.18 (mg/L/mg/L)
Calcium/Citrate	< 0.33	< 0.33		
Na/K	⩽ 3.5	⩽ 3.5		
Uric acid	< 815 mg/1.73 m^2 BS	< 0.65		< 0.56 mg < 0.03 mmol
Cystine	< 60 mg/1.73 m^2 BS	< 0.02 (mg/mg) < 0.01 (mmol/mmol)		
Magnesium	> 88 mg/1.73 m^2 BS			
Oxalate	< 50 mg/1.73 m^2 BS < 0.49 mmol/1.73 m^2 BS	Age 0-6 mo 7 mo-4 yr > 4 yr	(mg/mg) < 0.30 < 0.15 < 0.10	
Phosphate		TP/GFR: > 2.8 and < 4.4 mg/dL[1]		

[1]Phosphate tubular reabsorption by glomerular filtration rate. GFR: Glomerular filtration rate; BS: Body surface.

natriuria considered as an important dietary factor to be modified, in case of an inadequate urinary finding. Another possible dietary intervention is the reduction of animal derived protein intake (such as red meat)[85-87]. Protein metabolism end-products result in increased acidity, which should be buffered by bone-released bicarbonate[89-91]. When the bone resorption is excessive, decreased bone mineral density and hypercalciuria may appear[89-91]. Stone formation is also associated with ingestion of other sugars (sucrose, fructose), vitamins (vitamin C), while magnesium and phytate may impair calculus formation[92].

Fats and sugars need to be avoided, because they may predispose to obesity, lead to increased incidence of hypercalciuria and hyperoxaluria associated stones. Some errors in dietary guidelines are very common as the elimination of tomatoes, dairy products, chocolate, teas, *etc*. These are held beliefs in the population and difficult to change.

Exercise must be regular, since the incidence of stones is directly proportional to physical inactivity and obesity (in adults). However, we must emphasize the care with fluid replacement after exercise so as not to encourage the concentration and urinary saturation.

PHARMACOLOGICAL INTERVENTION

Idiopathic calcium stones

Hypercalciuria: The initial approach to hypercalciuric children consists of adequate high fluid intake, low sodium diet and the recommended ingestion (RDA) of protein and calcium[46,87,93-95]. Dietary compliance is particularly difficult in children and adolescents, leading to usage of pharmacotherapy[56]. Pharmacological therapy is typically added if dietary treatment fails[93-95].

A randomized controlled trial pointed to beneficial effects of citrate use in adults with Urolithiasis[96]. Improvement of bone mineral density was also described by Pak *et al*[97] in adults with calcium oxalate stones after long-term use of potassium citrate. Modifications regarding increased urine pH as well as citrate and potassium levels were described during treatment. Urolithiasis in the pediatric age group had the prognosis definitely changed by citrate, due to a decrease in recurrence rate, growth of residual lithiasic fragments after lithotripsy and in children with hypocitraturia[98,99]. In hypercalciuric osteopenic adults, both thiazide diuretics and potassium citrate were previously demonstrated to be effective in simultaneously reversing hypercalciuria and improving reduced BMD[100,101].

The first line therapy in pediatric urolithiasis consists of potassium citrate. The main reason is the fact of being considered as a supplement, but studies with more detailed information on its effects in the pediatric population are lacking[102]. Studies by Reusz *et al*[103] and Schwaderer *et al*[104] demonstrated the beneficial effects of thiazides and/or potassium citrate on bone mineral density in children with IH. According to Srivastava *et al*[102], drug therapy should be reserved for children with symptomatic hypercalcuria and/or rare monogenic disorders. In 2012, Moreira Guimarães Penido *et al*[46] demonstrated an improvement of bone mineral density Z-score in 84 pediatric hypercalciuric patients after treatment with potassium citrate and thiazides, suggesting a beneficial effect and potential need for treatment. The use of thiazides in adult patients, albeit normocalciuric patients in many cases, still remains a

prevalent option of drug treatment. The absorption of calcium in the proximal tubule is enhanced, probably due to volume contraction[105].

Hypocitraturia: The choice of potassium citrate over the alkaline preparation is warranted because the sodium load may interfere with calcium excretion, minimizing the impact of urine citrate increase[71]. Compared to placebo, administration of citrate in hypercalciuric stone formers led to significative reduction in stone forming[106,107].

Treatment of calcium stones should include not only citrate, which may raise urinary pH and propitiate calcium stone formation, but also maintain adequate fluid intake. Initial dose for children is 0.25-0.5 mEq/kg two times a day in order to increase urinary levels to a minimum of 180 mg/g creatinine (Table 1)[17,81]. Urinary acidity should be monitored and should not exceed 6.5[108]. An important side effect of citrate is stomach pain, which can sometimes disrupt the treatment adherence[71]. Increased ingestion of citrus (*i.e.*, orange and lemon juices) may modify the profile of citrate excretion, acting as an alternative to citrate preparations[71].

Hyperoxaluria: Increased urinary levels of oxalate may be due to primary hyperoxaluria. Different mechanisms, resembling distinct enzymatic defects, lead to classification of this genetic entity into 3 forms, namely primary hyperoxaluria Ⅰ (PH1), Ⅱ (PH2) and Ⅲ (PH3). Deficient production of the enzyme alanine-glyoxylate aminotransferase by the liver is responsible for the more serious form of the illness, leading to end-stage renal disease[71]. High fluid intake, thiazides diuretics, citrate, pyrophosphates and magnesium oxide compose the mainstay treatment[17]. Liver-kidney or sequential liver and kidney transplantation are the best medical options after diagnosis is confirmed. Discussion upon the most appropriate moment of transplantation still remains.

The hepatic enzymatic defect is the hallmark of hyperoxaluria and restriction of dietary oxalate rich-food does not play a pivotal role in the treatment. Ingestion of food with high oxalate content, *i.e.*, spinach, rhubarb, brown rice, berries and dark teas should be avoided, as well as ascorbic acid. Adequate calcium intake must be encouraged[17]. It is also recommended, reducing fat intake and avoid use of vitamin C.

Hepatocytic peroxisomes are dysfunctional, leading to an increased synthesis of oxalate due to impaired glyoxylate metabolism. Vitamin B6 (piridoxine) is a cofactor of AGTX and its supplementation on a minimal pharmacological dose of 30 mg twice a day is recommended in order to achieve reduction of urinary oxalate levels (possible in up to 30% of PHI patients)[109]. PH 2 is linked to glyoxylate reductase/hydroxypyruvate reductase defficiency. PH3 is a more benign form of disease and is caused by mutations in the 4-hydroxy-2-oxoglutarate aldolase 1[110].

Another therapeutic option to enhance colonic secretion of oxalate involves probiotics. Studies with a naturally occurring bacterium, *Oxalobacter formigenes*, showed an inverse association with the presence of calcium oxalate stones. Nevertheless, degradation of intestinal oxalate also acts sinergystically with the colonic secretion, reducing blood and urine oxalate levels[111-113]. Colonization or intestinal recolonization with Oxalobacter formigenes would be an attractive therapeutic or prophylactic strategy to prevent or limit the formation of calcium oxalate stones, however, more studies are necessary[113].

Absorptive hyperoxaluria may also be idiopathic or secondary to malabsorptive disorders, *i.e.*, pancreatic insufficiency and small bowel resection. Under these circumstances, the absorption of ingested oxalate is augmented as well as the renal excretion. Another situation (which is rare in children and adolescents) that may lead to a similar physiological behavior of the gut is bariatric surgery. Restriction of oxalate intake in the forementioned conditions is primordial[17,71].

Lactic acid bacteria (LAB) are Gram-positive organisms that produce lactic acid as a final product of carbohydrate fermentation. This group includes Lactobacillus, Enterococcus, Lactococcus among others. Experimentally, LAB can degradate oxalate. However, in vivo results are contradictory. Goldfarb *et al*[114] found that lactic acid bacteria are ineffective in patients with absorptive hypercalciuria. Effective reduction in urine oxalate excretion was described by Lieske *et al*[115] in patients with secondary absorptive hyperoxaluria associated with fat malabsorption. Drugs that act primarily as phosphate binders, such as sevelamer hydrochloride, were unsuccessful in reducing oxalate absorption[116,117].

Uric acid stones: A combination of diverse factors, *i.e.*, low urine output, hyperuricosuria and abnormal reduced urine pH leads to uric acid (UA) stone formation. Notwithstanding, the main determinant of uric acid precipitation remains low pH. This factor is remarkable in adult patients (which are mainly not hyperuricosuric) and may be a biochemical manifestation of insulin resistance[71]. Alkalinization is the pillar of treatment of UA stones. Potassium citrate preparations are preferred due to a possible increased calcium excretion secondary to sodium load in sodium citrate.

Treatment of children with uric acid stones is complex due to the need of multiple interventions. The initial dose of potassium citrate is 0.5 to 1.5 mEq/kg per day and urine pH should be between 6.0-6.5. Dietary purine restriction is also indicated (seafood, small fish - especially sardines, beans, peas, chicken liver, heart, guts) when urinary urate excretion is high. When the hyperuricosuria is refractory to these measures, attempt with xantine oxidase inhibitors, *e.g.*, allopurinol may be tried (50 mg daily for children younger than 10 years

and 100 mg for older patients)[71].

Cystine stones: The transport of dibasic amino acids (*i.e.*, cystine, lysine, arginine and ornithine) is essential to maintain adequate solubility of these compounds. Defective tubular and intestinal transport of cystine leads to cystinuria, a cause of recurrent urolithiasis in up to 4% of pediatric urinary stone formers. In areas where consanguinity is high, this proportion may be even higher[14].

Cystinuric patients produce stones with a high degree of cystine content. Infrequently, mixed content with calcium salts may occur[118]. Daily excretion of 250 to more than 1000 mg leads to a permanent need for urine dilution, alkalinization and chelation. Cystine should stay in a urine suspension with particular chemical conditions: concentration under 250 mg/L and urine pH around 7. There is an apparent correlation between urine volume and cystine excretion: in order to excrete 750 mg of cystine, 3 L of urine output are necessary. Fluid intake must be constant and well distributed along the day. Potassium citrate (1.0-3.0 mEq/kg) is recommended to raise pH up to 7.0. In case of stone recurrence despite these measures, cysteine-binding compounds may be added. Modification of the chemical structure of cystine is possible through re-arrangement of disulfide bonds with thiol-binding drugs, *i.e.*, D-penicillamine and tiopronin (alpha-mercaptopropionylglycine_alpha-MPG). Resulted compounds are 50-times more soluble than original cystine. D-penicillamine as well as alpha-MPG proved to be efficient in decreasing stone formation in cystinuric patients in whom hydration and the use of alkalis showed to be ineffective[17,71].

The use of D-penicillamine must be judicious, regarding its potential side effects, such as its anti-pyridoxine effect[119]. Supplementation with pyridoxine (vitamin B6) 25-50 mg, daily, is advocated. Despite the better availability of D-penicillamine, tiopronin carries a better profile regarding incidence as well as severity of adverse reactions. Conflicting results with ACE-inhibitors (Captopril), which is a sulfhydryl agent, were already reported. The potential hypotensive effect of this drug resulted in an indication of "rescue therapy", where other measures failed[17].

The development of new techniques allowed the conceivement future of alternative treatments for cystinuria. Inhibition of the cystine transporter[120] and of the cystine crystal growth (L-cystine dimethyl ester_L-CDME) are promising measures to prevent cystine Urolithiasis[121,122]. They appear to be effective even at low concentrations, improving the safety profile of this sort of treatment. Dietary modifications, such as sodium and protein-restriction (0.8-1.0 g/kg per day), may lead to a modest decrease of cystine excretion. Once eliminated, stone analysis in cystinuric patients should be performed. Admixture with calcium salts is possible when urine pH is above 7.0[71].

CONCLUSION

The belief that pediatric urolithiasis is rare has lead to delayed etiological diagnosis in the past. The complete metabolic investigation of every infant or child with stones is mandatory. General measures involving adequate fluid intake and dietary modifications are considered general metaphylaxis for all kind of stones. Novel treatment modalities are scarce and the challenge of treating certain types of stone-forming diseases, *i.e.*, cystinuria, still remains.

Additionally, hypercalciuria has been evaluated in many studies during the last decade. Emphasis was laid mainly on the effects of dietary modification, alkali use (particularly potassium citrate) and thiazides, regarding calcium stone formers. However, more studies are warranted to compare pharmacotherapy and dietary changes, single *vs* combination therapies, among others. New approaches such as the use of probiotics like *Oxalobacter formigenes*, which act as oxalate-degraders, appear to be promising in calcium oxalate stone formers. However, the results are not consistent[114,115]. Future alternative treatments of hyperoxaluria involve upregulation of intestinal secretion through the increase of the anion transporter activity (S1c26a6)[118]. Studies on the pathogenesis of pediatric urolithiasis and the potencial pathogenic role of Randall's plaque and the tubular retention of crystals are currently on the way[108].

Individualized approaches to stone forming conditions will be available in a near future and will allow the start of early and adequate treatment to prevent recurrence, reduce morbidity and prevent progression to end-stage kidney disease[2,3,17].

REFERENCES

1 **Ali SH**, Rifat UN. Etiological and clinical patterns of childhood urolithiasis in Iraq. *Pediatr Nephrol* 2005; **20**: 1453-1457 [PMID: 16010596]

2 **Evan AP**. Physiopathology and etiology of stone formation in the kidney and the urinary tract. *Pediatr Nephrol* 2010; **25**: 831-841 [PMID: 19198886 DOI: 10.1007/s00467-009-1116-y]

3 **Sas DJ**. An update on the changing epidemiology and metabolic risk factors in pediatric kidney stone disease. *Clin J Am Soc Nephrol* 2011; **6**: 2062-2068 [PMID: 21737846 DOI: 10.2215/CJN.11191210]

4 **Hesse A**, Brändle E, Wilbert D, Köhrmann KU, Alken P. Study on the prevalence and incidence of urolithiasis in Germany comparing the years 1979 vs. 2000. *Eur Urol* 2003; **44**: 709-713 [PMID: 14644124]

5 **Yasui T**, Iguchi M, Suzuki S, Kohri K. Prevalence and epidemiological characteristics of urolithiasis in Japan: national trends between 1965 and 2005. *Urology* 2008; **71**: 209-213 [PMID: 18308085 DOI: 10.1016/j.urology.2007.09.034]

6 **Romero V**, Akpinar H, Assimos DG. Kidney stones: a global picture of prevalence, incidence, and associated risk factors. *Rev Urol* 2010; **12**: e86-e96 [PMID: 20811557]

7 **Turney BW**, Reynard JM, Noble JG, Keoghane SR. Trends in urological stone disease. *BJU Int* 2012; **109**: 1082-1087 [PMID: 21883851 DOI: 10.1111/j.1464-410X.2011.10495.x]

8 **Edvardsson VO**, Indridason OS, Haraldsson G, Kjartansson O, Palsson R. Temporal trends in the incidence of kidney stone disease.

Kidney Int 2013; **83**: 146-152 [PMID: 22992468 DOI: 10.1038/ki.2012.320]
9 **VanDervoort K**, Wiesen J, Frank R, Vento S, Crosby V, Chandra M, Trachtman H. Urolithiasis in pediatric patients: a single center study of incidence, clinical presentation and outcome. *J Urol* 2007; **177**: 2300-2305 [PMID: 17509344]
10 **Bush NC**, Xu L, Brown BJ, Holzer MS, Gingrich A, Schuler B, Tong L, Baker LA. Hospitalizations for pediatric stone disease in United States, 2002-2007. *J Urol* 2010; **183**: 1151-1156 [PMID: 20096871 DOI: 10.1016/j.juro.2009.11.057]
11 **Sas DJ**, Hulsey TC, Shatat IF, Orak JK. Increasing incidence of kidney stones in children evaluated in the emergency department. *J Pediatr* 2010; **157**: 132-137 [PMID: 20362300 DOI: 10.1016/j.jpeds.2010.02.004]
12 **Routh JC**, Graham DA, Nelson CP. Epidemiological trends in pediatric urolithiasis at United States freestanding pediatric hospitals. *J Urol* 2010; **184**: 1100-1104 [PMID: 20650479 DOI: 10.1016/j.juro.2010.05.018]
13 **Dwyer ME**, Krambeck AE, Bergstralh EJ, Milliner DS, Lieske JC, Rule AD. Temporal trends in incidence of kidney stones among children: a 25-year population based study. *J Urol* 2012; **188**: 247-252 [PMID: 22595060 DOI: 10.1016/j.juro.2012.03.021]
14 **Penido MG**, Srivastava T, Alon US. Pediatric primary urolithiasis: 12-year experience at a Midwestern Children's Hospital. *J Urol* 2013; **189**: 1493-1497 [PMID: 23201378 DOI: 10.1016/j.juro.2012.11.107]
15 **Edvardsson V**, Elidottir H, Indridason OS, Palsson R. High incidence of kidney stones in Icelandic children. *Pediatr Nephrol* 2005; **20**: 940-944 [PMID: 15912382]
16 **Milošević D**, Batinić D, Turudić D, Batinić D, Topalović-Grković M, Gradiški IP. Demographic characteristics and metabolic risk factors in Croatian children with urolithiasis. *Eur J Pediatr* 2014; **173**: 353-359 [PMID: 24096520 DOI: 10.1007/s00431-013-2165-6]
17 **Alon US**. Medical treatment of pediatric urolithiasis. *Pediatr Nephrol* 2009; **24**: 2129-2135 [PMID: 18273648 DOI: 10.1007/s00467-007-0740-7]
18 **Laube N**, Schneider A, Hesse A. A new approach to calculate the risk of calcium oxalate crystallization from unprepared native urine. *Urol Res* 2000; **28**: 274-280 [PMID: 11011968]
19 **Laube N**, Labedzke V, Hergarten S, Hesse A. Determination of urinary calcium-oxalate formation risk with BONN-Risk-Index and EQUIL applied to a family. *J Chem Inf Comput Sci* 2002; **42**: 633-639 [PMID: 12086525]
20 **Porowski T**, Zoch-Zwierz W, Konstantynowicz J, Taranta-Janusz K. A new approach to the diagnosis of children's urolithiasis based on the Bonn Risk Index. *Pediatr Nephrol* 2008; **23**: 1123-1128 [PMID: 18335253 DOI: 10.1007/s00467-008-0786-1]
21 **Evan A**, Lingeman J, Coe FL, Worcester E. Randall's plaque: pathogenesis and role in calcium oxalate nephrolithiasis. *Kidney Int* 2006; **69**: 1313-1318 [PMID: 16614720]
22 **Bouchireb K**, Boyer O, Pietrement C, Nivet H, Martelli H, Dunand O, Nobili F, Sylvie GL, Niaudet P, Salomon R, Daudon M. Papillary stones with Randall's plaques in children: clinicobiological features and outcome. *Nephrol Dial Transplant* 2012; **27**: 1529-1534 [PMID: 21813830 DOI: 10.1093/ndt/gfr439]
23 **Safaei Asl A**, Maleknejad S. Pediatric urolithiasis: an experience of a single center. *Iran J Kidney Dis* 2011; **5**: 309-313 [PMID: 21876306]
24 **Copelovitch L**. Urolithiasis in children: medical approach. *Pediatr Clin North Am* 2012; **59**: 881-896 [PMID: 22857835 DOI: 10.1016/j.pcl.2012.05.009]
25 **Baştuğ F**, Düşünsel R. Pediatric urolithiasis: causative factors, diagnosis and medical management. *Nat Rev Urol* 2012; **9**: 138-146 [PMID: 22310215 DOI: 10.1038/nrurol.2012.4]
26 **Penido MG**, Lima EM, Souto MF, Marino VS, Tupinambá AL, França A. Hypocitraturia: a risk factor for reduced bone mineral density in idiopathic hypercalciuria? *Pediatr Nephrol* 2006; **21**: 74-78 [PMID: 16252112]
27 **Srivastava T**, Winston MJ, Auron A, Alon US. Urine calcium/citrate ratio in children with hypercalciuric stones. *Pediatr Res* 2009; **66**: 85-90 [PMID: 19287339 DOI: 10.1203/PDR.0b013e3181a2939e]
28 **DeFoor W**, Minevich E, Jackson E, Reddy P, Clark C, Sheldon C, Asplin J. Urinary metabolic evaluations in solitary and recurrent stone forming children. *J Urol* 2008; **179**: 2369-2372 [PMID: 18433777 DOI: 10.1016/j.juro.2008.01.151]
29 **Caudarella R**, Vescini F, Buffa A, Stefoni S. Citrate and mineral metabolism: kidney stones and bone disease. *Front Biosci* 2003; **8**: s1084-s1106 [PMID: 12957820]
30 **López M**, Hoppe B. History, epidemiology and regional diversities of urolithiasis. *Pediatr Nephrol* 2010; **25**: 49-59 [PMID: 21476230 DOI: 10.1007/s00467-008-0960-5]
31 **Giannini S**, Nobile M, Sartori L, Calò L, Tasca A, Dalle Carbonare L, Ciuffreda M, D'Angelo A, Pagano F, Crepaldi G. Bone density and skeletal metabolism are altered in idiopathic hypercalciuria. *Clin Nephrol* 1998; **50**: 94-100 [PMID: 9725780]
32 **Caudarella R**, Vescini F, Buffa A, Sinicropi G, Rizzoli E, La Manna G, Stefoni S. Bone mass loss in calcium stone disease: focus on hypercalciuria and metabolic factors. *J Nephrol* 2003; **16**: 260-266 [PMID: 12768074]
33 **Giannini S**, Nobile M, Sella S, Dalle Carbonare L. Bone disease in primary hypercalciuria. *Crit Rev Clin Lab Sci* 2005; **42**: 229-248 [PMID: 16047539]
34 **Asplin JR**, Donahue S, Kinder J, Coe FL. Urine calcium excretion predicts bone loss in idiopathic hypercalciuria. *Kidney Int* 2006; **70**: 1463-1467 [PMID: 16941029]
35 **Zerwekh JE**. Bone disease and idiopathic hypercalciuria. *Semin Nephrol* 2008; **28**: 133-142 [PMID: 18359394 DOI: 10.1016/j.semnephrol.2008.01.006]
36 **Stapleton FB**, Noe HN, Roy S, Jerkins G. Hypercalciuria in children with urolithiasis. *Am J Dis Child* 1982; **136**: 675-678 [PMID: 7102617]
37 **Stapleton FB**, McKay CP, Noe HN. Urolithiasis in children: the role of hypercalciuria. *Pediatr Ann* 1987; **16**: 980-981,984-992 [PMID: 3320916]
38 **Stapleton FB**, Jones DP, Miller LA. Evaluation of bone metabolism in children with hypercalciuria. *Semin Nephrol* 1989; **9**: 75-78 [PMID: 2740653]
39 **Perrone HC**, Lewin S, Langman CB, Toporovski J, Marone M, Schor N. Bone effects of the treatment of children with absorptive hypercalciuria. *Pediatr Nephrol* 1992; **6**: C115
40 **García-Nieto V**, Ferrández C, Monge M, de Sequera M, Rodrigo MD. Bone mineral density in pediatric patients with idiopathic hypercalciuria. *Pediatr Nephrol* 1997; **11**: 578-583 [PMID: 9323283]
41 **Freundlich M**, Alonzo E, Bellorin-Font E, Weisinger JR. Reduced bone mass in children with idiopathic hypercalciuria and in their asymptomatic mothers. *Nephrol Dial Transplant* 2002; **17**: 1396-1401 [PMID: 12147785]
42 **García-Nieto V**, Navarro JF, Monge M, García-Rodríguez VE. Bone mineral density in girls and their mothers with idiopathic hypercalciuria. *Nephron Clin Pract* 2003; **94**: c89-c93 [PMID: 12972718]
43 **Penido MG**, Lima EM, Marino VS, Tupinambá AL, França A, Souto MF. Bone alterations in children with idiopathic hypercalciuria at the time of diagnosis. *Pediatr Nephrol* 2003; **18**: 133-139 [PMID: 12579402]
44 **Skalova S**, Palicka V, Kutilek S. Bone mineral density and urinary N-acetyl-beta-D-glucosaminidase activity in paediatric patients with idiopathic hypercalciuria. *Nephrology* (Carlton) 2005; **10**: 99-102 [PMID: 15877664]
45 **García-Nieto V,** Sánchez Almeida E, Monge M, Luis Yanes MI, Hernández González MJ, Ibáñez A. Longitudinal study, bone mineral density in children diagnosed with idiopathic hipercalciuria (IH). *Pediatr Nephrol* 2009; **24**: 2083
46 **Moreira Guimarães Penido MG**, de Sousa Tavares M, Campos Linhares M, Silva Barbosa AC, Cunha M. Longitudinal study of bone mineral density in children with idiopathic hypercalciuria. *Pediatr Nephrol* 2012; **27**: 123-130 [PMID: 21779854 DOI: 10.1007/s00467-011-1952-4]
47 **Saggese G**, Baroncelli GI, Bertelloni S. Osteoporosis in children and adolescents: diagnosis, risk factors, and prevention. *J Pediatr Endocrinol Metab* 2001; **14**: 833-859 [PMID: 11515725]

48 **Baroncelli GI**, Bertelloni S, Sodini F, Saggese G. Osteoporosis in children and adolescents: etiology and management. *Paediatr Drugs* 2005; **7**: 295-323 [PMID: 16220996]
49 **Schalamon J**, Singer G, Schwantzer G, Nietosvaara Y. Quantitative ultrasound assessment in children with fractures. *J Bone Miner Res* 2004; **19**: 1276-1279 [PMID: 15231014]
50 **Clark EM**, Tobias JH, Ness AR. Association between bone density and fractures in children: a systematic review and meta-analysis. *Pediatrics* 2006; **117**: e291-e297 [PMID: 16452336]
51 **Loro ML**, Sayre J, Roe TF, Goran MI, Kaufman FR, Gilsanz V. Early identification of children predisposed to low peak bone mass and osteoporosis later in life. *J Clin Endocrinol Metab* 2000; **85**: 3908-3918 [PMID: 11061556]
52 **Gafni RI**, Baron J. Childhood bone mass acquisition and peak bone mass may not be important determinants of bone mass in late adulthood. *Pediatrics* 2007; **119** Suppl 2: S131-S136 [PMID: 17332232]
53 **Moreira Guimarães Penido MG**, de Sousa Tavares M. Bone disease in pediatric idiopathic hypercalciuria. *World J Nephrol* 2012; **1**: 54-62 [PMID: 24175242 DOI: 10.5527/wjn.v1.i2.54]
54 **Kieran K**, Giel DW, Morris BJ, Wan JY, Tidwell CD, Giem A, Jerkins GR, Williams MA. Pediatric urolithiasis--does body mass index influence stone presentation and treatment? *J Urol* 2010; **184**: 1810-1815 [PMID: 20728147 DOI: 10.1016/j.juro.2010.03.111]
55 **Rizvi SA**, Naqvi SA, Hussain Z, Hashmi A, Hussain M, Zafar MN, Sultan S, Mehdi H. Pediatric urolithiasis: developing nation perspectives. *J Urol* 2002; **168**: 1522-1525 [PMID: 12352448]
56 **Alon US**, Zimmerman H, Alon M. Evaluation and treatment of pediatric idiopathic urolithiasis-revisited. *Pediatr Nephrol* 2004; **19**: 516-520 [PMID: 15015063]
57 **Clark MA**, Fox MK. Nutritional quality of the diets of US public school children and the role of the school meal programs. *J Am Diet Assoc* 2009; **109**: S44-S56 [PMID: 19166672 DOI: 10.1016/j.jada.2008.10.060]
58 **Ticinesi A**, Nouvenne A, Maalouf NM, Borghi L, Meschi T. Salt and nephrolithiasis. *Nephrol Dial Transplant* 2014 Jul 16; Epub ahead of print [PMID: 25031016]
59 **Taylor EN**, Fung TT, Curhan GC. DASH-style diet associates with reduced risk for kidney stones. *J Am Soc Nephrol* 2009; **20**: 2253-2259 [PMID: 19679672 DOI: 10.1681/ASN.2009030276]
60 **Frassetto LA**, Morris RC, Sebastian A. Dietary sodium chloride intake independently predicts the degree of hyperchloremic metabolic acidosis in healthy humans consuming a net acid-producing diet. *Am J Physiol Renal Physiol* 2007; **293**: F521-F525 [PMID: 17522265]
61 **Cameron MA**, Sakhaee K, Moe OW. Nephrolithiasis in children. *Pediatr Nephrol* 2005; **20**: 1587-1592 [PMID: 16133066]
62 **Penido MGMG,** Diniz JSS, Moreira MLSF, Lima EM. Nefrolitiasis en pacientes pediátricos: Aspectos generales, evolución metabólica y acompañamiento. *Nefrologia* 1993; **13:** 126-130
63 **Coward RJ**, Peters CJ, Duffy PG, Corry D, Kellett MJ, Choong S, van't Hoff WG. Epidemiology of paediatric renal stone disease in the UK. *Arch Dis Child* 2003; **88**: 962-965 [PMID: 14612355]
64 **Hoppe B**, Kemper MJ. Diagnostic examination of the child with urolithiasis or nephrocalcinosis. *Pediatr Nephrol* 2010; **25**: 403-413 [PMID: 19104842]
65 **Spivacow FR**, Negri AL, del Valle EE, Calviño I, Fradinger E, Zanchetta JR. Metabolic risk factors in children with kidney stone disease. *Pediatr Nephrol* 2008; **23**: 1129-1133 [PMID: 18324422 DOI: 10.1007/s00467-008-0769-2]
66 **Alpay H**, Ozen A, Gokce I, Biyikli N. Clinical and metabolic features of urolithiasis and microlithiasis in children. *Pediatr Nephrol* 2009; **24**: 2203-2209 [PMID: 19603196 DOI: 10.1007/s00467-009-1231-9]
67 **Sternberg K**, Greenfield SP, Williot P, Wan J. Pediatric stone disease: an evolving experience. *J Urol* 2005; **174**: 1711-1714; discussion 1714 [PMID: 16148688]
68 **Güven AG**, Koyun M, Baysal YE, Akman S, Alimoglu E, Akbas H, Kabaalioglu A. Urolithiasis in the first year of life. *Pediatr Nephrol* 2010; **25**: 129-134 [PMID: 19705157 DOI: 10.1007/s00467-009-1296-5]
69 **Thomas BG**. Management of stones in childhood. *Curr Opin Urol* 2010; **20**: 159-162 [PMID: 19996750 DOI: 10.1097/MOU.0b013e3283353b80]
70 **Laerum E**, Ommundsen OE, Grønseth JE, Christiansen A, Fagertun HE. Oral diclofenac in the prophylactic treatment of recurrent renal colic. A double-blind comparison with placebo. *Eur Urol* 1995; **28**: 108-111 [PMID: 8529732]
71 **Xu H**, Zisman AL, Coe FL, Worcester EM. Kidney stones: an update on current pharmacological management and future directions. *Expert Opin Pharmacother* 2013; **14**: 435-447 [PMID: 23438422 DOI: 10.1517/14656566.2013.775250]
72 **Lande MB**, Varade W, Erkan E, Niederbracht Y, Schwartz GJ. Role of urinary supersaturation in the evaluation of children with urolithiasis. *Pediatr Nephrol* 2005; **20**: 491-494 [PMID: 15717161]
73 **Pietrow PK**, Pope JC, Adams MC, Shyr Y, Brock JW. Clinical outcome of pediatric stone disease. *J Urol* 2002; **167**: 670-673 [PMID: 11792950]
74 **Kalorin CM**, Zabinski A, Okpareke I, White M, Kogan BA. Pediatric urinary stone disease--does age matter? *J Urol* 2009; **181**: 2267-2271; discussion 2271 [PMID: 19296968 DOI: 10.1016/j.juro.2009.01.050]
75 **Miller OF**, Kane CJ. Time to stone passage for observed ureteral calculi: a guide for patient education. *J Urol* 1999; **162**: 688-690; discussion 690-691 [PMID: 10458343]
76 **Shouman AM**, Ziada AM, Ghoneim IA, Morsi HA. Extracorporeal shock wave lithotripsy monotherapy for renal stones & gt; 25 mm in children. *Urology* 2009; **74**: 109-111 [PMID: 19428070 DOI: 10.1016/j.urology.2008.09.083]
77 **Long CJ**, Srinivasan AK. Percutaneous nephrolithotomy and ureteroscopy in children: evolutions. *Urol Clin North Am* 2015; **42**: 1-17 [PMID: 25455168 DOI: 10.1016/j.ucl.2014.09.002]
78 **Sutherland JW**, Parks JH, Coe FL. Recurrence after a single renal stone in a community practice. *Miner Electrolyte Metab* 1985; **11**: 267-269 [PMID: 4033604]
79 **Milliner DS**, Murphy ME. Urolithiasis in pediatric patients. *Mayo Clin Proc* 1993; **68**: 241-248 [PMID: 8474265]
80 **Schwarz RD**, Dwyer NT. Pediatric kidney stones: long-term outcomes. *Urology* 2006; **67**: 812-816 [PMID: 16566973]
81 **Penido MG**, Diniz JS, Guimarães MM, Cardoso RB, Souto MF, Penido MG. Urinary excretion of calcium, uric acid and citrate in healthy children and adolescents. *J Pediatr* (Rio J) 2002; **78**: 153-160 [PMID: 14647798]
82 **van Woerden CS**, Huidekoper HH, Groothoff JW, Wijburg FA, Duran M. Postponing urine acidification for 24 h does not change the oxalate concentration. *Clin Chim Acta* 2007; **384**: 184-185 [PMID: 17659269]
83 **Pearle MS**, Goldfarb DS, Assimos DG, Curhan G, Denu-Ciocca CJ, Matlaga BR, Monga M, Penniston KL, Preminger GM, Turk TM, White JR. Medical management of kidney stones: AUA guideline. *J Urol* 2014; **192**: 316-324 [PMID: 24857648 DOI: 10.1016/j.juro.2014.05.006]
84 **Curhan GC**, Willett WC, Speizer FE, Stampfer MJ. Beverage use and risk for kidney stones in women. *Ann Intern Med* 1998; **128**: 534-540 [PMID: 9518397]
85 **Curhan GC**, Willett WC, Rimm EB, Spiegelman D, Stampfer MJ. Prospective study of beverage use and the risk of kidney stones. *Am J Epidemiol* 1996; **143**: 240-247 [PMID: 8561157]
86 **Shuster J**, Jenkins A, Logan C, Barnett T, Riehle R, Zackson D, Wolfe H, Dale R, Daley M, Malik I. Soft drink consumption and urinary stone recurrence: a randomized prevention trial. *J Clin Epidemiol* 1992; **45**: 911-916 [PMID: 1624973]
87 Nutrient Recommendations: Dietary Reference Intakes (DRI). 2015. Available from: URL: http://dietarysupplements.infonih.gov/health_Information/Dietary_Reference_Intakes.aspx
88 **Srivastava T**, Alon US. Pathophysiology of hypercalciuria in children. *Pediatr Nephrol* 2007; **22**: 1659-1673 [PMID: 17464515]
89 **Borghi L**, Schianchi T, Meschi T, Guerra A, Allegri F, Maggiore U, Novarini A. Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. *N Engl J Med* 2002; **346**: 77-84

[PMID: 11784873]
90 **Ince BA**, Anderson EJ, Neer RM. Lowering dietary protein to U.S. Recommended dietary allowance levels reduces urinary calcium excretion and bone resorption in young women. *J Clin Endocrinol Metab* 2004; **89**: 3801-3807 [PMID: 15292308]
91 **Breslau NA**, Brinkley L, Hill KD, Pak CY. Relationship of animal protein-rich diet to kidney stone formation and calcium metabolism. *J Clin Endocrinol Metab* 1988; **66**: 140-146 [PMID: 2826524]
92 **Curhan GC**. Epidemiology of stone disease. *Urol Clin North Am* 2007; **34**: 287-293 [PMID: 17678980]
93 **Tasian GE**, Copelovitch L. Evaluation and medical management of kidney stones in children. *J Urol* 2014; **192**: 1329-1336 [PMID: 24960469 DOI: 10.1016/j.juro.2014.04.108]
94 **Schwaderer A**, Srivastava T. Complications of hypercalciuria. *Front Biosci* (Elite Ed) 2009; **1**: 306-315 [PMID: 19482648]
95 **Penido MG**, Diniz JS, Moreira ML, Tupinambá AL, França A, Andrade BH, Souto MF. [Idiopathic hypercalciuria: presentation of 471 cases] *J Pediatr* (Rio J) 2001; **77**: 101-104 [PMID: 14647599]
96 **Hofbauer J**, Höbarth K, Szabo N, Marberger M. Alkali citrate prophylaxis in idiopathic recurrent calcium oxalate urolithiasis--a prospective randomized study. *Br J Urol* 1994; **73**: 362-365 [PMID: 8199822]
97 **Pak CY**, Peterson RD, Poindexter J. Prevention of spinal bone loss by potassium citrate in cases of calcium urolithiasis. *J Urol* 2002; **168**: 31-34 [PMID: 12050486]
98 **Tekin A**, Tekgul S, Atsu N, Bakkaloglu M, Kendi S. Oral potassium citrate treatment for idiopathic hypocitruria in children with calcium urolithiasis. *J Urol* 2002; **168**: 2572-2574 [PMID: 12441986]
99 **Sarica K**, Erturhan S, Yurtseven C, Yagci F. Effect of potassium citrate therapy on stone recurrence and regrowth after extracorporeal shockwave lithotripsy in children. *J Endourol* 2006; **20**: 875-879 [PMID: 17144854]
100 **LaCroix AZ**, Ott SM, Ichikawa L, Scholes D, Barlow WE. Low-dose hydrochlorothiazide and preservation of bone mineral density in older adults. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2000; **133**: 516-526 [PMID: 11015164]
101 **Sellmeyer DE**, Schloetter M, Sebastian A. Potassium citrate prevents increased urine calcium excretion and bone resorption induced by a high sodium chloride diet. *J Clin Endocrinol Metab* 2002; **87**: 2008-2012 [PMID: 11994333]
102 **Srivastava T**, Schwaderer A. Diagnosis and management of hypercalciuria in children. *Curr Opin Pediatr* 2009; **21**: 214-219 [PMID: 19307900 DOI: 10.1097/MOP.0b013e3283223db7]
103 **Reusz GS**, Dobos M, Vásárhelyi B, Sallay P, Szabó A, Horváth C, Szabó A, Byrd DJ, Thole HH, Tulassay T. Sodium transport and bone mineral density in hypercalciuria with thiazide treatment. *Pediatr Nephrol* 1998; **12**: 30-34 [PMID: 9502564]
104 **Schwaderer AL**, Cronin R, Mahan JD, Bates CM. Low bone density in children with hypercalciuria and/or nephrolithiasis. *Pediatr Nephrol* 2008; **23**: 2209-2214 [PMID: 18696122 DOI: 10.1007/s00467-008-0929-4]
105 **Nijenhuis T**, Vallon V, van der Kemp AW, Loffing J, Hoenderop JG, Bindels RJ. Enhanced passive Ca^{2+} reabsorption and reduced Mg^{2+} channel abundance explains thiazide-induced hypocalciuria and hypomagnesemia. *J Clin Invest* 2005; **115**: 1651-1658 [PMID: 15902302]
106 **Barcelo P**, Wuhl O, Servitge E, Rousaud A, Pak CY. Randomized double-blind study of potassium citrate in idiopathic hypocitraturic calcium nephrolithiasis. *J Urol* 1993; **150**: 1761-1764 [PMID: 8230497]
107 **Ettinger B**, Pak CY, Citron JT, Thomas C, Adams-Huet B, Vangessel A. Potassium-magnesium citrate is an effective prophylaxis against recurrent calcium oxalate nephrolithiasis. *J Urol* 1997; **158**: 2069-2073 [PMID: 9366314]
108 **Coe FL**, Evan A, Worcester E. Pathophysiology-based treatment of idiopathic calcium kidney stones. *Clin J Am Soc Nephrol* 2011; **6**: 2083-2092 [PMID: 21825103]
109 **Bobrowski AE**, Langman CB. The primary hyperoxalurias. *Semin Nephrol* 2008; **28**: 152-162 [PMID: 18359396]
110 **Monico CG**, Rossetti S, Olson JB, Milliner DS. Pyridoxine effect in type I primary hyperoxaluria is associated with the most common mutant allele. *Kidney Int* 2005; **67**: 1704-1709 [PMID: 15840016]
111 **Milliner D**. Treatment of the primary hyperoxalurias: a new chapter. *Kidney Int* 2006; **70**: 1198-1200 [PMID: 16988727]
112 **Hoppe B**, Beck B, Gatter N, von Unruh G, Tischer A, Hesse A, Laube N, Kaul P, Sidhu H. Oxalobacter formigenes: a potential tool for the treatment of primary hyperoxaluria type 1. *Kidney Int* 2006; **70**: 1305-1311 [PMID: 16850020]
113 **Ivanovski O**, Drüeke TB. A new era in the treatment of calcium oxalate stones? *Kidney Int* 2013; **83**: 998-1000 [PMID: 23728004 DOI: 10.1038/ki.2013.41]
114 **Goldfarb DS**, Modersitzki F, Asplin JR. A randomized, controlled trial of lactic acid bacteria for idiopathic hyperoxaluria. *Clin J Am Soc Nephrol* 2007; **2**: 745-749 [PMID: 17699491]
115 **Lieske JC**, Goldfarb DS, De Simone C, Regnier C. Use of a probiotic to decrease enteric hyperoxaluria. *Kidney Int* 2005; **68**: 1244-1249 [PMID: 16105057]
116 **Caravaca F**, Ruiz AB, Escola JM, Hernández Gallego R, Cerezo I, Fernández N, Barroso S, Martín MV. Either calcium carbonate or sevelamer decreases urinary oxalate excretion in chronic renal failure patients. *Nefrologia* 2007; **27**: 466-471 [PMID: 17944584]
117 **Lieske JC**, Regnier C, Dillon JJ. Use of sevelamer hydrochloride as an oxalate binder. *J Urol* 2008; **179**: 1407-1410 [PMID: 18289565]
118 **Worcester EM**, Coe FL. Nephrolithiasis. *Prim Care* 2008; **35**: 369-91, vii [PMID: 18486720]
119 **Chow GK**, Streem SB. Medical treatment of cystinuria: results of contemporary clinical practice. *J Urol* 1996; **156**: 1576-1578 [PMID: 8863541]
120 **Wendt-Nordahl G**, Sagi S, Bolenz C, Alken P, Michel MS, Knoll T. Evaluation of cystine transport in cultured human kidney cells and establishment of cystinuria type I phenotype by antisense technology. *Urol Res* 2008; **36**: 25-29 [PMID: 18074125]
121 **Rimer JD**, An Z, Zhu Z, Lee MH, Goldfarb DS, Wesson JA, Ward MD. Crystal growth inhibitors for the prevention of L-cystine kidney stones through molecular design. *Science* 2010; **330**: 337-341 [PMID: 20947757 DOI: 10.1126/science]
122 **Hassan HA**, Cheng M, Aronson PS. Cholinergic signaling inhibits oxalate transport by human intestinal T84 cells. *Am J Physiol Cell Physiol* 2012; **302**: C46-C58 [PMID: 21956166 DOI: 10.1152/ajpcell.00075.2011]

P- Reviewer: El-Assmy A, Markic D **S- Editor**: Ji FF **L- Editor**: A
E- Editor: Wu HL

World Journal of Nephrology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5527/wjn.v4.i4.455

World J Nephrol 2015 September 6; 4(4): 455-467
ISSN 2220-6124 (online)

FRONTIER

Update on immunoglobulin A nephropathy, Part I: Pathophysiology

Maurizio Salvadori, Giuseppina Rosso

Maurizio Salvadori, Department of Transplantation and Renal Diseases, Careggi University Hospital, 50139 Florence, Italy

Giuseppina Rosso, Division of Nephrology, San Luca Hospital, 55100 Lucca, Italy

Author contributions: Salvadori M and Rosso G both contributed to this paper.

Conflict-of-interest statement: No conflict of interest is declared by any of the authors.

Correspondence to: Maurizio Salvadori, Medical Doctor, Department of Transplantation and Renal Diseases, Careggi University Hospital, viale Pieraccini 18, 50139 Florence, Italy. maurizio.salvadori1@gmail.com
Telephone: +39-055-597151
Fax: +39-055-597151

Received: June 23, 2015
Peer-review started: June 23, 2015
First decision: August 4, 2015
Revised: August 24, 2015
Accepted: August 30, 2015
Article in press: August 31, 2015
Published online: September 6, 2015

Abstract

Immunoglobulin A (IgA) nephropathy is one of the most common glomerulonephritis and its frequency is probably underestimated because in most patients the disease has an indolent course and the kidney biopsy is essential for the diagnosis. In the last years its pathogenesis has been better identified even if still now several questions remain to be answered. The genetic wide association studies have allowed to identifying the relevance of genetics and several putative genes have been identified. The genetics has also allowed explaining why some ancestral groups are affected with higher frequency. To date is clear that IgA nephropathy is related to auto antibodies against immunoglobulin A1 (IgA1) with poor O-glycosylation. The role of mucosal infections is confirmed, but which are the pathogens involved and which is the role of Toll-like receptor polymorphism is less clear. Similarly to date whether the disease is due to the circulating immunocomplexes deposition on the mesangium or whether the antigen is already present on the mesangial cell as a "lanthanic" deposition remains to be clarified. Finally also the link between the mesangial and the podocyte injury and the tubulointerstitial scarring, as well as the mechanisms involved need to be better clarified.

Key words: Immunoglobulin A; Immunoglobulin A galactosylation; Genome-wide association studies; Auto antibodies; Complement in renal diseases; Mesangial linked growth factors

Core tip: For few glomerular diseases a new pathogenetic pathway has been recognized in the recent years as happened for the immunoglobulin A (IgA) nephropathy. Finding in the genetics allowed identifying several loci putative for the disease progression. Spectrometry mass studies and 3 dimension studies have allowed bettering clarifying the molecules involved at glomerular level. Molecular studies of the mesangium allowed identifying new receptors responsible for the IgA immune complexes deposition and for the binding to the mesangial structure. Finally molecular and cellular studies opened new ways to understanding the

link and the cross-talk between the glomeruli and the tubulointerstitial structure.

Salvadori M, Rosso G. Update on immunoglobulin A nephropathy, Part I: Pathophysiology. *World J Nephrol* 2015; 4(4): 455-467 Available from: URL: http://www.wjgnet.com/2220-6124/full/v4/i4/455.htm DOI: http://dx.doi.org/10.5527/wjn.v4.i4.455

INTRODUCTION AND EPIDEMIOLOGY

The immunoglobulin A (IgA) nephropathy (IgAN) is represented by a proliferation of glomerular mesangial cells jointed with the presence of IgA deposition in the mesangial area. The IgAN represents the most frequent glomerulonephritis and is represented by extremely different clinical signs and histopathologic features[1]. Because of the typical histopathological and immunological picture and the heterogeneous clinical aspects, the diagnosis of IgAN is principally based on the pathologic picture at the renal biopsy. As a consequence, the IgAN frequency is probably underestimated and the disease is the most prevalent glomerulonephritis in those countries where renal histology is more frequently used in the diagnostic algorithm. Its estimated frequency is approximately 2.5 cases/year per 100000 adults[2]. IgAN is worldwide diffused even if with different frequencies. IgAN has prevalence for male sex in the Caucasian race[3-5]. It is more frequent in some races (Asians, Hispanics, whites, American Indians) while is less frequent in other races as African and American blacks[6]. Recently new epidemiological findings, supported by the genetics, have allowed confirming that the disease incidence varies greatly according the geographical location. Indeed the IgA nephropathy is found in up to 40% of native kidney biopsies in Eastern Asia, but in less than 5% of native biopsies in central Africa[7]. In addition to the different criteria in performing renal biopsy, genetics is thought to play a significant role in explaining some geographical differences[8]. In addition, a diagnostic difficulty is represented by the huge difference in clinical presentation. Indeed, clinically, IgAN may present an asymptomatic course. Such patients are occasionally diagnosed during the work up for other diseases as hypertension or reduced glomerular filtration rate (GFR). Other patients present with macroscopic hematuria, often related to upper respiratory tract infections. In addition, some patients may present with rapidly progressive disease. Generally, the progression of the disease is related to the presence of well-known clinical risk factors that impact on the evolution of most glomerulonephritis as hypertension, proteinuria above 1 g/d, impaired renal function, smoking and obesity[9-11].

It is now clear that IgAN may be present in subjects apparently health as documented by biopsies of kidneys suitable for transplantation, or by data of autopsies not related to renal diseases[12,13]. This is further documented by the fact that most persons affected by IgAN may have a benign course or spontaneous resolution as documented by subjects followed for 10 years after diagnosis in China and in Spain[14,15]. Moreover, after transplantation of an IgAN kidney into a non IgAN recipient, disappearance of the glomerular changes has been documented, suggesting that the defect leading to IgAN is not related to the kidneys[16]. In addition, the high recurrence rates following kidney transplantation confirm that the key pathogenetic alteration in IgAN might reside outside the kidney[17].

PATHOGENESIS

As aforementioned, the IgAN is characterized by mesangioproliferative changes in the glomeruli with typical IgA deposits in the mesangial area. Deposits of IgG and C3 are also frequently present. The glomerular IgAs eluted from biopsies of patients affected by IgAN belong almost always to the IgA1 subclass and are principally polymeric. Interestingly, they are poorly glycosylated. In particular, these abnormal IgA1s exhibit a defect of galactose molecules that are normally linked to O-glycans in the hinge region. Defective glycosylated IgA1s exhibit higher blood levels in patients affected by IgAN than in normal subjects. However, this high circulatory level of galactose-deficient IgA1s (Gd-IgA1) *per se* is not able to determine the renal disease. Different steps or processes are needed for the clinical development and manifestation of the IgAN. New findings concerning these processes have been recently discovered, they are under the genetic control and genetics and immunobiology of IgAN are strictly linked[7,18].

A genome-wide association study (GWAS) performed by Gharavi *et al*[19] recently found five susceptibility loci for IgAN and allowed to identify the molecules responsible for the above mentioned steps.

These are represented by: (1) abnormal IgA1 glycosylation; (2) antibody production towards the abnormal IgA1; (3) binding of the anti-glycan antibodies to the abnormal IgA1 and consequent production of immune-complexes; and (4) deposition of the immune-complexes in the mesangial area and induction of the renal damage.

INSIGHTS FROM GENETICS

After the GWAS finding already mentioned[19], more recently a GWAS again has identified more candidate genes offering new views on the hits involved into the IgAN pathogenesis. The hits involved are represented by the antigen elaboration and presentation, the immunity mucosa-related, and the complement activation.

Antigen elaboration and presentation

The GWAS mentioned identified three different candidate loci that might impact on this pathway. They all have

Table 1 Common genetic determinants for immunoglobulin A nephropathy

Genetic locus	Genes	Function
6q21	*HLA-DRB1, HLADQA1* and *HLA-DQB1*	Class II major histocompatibility complex
	PSMB8/9 and *TAP/2*	Regulators for antigen processing and presentation
1q32	*CFHR1/3*	Modulators for complement activation and inflammation
22q12	*HORMAD2*	Unknown
17q13	*TNFSF13*	Important for B cell development and IgA isotype switching
8p23	*DEFA1*	Encoding a-defensins as a type of endogenous antimicrobial mediators
1p13	*VAV3*	Regulators for lymphocyte development and antigen presentation
9q34	*CARD9*	Participant in antigen-induced signalosome formation (CARD9-BCL 10-MALT1) and NF-κB activation
16p11	*ITGAM* and *ITGAX*	Mediators for immune cell adhesion and phagocytosis

IgA: Immunoglobulin A.

been identified on chromosome 6p21, are located on major histocompatibility complex (MHC) and are called: HLA-*DRB1/DQB1*, HLA-*DPB1/DPB2* and *TAP1/PSMB9*.

A strength link was identified in a different HLA region that includes the HLA-*DRB1-DQA1* genes[19]. The same region had been previously associated with several autoimmune diseases[20-27]. Another MHC locus has been found in the region that includes the *HLA-DPA1*, *BPB1* and *DPB2* genes.

Immunity mucosa-related: The clinical association of hematuria and infective episodes related to mucosal sites allowed to suspect that abnormalities in the IgA production might be responsible for the IgAN[28].

GWAS identified three loci involved in the mucosal pathogenesis of the IgAN. A locus is located on chromosome 17p13. This locus contains the gene *TNFS 13* that codes a proliferation-inducing ligand (APRIL). APRIL might determine the proliferation of IgA-producing cells[29,30] and APRIL serum levels may be higher in subjects affected by IgAN[31].

A second locus on chromosome 22q12 affects the circulatory IgA load and the susceptibility to develop IgAN[19]. This locus includes several genes among which the genes *LIF* and *OSM*, that encode cytokines[32]. The cytokines encoded by these genes belong to the interleukin 6 (IL-6) family and influence the immuno-regulation[33,34].

On the *DEFA* gene cluster located on the chromosome 8p23, another locus related to IgAN has been identified. It encodes the small peptides secreted by the mucosal cells with antimicrobial properties called α-defensin[35]. While α-defensin 1, 3 and 4 are secreted by neutrophil, α-defensin 5 and 6 are secreted into the gut by the Paneth cells.

Complement activation

On chromosome 1q32 is located the locus that contains the gene encoding complement factor H (CFH). GWAS found that the deletion of two CFH related genes (*CFHR3* and *CFHR1*) is a protective genetic factor for IgAN[19].

Indeed, the deletion of *CFHR3* and *CFHR1* is associated with the lacking of their products and CFHR1 is a competitive antagonist of CFH in regulating the complement activity[36]. As a consequence, the association of elevated CFH levels with the absence or low levels of CFHR1 determines a strong inhibition of complement activation. In addition, the relationship between mesangial C3 deposits and different CFH, CFH and CFHR1 levels suggests that these proteins are related to the pathogenic IgA-IC deposition[37].

In addition to the above mentioned pathways, recently performing a GWAS in 20612 patients affected by IgAN, other relevant possible genes have been found; four in *ITGAM-ITGAX*, *VAV3* and *CARD 9* and two in the HLA-*DQB1* and *DEFA* loci. Most loci carry genetic risk correlation with local intestinal pathogens, supporting the possibility that host pathogens might favor the IgAN in genetically predisposed patients[38]. All the candidate genes and their function are summarized in Table 1.

FOUR HITS FOR GENERATION OF RENAL INJURY

Several authors[7,18] have formulated the so called "four hits" pathogenesis of the IgAN. According several studies the IgAN pathogenesis is multivariate and implies the co-existence of several factors. Indeed, after an increase in galactose-deficient circulating IgA1 (Gd-IgA1), an antibody production against these IgA1 is essential for the disease initiation. Later on IC are formed that may deposit in the kidney and activate an inflammatory response (Table 2).

Step 1: Regulation of IgA1 glycosylation and genetic impact on galactose-deficient circulating IgA1

The IgA1 hinge region is located between the constant region domains CH1 and CH2 of the α 1 heavy chains. This region contains O-glycosylation sites composed of serine/threonine (Ser/Thr) and Proline residues. In normal condition only some of these sites are glycosylated[39,40]. A key role in the IgA O-glycosylation is exerted by core 1 β 1, 3 galactosyl-transferase (C1β3Gal-T) and its molecular chaperone core 1-1-phosphateuridyltransferase (Gal-T)-specific chaperone (Cosmc). Patients affected by IgAN have

Table 2 Summary of the four hits involved in the pathogenesis of immunoglobulin A nephropathy with distinction of the pathogenetic process (putative environmental factors involved, putative genetic factors involved, potential clinical biomarkers and potential novel therapeutic approaches)

Hit	Pathogenic process	Putative environmental factors involved	Putative genetic factors involved	Potential clinical biomarkers	Potential novel therapeutic approaches
1	Hereditary increase in circulating galactose-deficient IgA1	Potential role of mucosal exposure to infectious of dietary antigens	Strong evidence for high heritability of serum galactose-deficient IgA1 level Potential role of chromosome 22q12.2	Serum galactose-deficient IgA1 level (HAA-based ELISA)	Suppression of synthesis of galactose-deficient IgA1 Enzymatic boost of galactose transfer to IgA1 hinge- region O-glycans Suppression of sialylation of galactose-deficient O-glycans
2	Circulating antibody directed against galactose-deficient IgA1	Potential role of mucosal exposure to infectious or dietary antigens	Potential role of three MHC-II loci in antigen presentation and humoral response to galactose-deficient IgA1 O-glycans	Serum anti-glycan antibodies (dot blot assay)	Alteration of processing and presentation of galactose-deficient IgA1 O-glycopeptides Specific B-cell depletion therapy
3	Formation of pathogenic IgA1-containing immune complexes	Unknown	Unknown	Circulating and/or urinary immune complexes	Competitive blockade of immune complex formation by non-cross-linking anti-glycan antibodies or specific glycopeptides
4	Mesangial deposition of IgA1 containing immune complexes, cell activation and initiation of glomerular injury	Unknown	Protective effect of common deletion in CFHR1 and CFHR3	Circulating and/or urinary complement degradation products, or novel markers of glomerular injury	Suppression of the alternative complement pathway Targeted CFHR1/3 depletion Blocking mesangial cell signaling induced by nephritogenic IgA1-containing immune complexes

HAA: Helix Aspersa; ELISA: Enzyme-linked immunosorbent assay; CFHR3: Complement factor H receptor 3; IgA: Immunoglobulin A.

more elevated blood levels of IgA1 with the O-glycans poorly galactosylated and having either GalNac as terminal molecule or GalNac containing the secretory J component (Figure 1)[41]. A recent study, using cell lines from a human B-lymphoma documented that the T 2 helper cytokine IL-4 may control the glycosylation of the IgA[42]. Indeed, the IL-4 stimulation decreased the messenger RNA (mRNA) levels of both core the enzyme (C1β3Gal-T) and its molecular chaperone. Studies on animals confirmed the relevance of cytokines on IgA glycosylation[43,44]. O-glycan specific lectin initially allowed identifying the defective IgA1 O-glycosylation in IgAN[45]. More recently, other techniques as the liquid chromatography and the 3D mass spectrometry have allowed us to an improved understanding of the O-glycosylation process and the molecules involved[46,47].

The origin of the poor galactosylated IgA1s is still a not resolved question. Several studies have documented a significant difference in IgA1s generated in the systemic compartment with respect to the IgA1s generated on the mucosal surface[48]. Mucosal IgAs are predominantly polymeric (pIgA), while systemic IgAs are monomeric. Interestingly, in the IgAN the pathogenic IgA immune complexes (IgA-IC) principally contain poor galactosylated pIgA with the J secretory component[49].

The high serum level of mucosal-type IgAs in the IgAN patients might suggest that mucosal sites are the origin of poor galactosylated IgA1s. In contrast, in IgAN either systemic pIgAs directed against antigens typical of the mucosa and systemic pIgA plasma cells in systemic sites have been described[50,51]. Hence the hypothesis that the overproduction in the serum of poor galactosylated IgA1 might be the result of the movement of mucosal IgA1 committed B cells from the mucosa to the systemic compartment. A mucosal B cell mis-homing to systemic sites is the most likely mechanism[52].

The abnormal activity of Toll-like receptors (TLRs) might be another factor that contributes to the increased response to mucosal antigens in IgAN. Indeed, the association of increased Toll-like receptor 4 in circulating cells and signs of renal diseases have been reported by several studies[53]. Other studies examining the single nucleotide polymorphism, found an association between the TLR-9 polymorphism and the IgAN progression. This suggests that the involvement of TLR-9/MyD88 might exert its effect over the progression of IgAN[54].

Step 2: Synthesis of antibodies directed against GdIgA1

The synthesis of abnormally glycosylated IgAs is not "*per se*" enough to justify the mesangial lesions that characterize the IgAN. Indeed, comparing the IgA glycosylation of IgAs eluted from serum with those eluted from biopsy specimens we may observe that Gd-IgAs eluted from kidney biopsies are less glycosylated when compared to the glycosylation rate of serum IgAs from the same IgAN patients[55,56]. This fact highlights a GdIgA1 tropism for the mesangium which might contribute to explain the recurrence of IgA deposits on kidney allograft. Moreover, a study documented that in families affected by IgAN an abnormal glycosylation may be present both in IgAN patients and in asymptomatic relatives[57]. The latter observation confirms that the

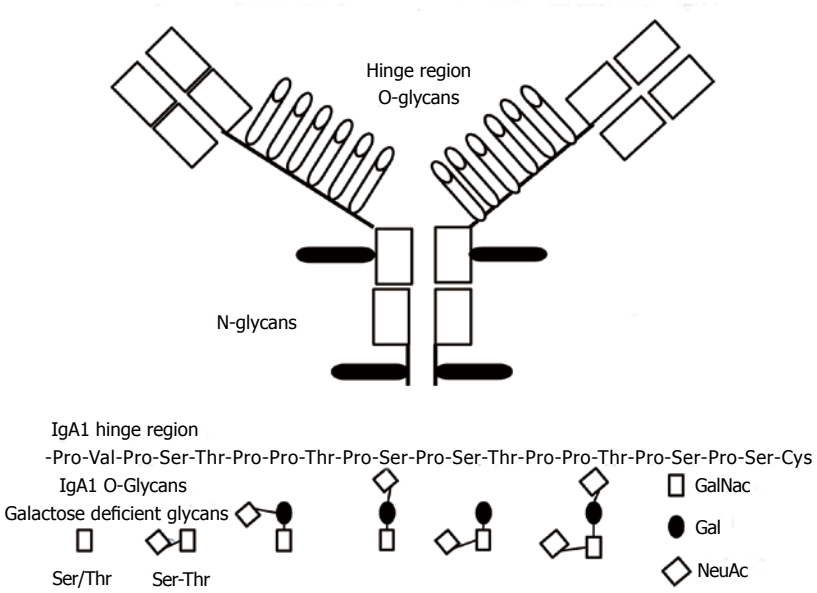

Figure 1 Immunoglobulin A1 and its hinge region with O-linked glycans (white) and N-linked glycans (black). Under the aminoacids chain of the hinge region. Sites of attachment are in bold. IgA: Immunoglobulin A.

presence of abnormally glycosylated IgAs does not "*per se*" justify the mesangial lesions and that other factors should be associated.

Recent studies suggest that auto antibodies recognizing the abnormally glycosylated IgA1s are essential in the pathogenesis of the disease[58,59]. These findings document that IgAN is an autoimmune disease due to the mesangial deposition of immunocomplexes containing GdpIgA1. Other molecules such as sCD89, fibronectin, collagen and laminin are also found in IgA1 containing immune complexes, even if their role remains to be determined[60].

Circulatory auto antibodies (IgG and/or IgA) bind to Gd-IgA1s and form large pathogenetic immune complex[61]. A better understanding of these antibodies is provided from an elegant experiment that used Epstein Barr virus (EBV-immortalized) lymphocytes from subjects affected by IgAN[62]. These B cells are able to product IgG that bind Gd-IgA1 and a subsequent analysis of the cloned chains of these IgG auto antibodies identified as their unique feature the complementary-determining region (CDR) 3 of the heavy chains[61]. In particular the third portion in CD3 is typically serine in patients with IgAN. Whether bone marrow or mucosal tissues are at the origin of IgA1s in circulating immune complexes is still now a matter of controversy. The acute onset of the disease is often accompanied by a concurrent infection of the upper respiratory tract and in this site cells are present able to produce polymeric IgA1s, typical of the pathogen IgA[29]. However, in other studies, polymeric IgA1s and J chain producing cells have been found in the bone marrow of subjects affected by IgAN[63-65]. The aforementioned mis-homing with transposition of plasma cells from the mucosa to systemic sites might explain this finding[52].

Recently Barratt *et al*[66,67] postulated the so called hypothesis of the "right antibodies in the wrong place at the wrong time". According this hypothesis, the "right" antigen represented by the mucosal derived Gd-IgA is in the systemic compartment that is the wrong place. Later on, when a large quantity of Gd-IgA1 is in circulation, a large quantity of the right antibody anti Gd-IgA1 is secreted at the wrong time.

The stimuli leading to the production of these auto antibodies remains to be explained.

A hypothesis might be that these antibodies are secreted against pathogen cell surface GalNac-containing glycoconiugates cross-reacting with GdIgA1, realizing a molecular mimicry[68]. A prevalence of IgA1 autoantibody response[61] anti GdIgA1 may justify the fact that some patients have only IgA1 antibody in the glomeruli[69].

In conclusion, a portion of the IgA1 molecules secreted by the plasma cells in patients affected by IgAN is Gal-deficient and is identified by the anti-glycan IgG (or IgA1) antibodies[70]. The formed IC, due to their size, cannot reach and bind the asialoglycoprotein receptor (ASGP-R) in the liver, and be metabolized. Moreover, the terminal GalNac residues, which might interact with the ASGP-R, are covered by specific antibodies that prevent such interaction[71]. As a consequence, a larger fraction of the IgA-IC may reach the glomerular capillaries overlying the mesangium.

Summarizing the two steps above described in the IgA pathogenesis, in the first time a high quantity of under-galactosylated IgA1 is present in the blood. At this regard several points remain to be clarified. The plasma cell defect is inherited or acquired? In addition, to justify the systemic presence of GdIgA1 high quantity, a plasma cell mis-homing from mucosa to systemic sites is needed or not?

In the second step we have the IgG auto antibodies production anti the GdIgA1. At this regard several questions remain to be answered.

Are these antibodies the result of a molecular mimicry triggered by infections?

In addition, are these antibodies the result of a Toll-like receptor polymorphism?

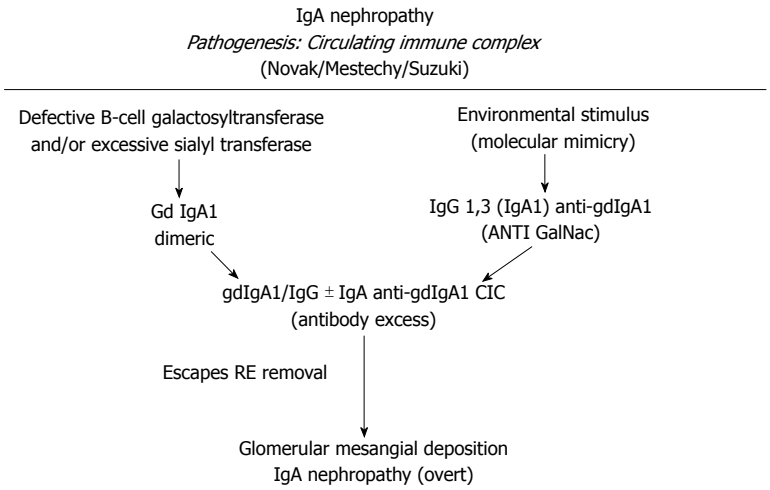

Figure 2 Schematic representation for the possible pathways involved in the generation of a circulating immune complex pathogenesis for the immunoglobulin A nephropathy. CIC: Circulating immuno complex; Gd IgA1: Galactose deficient immunoglobulin A1.

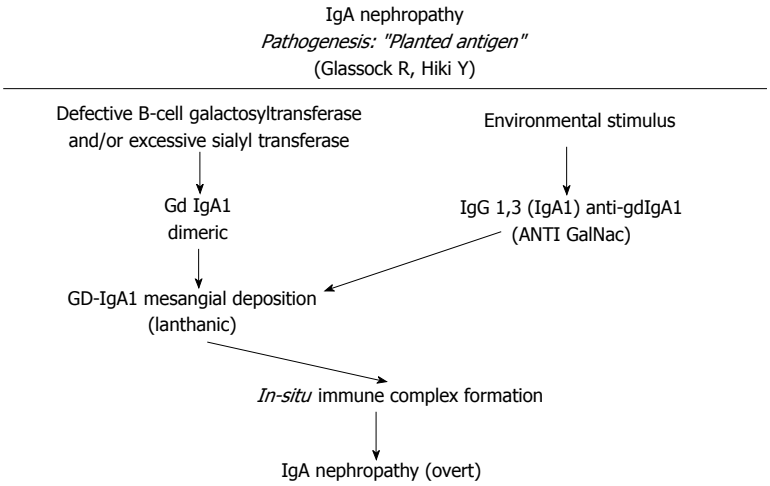

Figure 3 Schematic representation for the possible pathways involved in an *in situ* pathogenesis for the IgA nephropathy. IgA: Immunoglobulin A; Gd-IgA1: Galactose deficient immunoglobulin A1; ANTI GalNac: ANTI N-acetylgalactosamine.

Finally, is there a genetically determination induced by somatic mutations in the IgG heavy chains?

Step 3: Formation of pathogenic immune complexes containing IgA and their mesangial deposition

Circulating anti-glycan auto antibodies recognize Gd-IgA1 and pathogenic immune complexes are formed as a consequence. IgA1s must be within an immune complex to activate the mesangial cell proliferation; indeed not complexed GdIgA1s do not stimulate the proliferation of mesangial cells[72-74]. Additional components from serum need to be present to form stimulatory complex[72].

Several models have been proposed to explain the IgA1 immune complex depositions on the mesangial cells. Immune complexes containing IgA1/IgG or IgA could directly deposit on mesangial cell[61,62,75]. Another hypothesis is that poor glycosylated IgA1 might be present in the mesangial area as lanthanic deposits and later newly generated anti-glycan antibodies might bind and realize immune complexes in situ capable to activate mesangial cells[3] (Figures 2 and 3). In addition, a further theory is that self-aggregated Gd-IgA1s might deposit or bind to specific receptors in the mesangial area realizing "planted" depositions that are not pathogenic "*per se*". When an exposure to similar environmentally derived antigens occurs, an auto-antibody production and the involvement of several mediators cascade lead to the disease[76,77]. Further studies led to identify the relevance of IgA receptors (IgA-R) in the deposits. Several IgA-Rs have been recognized[78-80]. In the IgAN pathogenesis, two IgA-R expressing cells have been principally involved: (1) mesangial cells which have been documented to be implicated in kidney injury; and (2) myeloid cells (essentially kidney infiltrating macrophages) which have been documented to modulate the extent of the inflammatory response. Studies from several groups have ruled out that the mesangial expression of receptors as ASGP-R, CD 89 and pIgAR might have a role[81]. In addition, although on the mesangial cells is located the Fc alpha mu receptor (Fcα/μR), neither IgM nor the recombinant Fcα/μR inhibit the IgA1 binding to mesangium[82]. The transferrin receptor (TfR1 or CD71) has been identified as the mesangial IgA1 receptor implicated and the pIgA1 binding to TfR1 induces mesangial cells activation[83,84]. Moreover, TfR1 co-localizes with deposited IgA in the IgAN biopsies[85]. The same group documented that both glycosylation and size of IgA1 are relevant factors for the TfR-IgA1 interaction. This probably is the first step of the

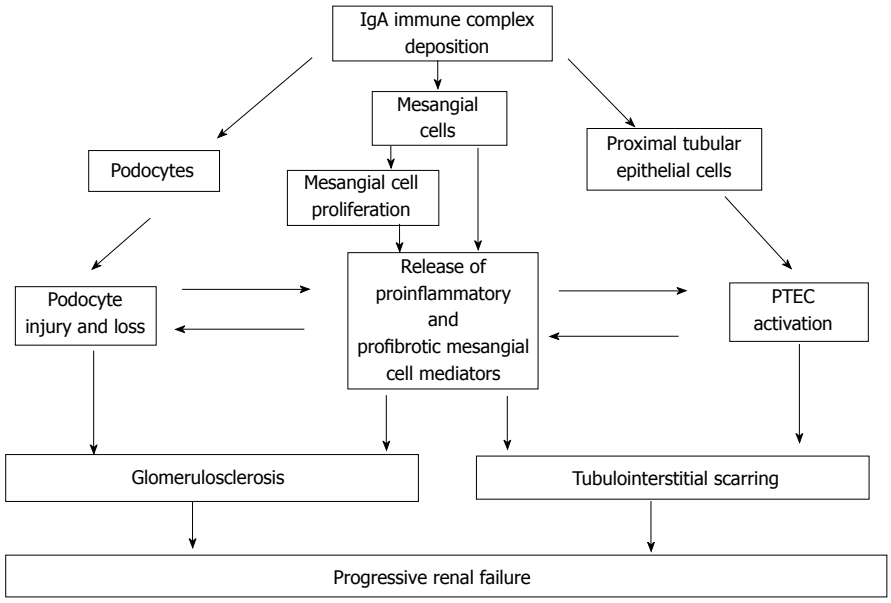

Figure 4 Pathways to glomerular damage and tubulointerstitial injury in Immunoglobulin A nephropathy. Deposition of IgA-ICs in the mesangium leads to activation of mesangial cells, triggering mesangial cell proliferation and release of proinflammatory and profibrotic mediators. Podocyte loss accentuates glomerular scarring and filtered mesangial cell-derived mediators and IgA-ICs stimulate PTEC to adopt a proinflammatory and profibrotic phenotype, which in turn drives tubulointerstitial scarring. IgA: Immunoglobulin A; PTEC: Proximal tubule epithelial cells.

IgAN injury[86]. Finally, as an alternative hypothesis, has been proposed that the soluble form of the Fcα receptor (sCD89) might "*per se*" generate complexes with Gd-IgA1[87]. The formation of circulating Gal deficient pIgA1 immune complexes (IgA1-CIC) induces an alteration in the interaction between IgA and CD89 that are found in the mesangial deposits and is implicated in the diseases exacerbation through the activation of pro-inflammatory cytokines and the secretion of chemokines[88,89].

Step 4: Mesangial and glomerular cells activation, glomerular injury and fibrosis

The renal damage after mesangial cell deposition of immune complexes may be distinguished into three phases: (1) mesangial cell activation; (2) podocyte injury; and (3) tubulo-interstitial scarring. All these kinds of renal injuries may be mediated by different pathways as the complement activation, the innate immunity activation, and the non-complement mediators of IgA nephropathy (Figure 4).

Mesangial cells are activated by IgAs and may transform into inflammatory and fibrotic cells after the exposure to IgA-IC. Indeed, the mesangial cells binding to IgA-IC containing poorly galactosylated IgA1 triggers the proliferation and the programmed death of the mesangial cells. In addition a reduced synthesis of vascular endothelial growth factor (VEGF), an abnormal integrin production and an abnormal production of extracellular matrix increase the renal damage[86,90-92].

The role of complement in the activation of the mesangial cells in IgAN has been recently reviewed by Maillard *et al*[93]. In IgAN, polymeric or aggregated IgA1s, principally Gd-IgA1s, may stimulate the alternative complement pathway, determine the C3 deposition and the production of the complement terminal complex (C5b-C9)[94-97]. Similarly the same pathways might be locally stimulated on the mesangial cells by polymeric Gd-IgA1s as well as by the secretory IgAs (SIgA)[97]. In addition, the complement involvement by the alternative and the mannan binding lectin (MBL) pathways may be activated by the polymeric IgA1, thus participating to the pathogenesis of the IgAN and characterizing a more severe disease.

Components of the innate immunity are similarly involved in the pathogenesis of the IgAN. Some studies have documented that the TLRs are able to induce the IgA production by the B cells[98]. It has also been documented a link between the TLRs stimulation, the overproduction of Gd-IgA1s, the more aggressive aspects of IgAN and the activation of the enzyme and molecules involved in the IgA glycosylation[54,99,100].

Mesangial injury: IgA1-ICs containing secretory IgA with a high sialic acid content and anionic IgA-IC stimulate mesangial cells, may stimulate the p42/p44 mitogen activated protein kinase, activator protein 1, and NF-kB signal transduction. Similarly other chemokines and cytokines are up-regulated, among which the IL-6, the transforming growth factor β (TGFβ), the tumor necrosis factor α (TNFα) and the monocyte chemo attractant protein (MCP-1)[101-103].

The platelet derived growth factors (PDGFs) are among the growth factors most involved in the mesangial cell proliferation[104]. The PDGFs are five potent mitogens and chemoattractants that play important roles in the mesangio-proliferative diseases, principally in the IgA nephropathy. The PDGF-BB and PDGF receptors (PDGFR-β) are over expressed in the experimental

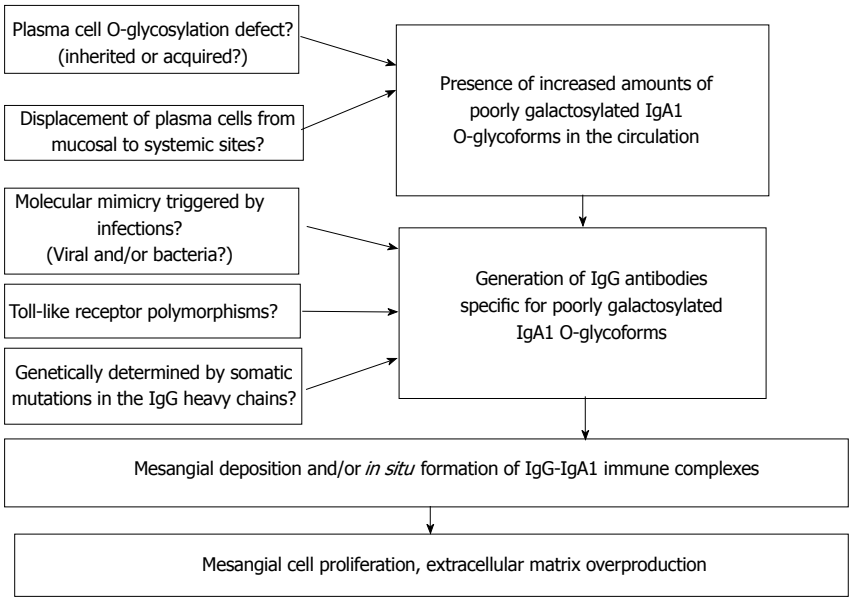

Figure 5 Doubts and different possibilities in generating the first two steps. IgA: Immunoglobulin A; IgG-IgA1: Immunoglobulin G-Immunoglobulin A1.

mesangio-proliferative nephritis and in the human IgAN[104].

The pathogen IgA1s are also able to activate the renin-angiotensin-aldosterone system (RAAS) intrarenally[105]. This system too is involved in the IgAN injury.

Finally a protective affect against mesangial cell activation by IgA-IC is exerted by bone morphogenetic protein 7 (BMP-7)[106]. BMP-7 suppresses TNFα induced synthesis of proinflammatory cytokines, and has an anti-fibrotic effect through antagonism of the cellular actions of TGF β[107,108].

Podocyte injury: Podocyte necrosis and detachment from the glomerular basal membrane has been reported in the IgAN and the degree of podocytopenia is closely related to the increasing severity of glomerular lesions[109]. Nephrin is a key component of the podocyte slit diaphragm and is essential for the maintenance of an intact glomerular filtration barrier. Interestingly, nephrin mRNA and extracellular nephrin expression are reduced in the IgAN[110,111]. In addition, evidence from in vitro studies suggests that the podocyte injury in the IgAN is likely to be mediated by both the mesangial cell derived soluble mediators and by the direct contact with filtered IgAs[112,113].

It has also been documented that IgA1-IC in IgAN patients might up regulate the production of CXCL1 and TGF beta from the mesangial cells. CXCL1 and TGF beta might exert a synergistic effect upon the podocytes, inducing podocyte dysfunction and podocyte death[114].

Tubulointerstitial scarring: It has until recently been thought that the mechanisms of the subsequent tubulointerstitial injury were generic and common to all forms of chronic kidney diseases. Recent studies have documented that specific mechanisms are operating in the IgAN.

Among the factors that are up regulated after stimulation of mesangial cells, the TGFβ is the most involved in generating fibrotic tissue related to the cell damage. It is generated by growth factors involved in the connective tissue generation[115,116]. In addition to producing fibrotic tissue, TGFβ also acts favoring the transformation of the tubular cells into a fibrotic phenotype.

With an increasing damage to the perm selective barrier, increasing amounts of high-molecular weight IgA-ICs enter the urine. In IgAN these IgA-ICs are enriched by GdIgA1s that reflects their localization within the mesangium[117]. Therefore the proximal tubule epithelial cells (PTEC) are constantly exposed to filtered IgA-ICs because of the impairment of the glomerular size barrier.

Recent studies suggest that there may be a direct and specific interaction between filtered IgA-ICs, mesangial cell-derived mediators, and PTEC. Indeed, when the mesangial cells are activated by the IgAs, they release mediators, which subsequently lead to up-regulation of angiotensin Ⅱ production, inflammatory changes and apoptosis of PTECs[118]. Similarly, the mesangial cell derived TNFα is known to activate the tubular cells inducing pro-inflammatory mediators, thus establishing an IgAs specific glomerular-tubular cross-talk[119]. There is also convincing in vitro evidence that the filtered mesangial cell-derived mediators also may determine a proinflammatory and profibrotic transformation of PTEC[118-121]. As a consequence, an IgA specific pathogenetic effects might exist, which further accelerate the progressive lost of renal function. In addition, a recent study documents that[122] IgAN might be associated to the Epithelial-mesenchimal

transition and the apoptosis of renal tubular epithelial cells favoring the renal scarring.

CONCLUSION

Figure 5 summarizes the four steps along which the IgAN pathogenesis develops. Every step is far to be completely understood. From one side several questions remain to be answered, from the other side new disease specific therapeutic approaches might be opened.

The first step is the presence in circulation of elevated levels of Gd-IgA1. This step is under the control of several putative genetic factors. Still opened questions are whether the IgA under-glycosylation defect is genetically or environmentally generated and whether there is an abnormal plasma cell mis-homing from mucosal to systemic areas.

Second step is represented by the production of auto antibodies against Gd-IgA1. GWAS has identified the possible role of MHC-Ⅱ loci involved either in the process of antigen elaboration or in the antibody response. Open questions at this regard are whether a molecular mimicry is triggered by infections and which is the role of Toll-like receptors and their polymorphisms. In addition, is not clear whether a somatic mutation genetically determined for the IgG heavy chains structure does exist.

The third step is the production of pathogenic immune complexes containing IgA and their following localization on the mesangium. Open questions are the exact composition of the immune complexes and whether there is a circulating immune complexes deposition or the Gd-IgA1 are already present in the mesangium as a lanthanic deposition followed by binding of auto antibodies.

The fourth step is represented by the renal injury IgA induced and caused by the mesangial IC deposition. The role of podocyte injury in determining the renal lesions is far to be clarified and similarly the tubulointerstitial scarring pathogenesis seems to be peculiar of IgAN, but still not completely clarified.

REFERENCES

1 **Wyatt RJ**, Julian BA. IgA nephropathy. *N Engl J Med* 2013; **368**: 2402-2414 [PMID: 23782179 DOI: 10.1056/NEJMra1206793]

2 **Floege J**, Moura IC, Daha MR. New insights into the pathogenesis of IgA nephropathy. *Semin Immunopathol* 2014; **36**: 431-442 [PMID: 24442210 DOI: 10.1007/s00281-013-0411-7]

3 **Glassock RJ**. The pathogenesis of IgA nephropathy. *Curr Opin Nephrol Hypertens* 2011; **20**: 153-160 [PMID: 21301336 DOI: 10.1097/MNH.0b013e3283436f5c]

4 **Briganti EM**, Dowling J, Finlay M, Hill PA, Jones CL, Kincaid-Smith PS, Sinclair R, McNeil JJ, Atkins RC. The incidence of biopsy-proven glomerulonephritis in Australia. *Nephrol Dial Transplant* 2001; **16**: 1364-1367 [PMID: 11427626 DOI: 10.1093/ndt/16.7.1364]

5 **McGrogan A**, Franssen CF, de Vries CS. The incidence of primary glomerulonephritis worldwide: a systematic review of the literature. *Nephrol Dial Transplant* 2011; **26**: 414-430 [PMID: 21068142 DOI: 10.1093/ndt/gfq665]

6 **Julian BA**, Wyatt RJ, Waldo FB, Koopman WJ, Jackson S, Schrohenloher RE, Galla JH, Mestecky J, Czerkinsky C. Immunological studies of IgA nephropathy: familial and racial aspects. *Adv Exp Med Biol* 1987; **216B**: 1489-1498 [PMID: 3425441]

7 **Kiryluk K**, Novak J. The genetics and immunobiology of IgA nephropathy. *J Clin Invest* 2014; **124**: 2325-2332 [PMID: 24892706 DOI: 10.1172/JCI74475]

8 **Novak J**, Rizk D, Takahashi K, Zhang X, Bian C, Ueda H, Ueda Y, Reily C, Lai L, Hao, C, Novak L, Huang ZQ, Renfrow MB, Suzuki H, Juliam BA. New insights into the pathogenesis of IgA nephropathy. *Kidney Dis* 2015; **1**: 8-18 [DOI: 10.1159/000382134]

9 **Berthoux F**, Mohey H, Laurent B, Mariat C, Afiani A, Thibaudin L. Predicting the risk for dialysis or death in IgA nephropathy. *J Am Soc Nephrol* 2011; **22**: 752-761 [PMID: 21258035 DOI: 10.1681/ASN.2010040355]

10 **Bonnet F**, Deprele C, Sassolas A, Moulin P, Alamartine E, Berthezène F, Berthoux F. Excessive body weight as a new independent risk factor for clinical and pathological progression in primary IgA nephritis. *Am J Kidney Dis* 2001; **37**: 720-727 [PMID: 11273871 DOI: 10.1016/S0272-6386(01)80120-7]

11 **Orth SR**, Stöckmann A, Conradt C, Ritz E, Ferro M, Kreusser W, Piccoli G, Rambausek M, Roccatello D, Schäfer K, Sieberth HG, Wanner C, Watschinger B, Zucchelli P. Smoking as a risk factor for end-stage renal failure in men with primary renal disease. *Kidney Int* 1998; **54**: 926-931 [PMID: 9734618 DOI: 10.1046/j.1523-1755.1998.00067.x]

12 **Waldherr R**, Rambausek M, Duncker WD, Ritz E. Frequency of mesangial IgA deposits in a non-selected autopsy series. *Nephrol Dial Transplant* 1989; **4**: 943-946 [PMID: 2516884]

13 **Suzuki K**, Honda K, Tanabe K, Toma H, Nihei H, Yamaguchi Y. Incidence of latent mesangial IgA deposition in renal allograft donors in Japan. *Kidney Int* 2003; **63**: 2286-2294 [PMID: 12753320 DOI: 10.1046/j.1523-1755.63.6s.2.x]

14 **Szeto CC**, Lai FM, To KF, Wong TY, Chow KM, Choi PC, Lui SF, Li PK. The natural history of immunoglobulin a nephropathy among patients with hematuria and minimal proteinuria. *Am J Med* 2001; **110**: 434-437 [PMID: 11331053 DOI: 10.1016/S0002-9343(01)00659-3]

15 **Gutiérrez E**, Zamora I, Ballarín JA, Arce Y, Jiménez S, Quereda C, Olea T, Martínez-Ara J, Segarra A, Bernis C, García A, Goicoechea M, García de Vinuesa S, Rojas-Rivera J, Praga M. Long-term outcomes of IgA nephropathy presenting with minimal or no proteinuria. *J Am Soc Nephrol* 2012; **23**: 1753-1760 [PMID: 22956820 DOI: 10.1681/ASN.2012010063]

16 **Floege J**. Recurrent IgA nephropathy after renal transplantation. *Semin Nephrol* 2004; **24**: 287-291 [PMID: 15156532 DOI: 10.1016/j.semnephrol.2004.01.008]

17 **Berger J**, Yaneva H, Nabarra B, Barbanel C. Recurrence of mesangial deposition of IgA after renal transplantation. *Kidney Int* 1975; **7**: 232-241 [PMID: 1095808]

18 **Suzuki H**, Kiryluk K, Novak J, Moldoveanu Z, Herr AB, Renfrow MB, Wyatt RJ, Scolari F, Mestecky J, Gharavi AG, Julian BA. The pathophysiology of IgA nephropathy. *J Am Soc Nephrol* 2011; **22**: 1795-1803 [PMID: 21949093 DOI: 10.1681/ASN.2011050464]

19 **Gharavi AG**, Kiryluk K, Choi M, Li Y, Hou P, Xie J, Sanna-Cherchi S, Men CJ, Julian BA, Wyatt RJ, Novak J, He JC, Wang H, Lv J, Zhu L, Wang W, Wang Z, Yasuno K, Gunel M, Mane S, Umlauf S, Tikhonova I, Beerman I, Savoldi S, Magistroni R, Ghiggeri GM, Bodria M, Lugani F, Ravani P, Ponticelli C, Allegri L, Boscutti G, Frasca G, Amore A, Peruzzi L, Coppo R, Izzi C, Viola BF, Prati E, Salvadori M, Mignani R, Gesualdo L, Bertinetto F, Mesiano P, Amoroso A, Scolari F, Chen N, Zhang H, Lifton RP. Genome-wide association study identifies susceptibility loci for IgA nephropathy. *Nat Genet* 2011; **43**: 321-327 [PMID: 21399633 DOI: 10.1038/ng.787]

20 **Wellcome Trust Case Control Consortium**. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* 2007; **447**: 661-678 [PMID: 17554300 DOI: 10.1038/nature05911]

21 **Radstake TR**, Gorlova O, Rueda B, Martin JE, Alizadeh BZ,

Palomino-Morales R, Coenen MJ, Vonk MC, Voskuyl AE, Schuerwegh AJ, Broen JC, van Riel PL, van 't Slot R, Italiaander A, Ophoff RA, Riemekasten G, Hunzelmann N, Simeon CP, Ortego-Centeno N, González-Gay MA, González-Escribano MF, Airo P, van Laar J, Herrick A, Worthington J, Hesselstrand R, Smith V, de Keyser F, Houssiau F, Chee MM, Madhok R, Shiels P, Westhovens R, Kreuter A, Kiener H, de Baere E, Witte T, Padykov L, Klareskog L, Beretta L, Scorza R, Lie BA, Hoffmann-Vold AM, Carreira P, Varga J, Hinchcliff M, Gregersen PK, Lee AT, Ying J, Han Y, Weng SF, Amos CI, Wigley FM, Hummers L, Nelson JL, Agarwal SK, Assassi S, Gourh P, Tan FK, Koeleman BP, Arnett FC, Martin J, Mayes MD. Genome-wide association study of systemic sclerosis identifies CD247 as a new susceptibility locus. *Nat Genet* 2010; **42**: 426-429 [PMID: 20383147 DOI: 10.1038/ng.565]

22 **Petukhova L**, Duvic M, Hordinsky M, Norris D, Price V, Shimomura Y, Kim H, Singh P, Lee A, Chen WV, Meyer KC, Paus R, Jahoda CA, Amos CI, Gregersen PK, Christiano AM. Genome-wide association study in alopecia areata implicates both innate and adaptive immunity. *Nature* 2010; **466**: 113-117 [PMID: 20596022 DOI: 10.1038/nature09114]

23 **Chu X**, Pan CM, Zhao SX, Liang J, Gao GQ, Zhang XM, Yuan GY, Li CG, Xue LQ, Shen M, Liu W, Xie F, Yang SY, Wang HF, Shi JY, Sun WW, Du WH, Zuo CL, Shi JX, Liu BL, Guo CC, Zhan M, Gu ZH, Zhang XN, Sun F, Wang ZQ, Song ZY, Zou CY, Sun WH, Guo T, Cao HM, Ma JH, Han B, Li P, Jiang H, Huang QH, Liang L, Liu LB, Chen G, Su Q, Peng YD, Zhao JJ, Ning G, Chen Z, Chen JL, Chen SJ, Huang W, Song HD. A genome-wide association study identifies two new risk loci for Graves' disease. *Nat Genet* 2011; **43**: 897-901 [PMID: 21841780 DOI: 10.1038/ng.898]

24 **Ferreira RC**, Pan-Hammarström Q, Graham RR, Gateva V, Fontán G, Lee AT, Ortmann W, Urcelay E, Fernández-Arquero M, Núñez C, Jorgensen G, Ludviksson BR, Koskinen S, Haimila K, Clark HF, Klareskog L, Gregersen PK, Behrens TW, Hammarström L. Association of IFIH1 and other autoimmunity risk alleles with selective IgA deficiency. *Nat Genet* 2010; **42**: 777-780 [PMID: 20694011 DOI: 10.1038/ng.644]

25 **Yang W**, Tang H, Zhang Y, Tang X, Zhang J, Sun L, Yang J, Cui Y, Zhang L, Hirankarn N, Cheng H, Pan HF, Gao J, Lee TL, Sheng Y, Lau CS, Li Y, Chan TM, Yin X, Ying D, Lu Q, Leung AM, Zuo X, Chen X, Tong KL, Zhou F, Diao Q, Tse NK, Xie H, Mok CC, Hao F, Wong SN, Shi B, Lee KW, Hui Y, Ho MH, Liang B, Lee PP, Cui H, Guo Q, Chung BH, Pu X, Liu Q, Zhang X, Zhang C, Chong CY, Fang H, Wong RW, Sun Y, Mok MY, Li XP, Avihingsanon Y, Zhai Z, Rianthavorn P, Deekajorndej T, Suphapeetiporn K, Gao F, Shotelersuk V, Kang X, Ying SK, Zhang L, Wong WH, Zhu D, Fung SK, Zeng F, Lai WM, Wong CM, Ng IO, Garcia-Barceló MM, Cherny SS, Shen N, Tam PK, Sham PC, Ye DQ, Yang S, Zhang X, Lau YL. Meta-analysis followed by replication identifies loci in or near CDKN1B, TET3, CD80, DRAM1, and ARID5B as associated with systemic lupus erythematosus in Asians. *Am J Hum Genet* 2013; **92**: 41-51 [PMID: 23273568 DOI: 10.1016/j.ajhg.2012.11.018]

26 **Hafler DA**, Compston A, Sawcer S, Lander ES, Daly MJ, De Jager PL, de Bakker PI, Gabriel SB, Mirel DB, Ivinson AJ, Pericak-Vance MA, Gregory SG, Rioux JD, McCauley JL, Haines JL, Barcellos LF, Cree B, Oksenberg JR, Hauser SL. Risk alleles for multiple sclerosis identified by a genomewide study. *N Engl J Med* 2007; **357**: 851-862 [PMID: 17660530 DOI: 10.1056/NEJMoa073493]

27 **Okada Y**, Yamazaki K, Umeno J, Takahashi A, Kumasaka N, Ashikawa K, Aoi T, Takazoe M, Matsui T, Hirano A, Matsumoto T, Kamatani N, Nakamura Y, Yamamoto K, Kubo M. HLA-Cw*1202-B*5201-DRB1*1502 haplotype increases risk for ulcerative colitis but reduces risk for Crohn's disease. *Gastroenterology* 2011; **141**: 864-871.e1-5 [PMID: 21699788 DOI: 10.1053/j.gastro.2011.05.048]

28 **Béné MC**, Faure GC. Mesangial IgA in IgA nephropathy arises from the mucosa. *Am J Kidney Dis* 1988; **12**: 406-409 [PMID: 3055966]

29 **Stein JV**, López-Fraga M, Elustondo FA, Carvalho-Pinto CE, Rodríguez D, Gómez-Caro R, De Jong J, Martínez-A C, Medema JP, Hahne M. APRIL modulates B and T cell immunity. *J Clin Invest* 2002; **109**: 1587-1598 [PMID: 12070306 DOI: 10.1172/JCI200215034]

30 **He B**, Xu W, Santini PA, Polydorides AD, Chiu A, Estrella J, Shan M, Chadburn A, Villanacci V, Plebani A, Knowles DM, Rescigno M, Cerutti A. Intestinal bacteria trigger T cell-independent immunoglobulin A(2) class switching by inducing epithelial-cell secretion of the cytokine APRIL. *Immunity* 2007; **26**: 812-826 [PMID: 17570691]

31 **McCarthy DD**, Kujawa J, Wilson C, Papandile A, Poreci U, Porfilio EA, Ward L, Lawson MA, Macpherson AJ, McCoy KD, Pei Y, Novak L, Lee JY, Julian BA, Novak J, Ranger A, Gommerman JL, Browning JL. Mice overexpressing BAFF develop a commensal flora-dependent, IgA-associated nephropathy. *J Clin Invest* 2011; **121**: 3991-4002 [PMID: 21881212 DOI: 10.1172/JCI45563]

32 **Feehally J**, Farrall M, Boland A, Gale DP, Gut I, Heath S, Kumar A, Peden JF, Maxwell PH, Morris DL, Padmanabhan S, Vyse TJ, Zawadzka A, Rees AJ, Lathrop M, Ratcliffe PJ. HLA has strongest association with IgA nephropathy in genome-wide analysis. *J Am Soc Nephrol* 2010; **21**: 1791-1797 [PMID: 20595679 DOI: 10.1681/ASN.2010010076]

33 **Rockman SP**, Demmler K, Roczo N, Cosgriff A, Phillips WA, Thomas RJ, Whitehead RH. Expression of interleukin-6, leukemia inhibitory factor and their receptors by colonic epithelium and pericryptal fibroblasts. *J Gastroenterol Hepatol* 2001; **16**: 991-1000 [PMID: 11595063 DOI: 10.1046/j.1440-1746.2001.02588.x]

34 **Guimbaud R**, Abitbol V, Bertrand V, Quartier G, Chauvelot-Moachon L, Giroud J, Couturier D, Chaussade DC. Leukemia inhibitory factor involvement in human ulcerative colitis and its potential role in malignant course. *Eur Cytokine Netw* 1998; **9**: 607-612 [PMID: 9889404]

35 **Lehrer RI**, Lu W. α-Defensins in human innate immunity. *Immunol Rev* 2012; **245**: 84-112 [PMID: 22168415 DOI: 10.1111/j.1600-065X.2011.01082.x]

36 **Goicoechea de Jorge E**, Caesar JJ, Malik TH, Patel M, Colledge M, Johnson S, Hakobyan S, Morgan BP, Harris CL, Pickering MC, Lea SM. Dimerization of complement factor H-related proteins modulates complement activation in vivo. *Proc Natl Acad Sci USA* 2013; **110**: 4685-4690 [PMID: 23487775 DOI: 10.1073/pnas.1219260110]

37 **Zhu L**, Zhai YL, Wang FM, Hou P, Lv JC, Xu DM, Shi SF, Liu LJ, Yu F, Zhao MH, Novak J, Gharavi AG, Zhang H. Variants in Complement Factor H and Complement Factor H-Related Protein Genes, CFHR3 and CFHR1, Affect Complement Activation in IgA Nephropathy. *J Am Soc Nephrol* 2015; **26**: 1195-1204 [PMID: 25205734 DOI: 10.1681/ASN.2014010096]

38 **Kiryluk K**, Li Y, Scolari F, Sanna-Cherchi S, Choi M, Verbitsky M, Fasel D, Lata S, Prakash S, Shapiro S, Fischman C, Snyder HJ, Appel G, Izzi C, Viola BF, Dallera N, Del Vecchio L, Barlassina C, Salvi E, Bertinetto FE, Amoroso A, Savoldi S, Rocchietti M, Amore A, Peruzzi L, Coppo R, Salvadori M, Ravani P, Magistroni R, Ghiggeri GM, Caridi G, Bodria M, Lugani F, Allegri L, Delsante M, Maiorana M, Magnano A, Frasca G, Boer E, Boscutti G, Ponticelli C, Mignani R, Marcantoni C, Di Landro D, Santoro D, Pani A, Polci R, Feriozzi S, Chicca S, Galliani M, Gigante M, Gesualdo L, Zamboli P, Battaglia GG, Garozzo M, Maixnerová D, Tesar V, Eitner F, Rauen T, Floege J, Kovacs T, Nagy J, Mucha K, Pączek L, Zaniew M, Mizerska-Wasiak M, Roszkowska-Blaim M, Pawlaczyk K, Gale D, Barratt J, Thibaudin L, Berthoux F, Canaud G, Boland A, Metzger M, Panzer U, Suzuki H, Goto S, Narita I, Caliskan Y, Xie J, Hou P, Chen N, Zhang H, Wyatt RJ, Novak J, Julian BA, Feehally J, Stengel B, Cusi D, Lifton RP, Gharavi AG. Discovery of new risk loci for IgA nephropathy implicates genes involved in immunity against intestinal pathogens. *Nat Genet* 2014; **46**: 1187-1196 [PMID: 25305756 DOI: 10.1038/ng.3118]

39 **Renfrow MB**, Mackay CL, Chalmers MJ, Julian BA, Mestecky J, Kilian M, Poulsen K, Emmett MR, Marshall AG, Novak J. Analysis of O-glycan heterogeneity in IgA1 myeloma proteins by Fourier transform ion cyclotron resonance mass spectrometry: implications for IgA nephropathy. *Anal Bioanal Chem* 2007; **389**: 1397-1407

[PMID: 17712550]
40 **Takahashi K**, Smith AD, Poulsen K, Kilian M, Julian BA, Mestecky J, Novak J, Renfrow MB. Naturally occurring structural isomers in serum IgA1 o-glycosylation. *J Proteome Res* 2012; **11**: 692-702 [PMID: 22067045 DOI: 10.1021/pr200608q]
41 **de Wolff JF**, Dickinson SJ, Smith AC, Molyneux K, Feehally J, Simon A, Barratt J. Abnormal IgD and IgA1 O-glycosylation in hyperimmunoglobulinaemia D and periodic fever syndrome. *Clin Exp Med* 2009; **9**: 291-296 [PMID: 19543954 DOI: 10.1681/ASN.2005101115]
42 **Yamada K**, Kobayashi N, Ikeda T, Suzuki Y, Tsuge T, Horikoshi S, Emancipator SN, Tomino Y. Down-regulation of core 1 beta1,3-galactosyltransferase and Cosmc by Th2 cytokine alters O-glycosylation of IgA1. *Nephrol Dial Transplant* 2010; **25**: 3890-3897 [PMID: 20551088 DOI: 10.1093/ndt/gfq325]
43 **Kobayashi I**, Nogaki F, Kusano H, Ono T, Miyawaki S, Yoshida H, Muso E. Interleukin-12 alters the physicochemical characteristics of serum and glomerular IgA and modifies glycosylation in a ddY mouse strain having high IgA levels. *Nephrol Dial Transplant* 2002; **17**: 2108-2116 [PMID: 12454220 DOI: 10.1093/ndt/17.12.2108]
44 **Chintalacharuvu SR**, Emancipator SN. The glycosylation of IgA produced by murine B cells is altered by Th2 cytokines. *J Immunol* 1997; **159**: 2327-2333 [PMID: 9278322]
45 **Moore JS**, Kulhavy R, Tomana M, Moldoveanu Z, Suzuki H, Brown R, Hall S, Kilian M, Poulsen K, Mestecky J, Julian BA, Novak J. Reactivities of N-acetylgalactosamine-specific lectins with human IgA1 proteins. *Mol Immunol* 2007; **44**: 2598-2604 [PMID: 17275907 DOI: 10.1016/j.molimm.2006.12.011]
46 **Novak J**, Tomana M, Kilian M, Coward L, Kulhavy R, Barnes S, Mestecky J. Heterogeneity of O-glycosylation in the hinge region of human IgA1. *Mol Immunol* 2000; **37**: 1047-1056 [PMID: 11399322 DOI: 10.1016/S0161-5890(01)00019-0]
47 **Woof JM**, Russell MW. Structure and function relationships in IgA. *Mucosal Immunol* 2011; **4**: 590-597 [PMID: 21937984 DOI: 10.1038/mi.2011.39]
48 **Smith AC**, Molyneux K, Feehally J, Barratt J. O-glycosylation of serum IgA1 antibodies against mucosal and systemic antigens in IgA nephropathy. *J Am Soc Nephrol* 2006; **17**: 3520-3528 [PMID: 17093066 DOI: 10.1681/ASN.2006060658]
49 **Novak J**, Julian BA, Tomana M, Mestecky J. IgA glycosylation and IgA immune complexes in the pathogenesis of IgA nephropathy. *Semin Nephrol* 2008; **28**: 78-87 [PMID: 18222349 DOI: 10.1016/j.semnephrol.2007.10.009]
50 **van den Wall Bake AW**, Daha MR, Haaijman JJ, Radl J, van der Ark A, van Es LA. Elevated production of polymeric and monomeric IgA1 by the bone marrow in IgA nephropathy. *Kidney Int* 1989; **35**: 1400-1404 [PMID: 2770118]
51 **Barratt J**, Bailey EM, Buck KS, Mailley J, Moayyedi P, Feehally J, Turney JH, Crabtree JE, Allen AC. Exaggerated systemic antibody response to mucosal Helicobacter pylori infection in IgA nephropathy. *Am J Kidney Dis* 1999; **33**: 1049-1057 [PMID: 10352192 DOI: 10.1016/S0272-6386(99)70141-1]
52 **Barratt J**, Feehally J. Primary IgA nephropathy: new insights into pathogenesis. *Semin Nephrol* 2011; **31**: 349-360 [PMID: 21839368 DOI: 10.1016/j.semnephrol.2011.06.006]
53 **Coppo R**, Camilla R, Amore A, Peruzzi L, Daprà V, Loiacono E, Vatrano S, Rollino C, Sepe V, Rampino T, Dal Canton A. Toll-like receptor 4 expression is increased in circulating mononuclear cells of patients with immunoglobulin A nephropathy. *Clin Exp Immunol* 2010; **159**: 73-81 [PMID: 19891659 DOI: 10.1111/j.1365-2249]
54 **Suzuki H**, Suzuki Y, Narita I, Aizawa M, Kihara M, Yamanaka T, Kanou T, Tsukaguchi H, Novak J, Horikoshi S, Tomino Y. Toll-like receptor 9 affects severity of IgA nephropathy. *J Am Soc Nephrol* 2008; **19**: 2384-2395 [PMID: 18776126 DOI: 10.1681/ASN.2007121311]
55 **Hiki Y**, Odani H, Takahashi M, Yasuda Y, Nishimoto A, Iwase H, Shinzato T, Kobayashi Y, Maeda K. Mass spectrometry proves under-O-glycosylation of glomerular IgA1 in IgA nephropathy. *Kidney Int* 2001; **59**: 1077-1085 [PMID: 11231363 DOI: 10.1046/j.1523-1755.2001.0590031077.x]
56 **Allen AC**, Bailey EM, Brenchley PE, Buck KS, Barratt J, Feehally J. Mesangial IgA1 in IgA nephropathy exhibits aberrant O-glycosylation: observations in three patients. *Kidney Int* 2001; **60**: 969-973 [PMID: 11532091 DOI: 10.1046/j.1523-1755.2001.060003969.x]
57 **Gharavi AG**, Moldoveanu Z, Wyatt RJ, Barker CV, Woodford SY, Lifton RP, Mestecky J, Novak J, Julian BA. Aberrant IgA1 glycosylation is inherited in familial and sporadic IgA nephropathy. *J Am Soc Nephrol* 2008; **19**: 1008-1014 [PMID: 18272841 DOI: 10.1681/ASN.2007091052]
58 **Zhao N**, Hou P, Lv J, Moldoveanu Z, Li Y, Kiryluk K, Gharavi AG, Novak J, Zhang H. The level of galactose-deficient IgA1 in the sera of patients with IgA nephropathy is associated with disease progression. *Kidney Int* 2012; **82**: 790-796 [PMID: 22673888 DOI: 10.1038/ki.2012.197]
59 **Berthoux F**, Suzuki H, Thibaudin L, Yanagawa H, Maillard N, Mariat C, Tomino Y, Julian BA, Novak J. Autoantibodies targeting galactose-deficient IgA1 associate with progression of IgA nephropathy. *J Am Soc Nephrol* 2012; **23**: 1579-1587 [PMID: 22904352 DOI: 10.1681/ASN.2012010053]
60 **Monteiro RC**, Moura IC, Launay P, Tsuge T, Haddad E, Benhamou M, Cooper MD, Arcos-Fajardo M. Pathogenic significance of IgA receptor interactions in IgA nephropathy. *Trends Mol Med* 2002; **8**: 464-468 [PMID: 12383768 DOI: 10.1016/S1471-4914(02)02405-X]
61 **Tomana M**, Novak J, Julian BA, Matousovic K, Konecny K, Mestecky J. Circulating immune complexes in IgA nephropathy consist of IgA1 with galactose-deficient hinge region and antiglycan antibodies. *J Clin Invest* 1999; **104**: 73-81 [PMID: 10393701]
62 **Suzuki H**, Fan R, Zhang Z, Brown R, Hall S, Julian BA, Chatham WW, Suzuki Y, Wyatt RJ, Moldoveanu Z, Lee JY, Robinson J, Tomana M, Tomino Y, Mestecky J, Novak J. Aberrantly glycosylated IgA1 in IgA nephropathy patients is recognized by IgG antibodies with restricted heterogeneity. *J Clin Invest* 2009; **119**: 1668-1677 [PMID: 19478457 DOI: 10.1172/JCI38468]
63 **Harper SJ**, Allen AC, Layward L, Hattersley J, Veitch PS, Feehally J. Increased immunoglobulin A and immunoglobulin A1 cells in bone marrow trephine biopsy specimens in immunoglobulin A nephropathy. *Am J Kidney Dis* 1994; **24**: 888-892 [PMID: 7985665]
64 **Harper SJ**, Feehally J. The pathogenic role of immunoglobulin A polymers in immunoglobulin A nephropathy. *Nephron* 1993; **65**: 337-345 [PMID: 8289980]
65 **Harper SJ**, Pringle JH, Gillies A, Allen AC, Layward L, Feehally J, Lauder I. Simultaneous in situ hybridisation of native mRNA and immunoglobulin detection by conventional immunofluorescence in paraffin wax embedded sections. *J Clin Pathol* 1992; **45**: 114-119 [PMID: 1541690]
66 **Barratt J**, Eitner F, Feehally J, Floege J. Immune complex formation in IgA nephropathy: a case of the 'right' antibodies in the 'wrong' place at the 'wrong' time? *Nephrol Dial Transplant* 2009; **24**: 3620-3623 [PMID: 19729461 DOI: 10.1093/ndt/gfp441]
67 **Barratt J**, Smith AC, Molyneux K, Feehally J. Immunopathogenesis of IgAN. *Semin Immunopathol* 2007; **29**: 427-443 [PMID: 17851660 DOI: 10.1007/s00281-007-0089-9]
68 **Agmon-Levin N**, Blank M, Paz Z, Shoenfeld Y. Molecular mimicry in systemic lupus erythematosus. *Lupus* 2009; **18**: 1181-1185 [PMID: 19880565 DOI: 10.1177/0961203309346653]
69 **Bellur SS**, Troyanov S, Cook HT, Roberts IS. Immunostaining findings in IgA nephropathy: correlation with histology and clinical outcome in the Oxford classification patient cohort. *Nephrol Dial Transplant* 2011; **26**: 2533-2536 [PMID: 21273233 DOI: 10.1093/ndt/gfq812]
70 **Mestecky J**, Novak J, Julian BA, Tomana M Pathogenetic potential of galactose-deficient IgA1 in IgA nephropathy. *Nephrology* 2002; **7**: S92-S99
71 **Mestecky J**, Tomana M, Moldoveanu Z, Julian BA, Suzuki H, Matousovic K, Renfrow MB, Novak L, Wyatt RJ, Novak J. Role of aberrant glycosylation of IgA1 molecules in the pathogenesis of IgA nephropathy. *Kidney Blood Press Res* 2008; **31**: 29-37 [PMID: 18182777 DOI: 10.1159/000112922]
72 Yanagihara T, Brown R, Hall S, Moldoveanu Z, Goepfert A,

Tomana M, Julian BA, Mestecky J, Novak J. In vitro-generated immune complexes containing galactose-deficient IgA1 stimulate proliferation of mesangial cells. *Results Immunol* 2012; **2**: 166-172 [PMID: 24052934 DOI: 10.1016/j.rinim.2012.08.002]

73 **Novak J**, Raskova Kafkova L, Suzuki H, Tomana M, Matousovic K, Brown R, Hall S, Sanders JT, Eison TM, Moldoveanu Z, Novak L, Novak Z, Mayne R, Julian BA, Mestecky J, Wyatt RJ. IgA1 immune complexes from pediatric patients with IgA nephropathy activate cultured human mesangial cells. *Nephrol Dial Transplant* 2011; **26**: 3451-3457 [PMID: 21828345 DOI: 10.1093/ndt/gfr448]

74 **Novak J**, Tomana M, Matousovic K, Brown R, Hall S, Novak L, Julian BA, Wyatt RJ, Mestecky J. IgA1-containing immune complexes in IgA nephropathy differentially affect proliferation of mesangial cells. *Kidney Int* 2005; **67**: 504-513 [PMID: 15673298 DOI: 10.1111/j.1523-1755.2005.67107.x]

75 **Julian BA**, Novak J. IgA nephropathy: an update. *Curr Opin Nephrol Hypertens* 2004; **13**: 171-179 [PMID: 15202611]

76 **Glassock RJ**. Future prospects for IgA nephropathy. In: Lai KN, editor. Recent advances in IgA nephropathy. Singapore: World Scientific, 2009: 403-412

77 **Glassock RJ**. Analyzing antibody activity in IgA nephropathy. *J Clin Invest* 2009; **119**: 1450-1452 [PMID: 19504718 DOI: 10.1172/JCI39189]

78 **Monteiro RC**, Van De Winkel JG. IgA Fc receptors. *Annu Rev Immunol* 2003; **21**: 177-204 [PMID: 12524384 DOI: 10.1146/annurev.immunol.21.120601.141011]

79 **Baumann J**, Park CG, Mantis NJ. Recognition of secretory IgA by DC-SIGN: implications for immune surveillance in the intestine. *Immunol Lett* 2010; **131**: 59-66 [PMID: 20362001 DOI: 10.1016/j.imlet.2010.03.005]

80 **Diana J**, Moura IC, Vaugier C, Gestin A, Tissandie E, Beaudoin L, Corthésy B, Hocini H, Lehuen A, Monteiro RC. Secretory IgA induces tolerogenic dendritic cells through SIGNR1 dampening autoimmunity in mice. *J Immunol* 2013; **191**: 2335-2343 [PMID: 23926325 DOI: 10.4049/jimmunol.1300864]

81 **Leung JC**, Tsang AW, Chan DT, Lai KN. Absence of CD89, polymeric immunoglobulin receptor, and asialoglycoprotein receptor on human mesangial cells. *J Am Soc Nephrol* 2000; **11**: 241-249 [PMID: 10665931]

82 **McDonald KJ**, Cameron AJ, Allen JM, Jardine AG. Expression of Fc alpha/mu receptor by human mesangial cells: a candidate receptor for immune complex deposition in IgA nephropathy. *Biochem Biophys Res Commun* 2002; **290**: 438-442 [PMID: 11779189 DOI: 10.1006/bbrc.2001.6218]

83 **Moura IC**, Benhamou M, Launay P, Vrtovsnik F, Blank U, Monteiro RC. The glomerular response to IgA deposition in IgA nephropathy. *Semin Nephrol* 2008; **28**: 88-95 [PMID: 18222350 DOI: 10.1016/j.semnephrol.2007.10.010]

84 **Moura IC**, Centelles MN, Arcos-Fajardo M, Malheiros DM, Collawn JF, Cooper MD, Monteiro RC. Identification of the transferrin receptor as a novel immunoglobulin (Ig)A1 receptor and its enhanced expression on mesangial cells in IgA nephropathy. *J Exp Med* 2001; **194**: 417-425 [PMID: 11514599 DOI: 10.1084/jem.194.4.417]

85 **Haddad E**, Moura IC, Arcos-Fajardo M, Macher MA, Baudouin V, Alberti C, Loirat C, Monteiro RC, Peuchmaur M. Enhanced expression of the CD71 mesangial IgA1 receptor in Berger disease and Henoch-Schönlein nephritis: association between CD71 expression and IgA deposits. *J Am Soc Nephrol* 2003; **14**: 327-337 [PMID: 12538733 DOI: 10.1097/01.ASN.0000046961.04917.83]

86 **Moura IC**, Arcos-Fajardo M, Sadaka C, Leroy V, Benhamou M, Novak J, Vrtovsnik F, Haddad E, Chintalacharuvu KR, Monteiro RC. Glycosylation and size of IgA1 are essential for interaction with mesangial transferrin receptor in IgA nephropathy. *J Am Soc Nephrol* 2004; **15**: 622-634 [PMID: 14978164 DOI: 10.1097/01.ASN.0000115401.07980.0C]

87 **Monteiro RC**. Pathogenic role of IgA receptors in IgA nephropathy. *Contrib Nephrol* 2007; **157**: 64-69 [PMID: 17495439 DOI: 10.1159/0000102306]

88 **Berthelot L**, Papista C, Maciel TT, Biarnes-Pelicot M, Tissandie E, Wang PH, Tamouza H, Jamin A, Bex-Coudrat J, Gestin A, Boumediene A, Arcos-Fajardo M, England P, Pillebout E, Walker F, Daugas E, Vrtosvnik F, Flamant M, Benhamou M, Cogné M, Moura IC, Monteiro RC. Transglutaminase is essential for IgA nephropathy development acting through IgA receptors. *J Exp Med* 2012; **209**: 793-806 [PMID: 22451718 DOI: 10.1084/jem.20112005]

89 **Monteiro RC**. The role of IgA and IgA Fc receptors as anti-inflammatory agents. *J Clin Immunol* 2010; **30** Suppl 1: S61-S64 [PMID: 20405182 DOI: 10.1007/s10875-010-9397-2]

90 **Amore A**, Cirina P, Conti G, Brusa P, Peruzzi L, Coppo R. Glycosylation of circulating IgA in patients with IgA nephropathy modulates proliferation and apoptosis of mesangial cells. *J Am Soc Nephrol* 2001; **12**: 1862-1871 [PMID: 11518779]

91 **Amore A**, Conti G, Cirina P, Peruzzi L, Alpa M, Bussolino F, Coppo R. Aberrantly glycosylated IgA molecules downregulate the synthesis and secretion of vascular endothelial growth factor in human mesangial cells. *Am J Kidney Dis* 2000; **36**: 1242-1252 [PMID: 11096049]

92 **Novak J**, Vu HL, Novak L, Julian BA, Mestecky J, Tomana M. Interactions of human mesangial cells with IgA and IgA-containing immune complexes. *Kidney Int* 2002; **62**: 465-475 [PMID: 12110007 DOI: 10.1046/j.1523-1755.2002.00477.x]

93 **Maillard N**, Wyatt RJ, Julian BA, Kiryluk K, Gharavi A, Fremeaux-Bacchi V, Novak J. Current Understanding of the Role of Complement in IgA Nephropathy. *J Am Soc Nephrol* 2015; **26**: 1503-1512 [PMID: 25694468 DOI: 10.1681/ASN.2014101000]

94 **Chen M**, Daha MR, Kallenberg CG. The complement system in systemic autoimmune disease. *J Autoimmun* 2010; **34**: J276-J286 [PMID: 20005073 DOI: 10.1016/j.jaut.2009.11.014]

95 **Roos A**, Rastaldi MP, Calvaresi N, Oortwijn BD, Schlagwein N, van Gijlswijk-Janssen DJ, Stahl GL, Matsushita M, Fujita T, van Kooten C, Daha MR. Glomerular activation of the lectin pathway of complement in IgA nephropathy is associated with more severe renal disease. *J Am Soc Nephrol* 2006; **17**: 1724-1734 [PMID: 16687629 DOI: 10.1681/ASN.2005090923]

96 **Oortwijn BD**, Eijgenraam JW, Rastaldi MP, Roos A, Daha MR, van Kooten C. The role of secretory IgA and complement in IgA nephropathy. *Semin Nephrol* 2008; **28**: 58-65 [PMID: 18222347 DOI: 10.1016/j.semnephrol.2007]

97 **Stangou M**, Alexopoulos E, Pantzaki A, Leonstini M, Memmos D. C5b-9 glomerular deposition and tubular alpha3beta1-integrin expression are implicated in the development of chronic lesions and predict renal function outcome in immunoglobulin A nephropathy. *Scand J Urol Nephrol* 2008; **42**: 373-380 [PMID: 19230171]

98 **Coppo R**, Amore A, Peruzzi L, Vergano L, Camilla R. Innate immunity and IgA nephropathy. *J Nephrol* 2010; **23**: 626-632 [PMID: 20383870]

99 **Qin W**, Zhong X, Fan JM, Zhang YJ, Liu XR, Ma XY. External suppression causes the low expression of the Cosmc gene in IgA nephropathy. *Nephrol Dial Transplant* 2008; **23**: 1608-1614 [PMID: 18202089 DOI: 10.1093/ndt/gfm781]

100 **Eijgenraam JW**, Woltman AM, Kamerling SW, Briere F, de Fijter JW, Daha MR, van Kooten C. Dendritic cells of IgA nephropathy patients have an impaired capacity to induce IgA production in naïve B cells. *Kidney Int* 2005; **68**: 1604-1612 [PMID: 16164637 DOI: 10.1111/j.1523-1755.2005.00572]

101 **Oortwijn BD**, van der Boog PJ, Roos A, van der Geest RN, de Fijter JW, Daha MR, van Kooten C. A pathogenic role for secretory IgA in IgA nephropathy. *Kidney Int* 2006; **69**: 1131-1138 [PMID: 16395264 DOI: 10.1038/sj.ki.5000074]

102 **Leung JC**, Tang SC, Chan LY, Tsang AW, Lan HY, Lai KN. Polymeric IgA increases the synthesis of macrophage migration inhibitory factor by human mesangial cells in IgA nephropathy. *Nephrol Dial Transplant* 2003; **18**: 36-45 [PMID: 12480958 DOI: 10.1093/ndt/18.1.36]

103 **Lai KN**, Tang SC, Guh JY, Chuang TD, Lam MF, Chan LY, Tsang AW, Leung JC. Polymeric IgA1 from patients with IgA nephropathy upregulates transforming growth factor-beta synthesis and signal transduction in human mesangial cells via the renin-angiotensin system. *J Am Soc Nephrol* 2003; **14**: 3127-3137 [PMID: 14638911 DOI: 10.1097/01.ASN.0000095639.56212.BF]

104 **Boor P**, Ostendorf T, Floege J. PDGF and the progression of renal

disease. *Nephrol Dial Transplant* 2014; **29** Suppl 1: i45-i54 [PMID: 24493869 DOI: 10.1093/ndt/gft273]
105 **Lai KN**, Leung JCK. Renin-angiotensin system. In: Lai KN, editor. Recent advances in IgA nephropathy. Singapore: World Scientific, 2009: 289-308
106 **Chan WL**, Leung JC, Chan LY, Tam KY, Tang SC, Lai KN. BMP-7 protects mesangial cells from injury by polymeric IgA. *Kidney Int* 2008; **74**: 1026-1039 [PMID: 18496506 DOI: 10.1038/ki.2008.209]
107 **Gould SE**, Day M, Jones SS, Dorai H. BMP-7 regulates chemokine, cytokine, and hemodynamic gene expression in proximal tubule cells. *Kidney Int* 2002; **61**: 51-60 [PMID: 11786084 DOI: 10.1046/j.1523-1755.2002.00103.x]
108 **Wang S**, Hirschberg R. BMP7 antagonizes TGF-beta -dependent fibrogenesis in mesangial cells. *Am J Physiol Renal Physiol* 2003; **284**: F1006-F1013 [PMID: 12676736 DOI: 10.1152/ajprenal.00382.2002]
109 **Lemley KV**, Lafayette RA, Safai M, Derby G, Blouch K, Squarer A, Myers BD. Podocytopenia and disease severity in IgA nephropathy. *Kidney Int* 2002; **61**: 1475-1485 [PMID: 11918755 DOI: 10.1046/j.1523-1755.2002.00269.x]
110 **Gagliardini E**, Benigni A, Tomasoni S, Abbate M, Kalluri R, Remuzzi G. Targeted downregulation of extracellular nephrin in human IgA nephropathy. *Am J Nephrol* 2003; **23**: 277-286 [PMID: 12853730]
111 **Doublier S**, Ruotsalainen V, Salvidio G, Lupia E, Biancone L, Conaldi PG, Reponen P, Tryggvason K, Camussi G. Nephrin redistribution on podocytes is a potential mechanism for proteinuria in patients with primary acquired nephrotic syndrome. *Am J Pathol* 2001; **158**: 1723-1731 [PMID: 11337370 DOI: 10.1016/S0002-9440(10)64128-4]
112 **Lai KN**, Leung JC, Chan LY, Saleem MA, Mathieson PW, Lai FM, Tang SC. Activation of podocytes by mesangial-derived TNF-alpha: glomerulo-podocytic communication in IgA nephropathy. *Am J Physiol Renal Physiol* 2008; **294**: F945-F955 [PMID: 18256312 DOI: 10.1152/ajprenal.00423.2007]
113 **Wang C**, Ye Z, Peng H, Tang H, Liu X, Chen Z, Yu X, Lou T. Effect of aggregated immunoglobulin A1 from immunoglobulin A nephropathy patients on nephrin expression in podocytes. *Nephrology* (Carlton) 2009; **14**: 213-218 [PMID: 19019169 DOI: 10.1111/j.1440-1797.2008.01025.x]
114 **Zhu L**, Zhang Q, Shi S, Liu L, Lv J, Zhang H. Synergistic effect of mesangial cell-induced CXCL1 and TGF-β1 in promoting podocyte loss in IgA nephropathy. *PLoS One* 2013; **8**: e73425 [PMID: 24023680 DOI: 10.1371/journal.pone.0073425]
115 **Floege J**, van Roeyen C, Boor P, Ostendorf T. The role of PDGF-D in mesangioproliferative glomerulonephritis. *Contrib Nephrol* 2007; **157**: 153-158 [PMID: 17495455]
116 **Floege J**, Ostendorf T. Cytokines and growth factors. In: Lai KN, editor. Recent advances in IgA nephropathy. Singapore: World Scientific, 2009: 289-308
117 **Matousovic K**, Novak J, Yanagihara T, Tomana M, Moldoveanu Z, Kulhavy R, Julian BA, Konecny K, Mestecky J. IgA-containing immune complexes in the urine of IgA nephropathy patients. *Nephrol Dial Transplant* 2006; **21**: 2478-2484 [PMID: 16757497 DOI: 10.1093/ndt/gfl240]
118 **Chan LY**, Leung JC, Tang SC, Choy CB, Lai KN. Tubular expression of angiotensin II receptors and their regulation in IgA nephropathy. *J Am Soc Nephrol* 2005; **16**: 2306-2317 [PMID: 15930094 DOI: 10.1681/ASN.2004121117]
119 **Chan LY**, Leung JC, Tsang AW, Tang SC, Lai KN. Activation of tubular epithelial cells by mesangial-derived TNF-alpha: glomerulotubular communication in IgA nephropathy. *Kidney Int* 2005; **67**: 602-612 [PMID: 15673307 DOI: 10.1111/j.1523-1755.2005.67116.x]
120 **Xiao J**, Leung JC, Chan LY, Guo H, Lai KN. Protective effect of peroxisome proliferator-activated receptor-gamma agonists on activated renal proximal tubular epithelial cells in IgA nephropathy. *Nephrol Dial Transplant* 2009; **24**: 2067-2077 [PMID: 19155534 DOI: 10.1093/ndt/gfn746]
121 **Xiao J**, Leung JC, Chan LY, Tang SC, Lai KN. Crosstalk between peroxisome proliferator-activated receptor-gamma and angiotensin II in renal tubular epithelial cells in IgA nephropathy. *Clin Immunol* 2009; **132**: 266-276 [PMID: 19443277 DOI: 10.1016/j.clim.2009.04.004]
122 **Yao J**, Ke Z, Wang X, Peng F, Li B, Wu R. Epithelial-mesenchymal transition and apoptosis of renal tubular epithelial cells are associated with disease progression in patients with IgA nephropathy. *Mol Med Rep* 2014; **10**: 39-44 [PMID: 24788122 DOI: 10.3892/mmr.2014.2179]

P- Reviewer: Roberto S, Tanaka H, Watanabe T **S- Editor**: Qiu S
L- Editor: A **E- Editor**: Wu HL

World Journal of Nephrology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5527/wjn.v4.i4.468

World J Nephrol 2015 September 6; 4(4): 468-479
ISSN 2220-6124 (online)

REVIEW

Current management of autosomal dominant polycystic kidney disease

Jacob A Akoh

Jacob A Akoh, South West Transplant Centre, Plymouth Hospitals NHS Trust, Derriford Hospital, Plymouth PL6 8DH, United Kingdom

Author contributions: Akoh JA solely contributed to this paper.

Conflict-of-interest statement: The author has no conflict of interest.

Correspondence to: Jacob A Akoh, FRCSEd, FRCS (Gen), Consultant General and Transplant Surgeon, South West Transplant Centre, Plymouth Hospitals NHS Trust, Derriford Hospital, Level 04, Plymouth PL6 8DH, United Kingdom. jacob.akoh@nhs.net
Telephone:: +44-1752-432650
Fax: +44-1752-517576

Received: June 1, 2015
Peer-review started: June 2, 2015
First decision: June 18, 2015
Revised: August 17, 2015
Accepted: August 30, 2015
Article in press: August 31, 2015
Published online: September 6, 2015

Abstract

Autosomal dominant polycystic kidney disease (ADPKD), the most frequent cause of genetic renal disease affecting approximately 4 to 7 million individuals worldwide and accounting for 7%-15% of patients on renal replacement therapy, is a systemic disorder mainly involving the kidney but cysts can also occur in other organs such as the liver, pancreas, arachnoid membrane and seminal vesicles. Though computed tomography and magnetic resonance imaging (MRI) were similar in evaluating 81% of cystic lesions of the kidney, MRI may depict septa, wall thickening or enhancement leading to upgrade in cyst classification that can affect management. A screening strategy for intracranial aneurysms would provide 1.0 additional year of life without neurological disability to a 20-year-old patient with ADPKD and reduce the financial impact on society of the disease. Current treatment strategies include reducing: cyclic adenosine monophosphate levels, cell proliferation and fluid secretion. Several randomised clinical trials (RCT) including mammalian target of rapamycin inhibitors, somatostatin analogues and a vasopressin V2 receptor antagonist have been performed to study the effect of diverse drugs on growth of renal and hepatic cysts, and on deterioration of renal function. Prophylactic native nephrectomy is indicated in patients with a history of cyst infection or recurrent haemorrhage or to those in whom space must be made to implant the graft. The absence of large RCT on various aspects of the disease and its treatment leaves considerable uncertainty and ambiguity in many aspects of ADPKD patient care as it relates to end stage renal disease (ESRD). The outlook of patients with ADPKD is improving and is in fact much better than that for patients in ESRD due to other causes. This review highlights the need for well-structured RCTs as a first step towards trying newer interventions so as to develop updated clinical management guidelines.

Key words: Autosomal dominant polycystic kidney disease; Native nephrectomy; Cyst decortication; Kidney transplantation; Hypertension; Drug therapy; End stage renal disease; Extrarenal manifestatation; Total kidney volume

Core tip: Autosomal dominant polycystic kidney disease

(ADPKD), the most frequent cause of genetic kidney disease affecting approximately 4 to 7 million individuals worldwide (7%-15% of patients on renal replacement therapy), is a systemic disorder mainly involving the kidney but cysts can also occur in other organs such as the liver, pancreas and arachnoid membrane. This paper discusses radiological evaluation of ADPKD, necessity for screening for intracranial aneurysms and current treatment strategies include reducing: cyclic adenosine monophosphate levels, cell proliferation and fluid secretion. It further discusses the role of surgery in managing ADPKD patients and highlights areas of new research.

Akoh JA. Current management of autosomal dominant polycystic kidney disease. *World J Nephrol* 2015; 4(4): 468-479 Available from: URL: http://www.wjgnet.com/2220-6124/full/v4/i4/468.htm DOI: http://dx.doi.org/10.5527/wjn.v4.i4.468

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is a monogenetic disorder characterised by bilateral renal cysts and possibly kidney pain, urinary tract infection, haematuria, nephrolithiasis, hypertension and progressive renal failure due to progressive enlargement of cysts and fibrosis[1,2]. It is a leading cause of end-stage renal disease (ESRD) and the most common inherited kidney disease[3,4]. ADPKD is a systemic disorder mainly involving the kidney but cysts can also occur in other organs such as the liver, pancreas, arachnoid membrane and seminal vesicles[5]. In contrast to ADPKD, autosomal recessive polycystic kidney disease produces kidneys which are hugely enlarged due to multiple cysts, hypertension, and congenital hepatic fibrosis characterised by dilated bile ducts and portal hypertension[6]. Autosomal recessive polycystic kidney disease and other cystic lesions of the kidneys present a different set of challenges and will not be discussed further in this review.

The work of Thong *et al*[3] suggest that the age of diagnosis of ADPKD and mean kidney length can be used to predict ESRD at least 10 years in advance and thus enable patients at higher risk of developing it to be identified early for treatment. The quality of life (QOL) of patients with ADPKD is indirectly linked to the total kidney and liver volume by virtue of its close correlation with abdominal distention that exerts an important influence on QOL. Other associated symptoms of ADPKD such as pain, sleep disturbance, heartburn, fever, gross hematuria and anorexia (though not always correlated with total liver and kidney volumes) affected QOL[7]. Improving these symptoms and reducing abdominal distention can enhance the QOL of patients.

ADPKD remains a therapeutic challenge as effective treatment to retard the growth of kidney and liver cysts has not been achieved despite decades of basic and clinical research[4,8]. The Spanish Working Group on Inherited Kidney Diseases, in the absence of good evidence, only made recommendations relating to management of hypertension, pain, cyst infections and bleeding, extra-renal involvement including polycystic liver disease, intracranial aneurysms, ESRD, and management of children with ADPKD; but none on specific ADPKD therapies[9]. There are no clinical guidelines on management of this common cause of ESRD. The aim of this review is to present a concise account of the current status of managing patients with ADPKD including the surgical options.

EPIDEMIOLOGY

ADPKD is the commonest cause of genetic renal disease affecting approximately 4 to 7 million individuals worldwide and accounting for 7%-11% of patients on renal replacement therapy (RRT) in Europe[5,10-13] and about 10%-15% of patients requiring dialysis in the United States[14].

According to the Danish National Registry on Regular Dialysis and Transplantation, 693 patients with ADPKD reached ESRD between 1990 and 2007. Analysis of the data showed that progression to ESRD increased from 6.45 per million people in 1990-1995 to 7.59 per million people in 2002-2007. In addition, the mean age at onset of ESRD increased by 4.7 years and patient survival improved by 38%[15]. In a study of the Catalan registry (1984-2009), Martínez *et al*[11] found 1586 (7.9%) of 20033 ESRD patients with ADPKD. The survival rate of ADPKD patients on renal replacement therapy was significantly higher than that of non-ADPKD patients. Review of the United States Renal Data System shows that of the 375152 patients initiated on ESRD therapy between 1992 and 1997, 5799 (1.5%) had polycystic kidney disease. As with the Catalan registry, patients with polycystic kidney disease had lower mortality compared to patients with other causes of ESRD[16].

In a retrospective comparison of clinical characteristics of 837 patients with ADPKD between 1961-1990 and 1991-2011, Helal *et al*[17] reported an earlier age of disease diagnosis (29 years *vs* 35 years), lower mean blood pressure (129/82 mmHg *vs* 142/91 mmHg), better estimated glomerular filtration rate (eGFR) (63.6 mL/min *vs* 44.6 mL/min), and more use of renin-angiotensin-aldosterone system (RAAS) inhibitors (42.5% *vs* 13.6%) during the later period.

PATHOLOGICAL CONSIDERATIONS

In 85%-90% of cases, ADPKD results from a mutation in the *PKD1* gene, and the other 10%-15% of cases are accounted for by mutations in *PKD2*. *PKD1* and *PKD2* encode for polycystin-1 and polycystin-2 proteins (polycystin signaling complex) which regulate different signals including 3',5'-cyclic adenosine monophosphate (cAMP), mammalian target of rapamycin (mTOR) and

epidermal growth factor receptor pathways. Abnormal activation of these signals causes an increased cell proliferation which is an important component of this disease[18]. ADPKD is characterized by the progressive development of cysts in renal tubular epithelial cells that gradually compress the parenchyma and compromise renal function. There is considerable interest in the primary cilia as a site of the proteins that are involved in renal cystogenesis in ADPKD[19,20]. Research on primary cilia has increased significantly during the last decade[21]. Cyst enlargement is thought to result from increased fluid secretion; and abnormal cell replication by the epithelium lining the cyst[22]. The processes underlying the decline in renal function include disruption of glomerular filtration and urine concentrating mechanisms, coupled with compression of adjacent nephrons in the cortex, medulla and papilla. Cyst-derived chemokines, cytokines and growth factors cause fibrosis that is similar to development of other progressive ESRD[23]. This concept that attributes important roles to tubular cell ciliary functioning, cell proliferation and fluid secretion, alterations in levels of intracellular calcium, cAMP and activation of cellular kinases, including mTOR[12] is the basis of potentially effective treatments discussed below.

Animal studies indicate that excessive activation of the alternative complement pathway is associated with ADPKD progression, probably mediated through cyst-lining cell proliferation, tubulointerstitial inflammatory cell infiltration and fibrosis. Regulating activation of the complement system might represent a new treatment strategy for ADPKD[24]. Cyst expansion causes ischemia within the kidney and activation of RAAS leading to the development and/or maintenance of hypertension. The features of disease progression in ADPKD include increasing total kidney volume (TKV), hypertension, cardiovascular complications, proteinuria and progression to ESRD[25].

Extrarenal manifestations

Apart from renal cysts, patients often have extra-renal disease encompassing cysts in the liver (94%), seminal vesicle (40%), pancreas (9%), arachnoid membrane (8%), and spinal meninges (2%); and connective tissue abnormalities such as mitral valve prolapse (25%), intracranial aneurysms (8%), diverticular disease (20%-25%) and abdominal hernia (10%); hypertension and left ventricular hypertrophy[26-28]. Recognition of extrarenal manifestations (ERM) reduces diagnostic uncertainty and may influence choice of treatment option[29].

Cardiovascular system

Other cardiovascular abnormalities include aortic aneurysms, arachnoid aneurysms, cerebral artery dolichoectasia, mitral regurgitation, aortic insufficiency, and tricuspid regurgitation. There is evidence to suggest that ADPKD is associated with an increased incidence of coronary aneurysms and dissection[30,31]. Cardiovascular complications are responsible for 80% more deaths in ADPKD than ESRD. Furthermore, intracranial aneurysms affect 4%-41.2% of ADPKD patients, with a risk of rupture about five times higher than in the general population[2,32].

Hypertension: Hypertension develops in about 50%-70% of patients with ADPKD and is associated with an increased risk of progression to ESRD. Stimulation of RAAS plays a significant role in the development of hypertension. The presence of cardiovascular changes such as carotid intima-media thickness, and arterial stiffness in young normotensive patients with ADPKD suggests that cardiovascular involvement starts early in these patients. Early diagnosis and treatment of hypertension with RAAS inhibitors, has the likely benefit of reducing the cardiovascular complications and slowing the progression of kidney dysfunction[33].

Left ventricular hypertrophy: Left ventricular hypertrophy (LVH) has been recognised as an early complication in patients with ADPKD. LVH is associated with arrhythmias, congestive heart failure, and increased cardiac mortality. Observational studies using echocardiography have estimated the prevalence of LVH in adults to range from 20%-40%[34]. The recently observed decline in the incidence of LVH may be as a result of earlier detection, treatment and more rigorous control of blood pressure including the increasing use of RAAS antagonists.

Miscellaneous

Another cited ERM is thoracic aortic dissection, which can cause high mortality and morbidity rates[35]. Also pulmonary dysfunction should be recognised as one of the extrarenal complications of ADPKD due to the demonstrable improvement in lung function following renal transarterial embolism[36].

Complications of ADPKD

Complications in ADPKD usually result from kidney involvement and include cyst bleeding and cyst infection. However, serious extrarenal features such as subarachnoid haemorrhage can also occur[5].

Cyst infection/Urinary tract infection Idrizi *et al*[37] studied 180 patients with ADPKD (2003 to 2008) and reported urinary tract infections caused by gram negative enteric organisms in 60% (108 patients). The episodes of isolated cyst infections (negative urine culture and no urinary white blood cell casts) were more frequent than those of acute or chronic pyelonephritis (urinary sediment containing white blood cell casts). The key challenge is how to distinguish between cyst infection and acute or chronic pyelonephritis. Hepatic pyocyst is an uncommon but potentially life-threatening complication of ADPKD. With extensive hepatic cystic disease, localization of a pyocyst and targeted aspiration or drainage is often a diagnostic challenge. Two ADPKD patients with recurrent gram-negative sepsis were

investigated with ^{67}Ga SPECT/CT to look for the source of infection - with accurate localisation in both cases[38].

Screening/surveillance

Ultrasonography remains the first choice imaging modality for diagnosing ADPKD[26]. However, computed tomography (CT) scanning is particularly useful in assessing pain, complex renal or hepatic cysts and in cyst aspiration[39]. New magnetic resonance imaging (MRI) methods developed by the Consortium for Radiologic Imaging for the Study of Polycystic Kidney Disease allow accurate estimates of change in TKV over time in ADPKD patients with intact renal function. PKD1 status, male sex, hypertension, reduced renal blood flow, and proteinuria are associated with increased renal volume and change in renal volume over time[25]. MRI has advantages when there is suspicion of malignancy and similar to CT, is useful in the assessment of living kidney donors[39].

Following a comprehensive literature review of articles published from 1998 to 2013, Ellimoottil *et al*[40] concluded that CT and MRI with/without contrast enhancement remained the gold standard for evaluating cystic lesions of the kidney. However, diffusion-weighted MRI and contrast enhanced ultrasound have surfaced as new tools for assessment of complex cysts. In a retrospective analysis, Israel *et al*[41] reported that findings on CT and MRI were similar in 81% of lesions. MRI may depict septa, wall thickening or enhancement leading to upgrade in cyst classification that can affect management.

Kawano *et al*[42] explored urinary biomarkers in ADPKD in human and in an animal model using gene expression analysis of the kidney from DBA/2FG-pcy mice (ADPKD model animals) to identify prospective biomarkers. Their study suggests that NGAL, M-CSF, MCP-1 are potential candidates for urinary biomarkers in ADPKD.

Intracranial aneurysms

Though the prevalence of IA is higher in patients with ADPKD than the general population (4%-41.2% *vs* 0.4%-6%), the mortality rate of aneurysm rupture is similar. Levey *et al*[43] showed that routine arteriographic screening for cerebral aneurysms in patients with ADPKD was not of significant benefit. Butler *et al*[44] reexamined this question by comparing an MRI screening strategy with a non screening strategy. Aneurysms detected by MRI screening were managed neurosurgically whereas the patients in the non screening arm received cerebrovascular care only in the event of subarachnoid hemorrhage. Taking into consideration a host of factors including the prevalence of asymptomatic aneurysms in ADPKD patients (15%); the annual incidence of aneurysmal rupture (1.6%); the morbidity and mortality rates associated with subarachnoid haemorrhage (70% and 56%, respectively); and the life expectancy of patients with ADPKD, the model predicted that the screening strategy would provide 1.0 additional year of life without neurological disability to a 20-year-old patient with ADPKD. Furthermore, a financial analysis showed that a screening strategy is likely to be more cost effective. Rozenfeld *et al*[10] performed a critical appraisal of the estimated value of screening for IA in the setting of ADPKD noting the variable length of the preclinical phase of aneurysm development and the fact that the clinical phase (symptoms to haemorrhage or death) can be quite short, they recommended only screening patients who have a family history of aneurysm or subarachnoid haemorrhage, high risk occupation, undergoing major surgery, exhibiting severe anxiety about the issue or if anticoagulation is contemplated for any reason.

Jiang *et al*[45] screened and followed up unruptured intracranial aneurysms (UIAs) and concluded that 3.0 T 3D-TOF (time of flight) MRA was feasible for UIAs follow-up in ADPKD patients. However, the risk of enlargement and rupture of UIAs in ADPKD patients was not higher than in the general population. The jury is therefore out on whether to screen ADPKD patients or not. A pragmatic way forward may be to define the population at risk and screen those.

Sixty-eight adults, pre-dialysis ADPKD patients underwent both screening for intracranial aneurysms with MRI of the brain and ambulatory blood pressure monitoring with a view to establishing an association between these in ADPKD. Ten of the 68 patients had intracranial aneurysms while 58 had none. The night time maximum diastolic blood pressure, maximum increase in diastolic BP from measurement to measurement at night, and the standard deviation of the daytime mean arterial pressure were significantly higher in patients with aneurysm. Additionally, those over 45 years of age with aneurysm had significantly worse parameters. They concluded after a series of analyses that hypertensive ADPKD patients with substantial fluctuations in BP assessed by automated blood pressure monitoring, especially those after 45 years-of-age, should become candidates for screening for intracranial aneurysms[46].

TREATMENT OF ADPKD

There is presently no effective treatment for ADPKD and management measures are focused mainly on managing the complications of the disease, not on slowing cyst development or preventing progression to kidney failure. Current treatment strategies include: lowering cAMP levels; inhibiting cell proliferation; and reducing fluid secretion[47]. Many clinical trials have been undertaken to study the effect of diverse drugs on the growth of renal and hepatic cysts, and on deterioration of renal function. The drug classes that have been tested in randomised clinical trials (RCT) include mTOR inhibitors (sirolimus and everolimus), somatostatin analogues (octreotide, lanreotide, pasireotide), and most recently, vasopressin V2 receptor antagonist,

tolvaptan. Other drugs being tested include bosutinib [sarcoma proto-oncogene Abelson murine leukaemia oncogene (SRC-ABL) tyrosine kinase inhibitor] and triptolide, a traditional Chinese herbal medication. Additional therapeutic strategies to retard cyst growth aim at blood pressure control *via* inhibition of RAAS and the sympathetic nervous system[8]. Also, targeting up or down regulated molecules in the renal epithelial cells are being tested[5].

Overactivity of both mTOR and cystic fibrosis transmembrane conductance regulator is thought to contribute to the progressive expansion of renal cysts in ADPKD. Recent research has established that AMP-activated kinase can suppress the activity of each of these proteins. Clinical AMP kinase activators such as metformin and berberine may thus have potential in the clinical management of ADPKD. The use of berberine in diarrhea may be due to the inhibitory impact of AMPK on chloride extrusion by small intestinal enterocytes[48].

Drug therapy for ADPKD

Rapamycin: He *et al*[49] conducted a meta-analysis of 4 RCTs (564 patients) regarding mTOR inhibitor therapy in patients with ADPKD investigating changes in patients' GFR, urinary protein, TKV, cyst volume, parenchymal volume, lipid profile and the frequency of adverse events. Their main findings were that though mTOR inhibitor therapy was associated with a smaller TKV than the control group, it did not slow down the decline of renal function. This agrees with the findings of a randomised, crossover study (The SIRENA Study)[50]. However, another meta-analysis of RCTs (5 studies, 619 patients) that used mTOR inhibitors to halt the progression of ADPKD failed to demonstrate any significant reduction in TKV or GFR between the TORI-treated and control groups[51]. These findings, in addition to a significantly higher level of proteinuria in the mTOR inhibitor-treated group than in the control group, were similar to those of another meta-analysis[52].

The above studies of mTOR inhibitor treatment of ADPKD showed no clear benefit on the primary endpoint of TKV or eGFR. Another trial evaluated two levels of rapamycin on the 12-mo change in (125)I-iothalamate GFR (iGFR) as the primary endpoint and TKV secondarily[53]. In a study of 30 adult patients with ADPKD randomised to low-dose rapamycin (trough level, 2-5 ng/mL; n = 10), standard-dose rapamycin trough level (> 5-8 ng/mL; n = 10), or standard care (SC group, n = 10), Braun *et al*[53] showed that patients receiving low dose rapamycin demonstrated a significantly better iGFR but without a significant effect on TKV after 12 mo.

Somotatostatin analogues: Therapy with somatostatin analogues is meant to regulate the activity of the tubular epithelial lining the cysts *via* secondary chloride transport thereby shrinking the renal cysts. A randomised, cross-over, placebo-controlled trial compared the risk/benefit profile of a 6-mo treatment with long-acting somatostatin (octreotide-LAR, 40 mg intramuscularly every 28 d) or placebo in ADPKD patients with mild-to-moderate renal insufficiency showed a significantly slower increase in TKV for patients on somatostatin compared to placebo[54]. The work of Hogan *et al*[55] agrees with this. In another study involving long term treatment with octreotide, Caroli *et al*[56] assessed the effect of 3 years of octreotide-LAR treatment on kidney and cyst growth and renal function decline in participants with ADPKD. They performed a multicentre, randomised, single-blind, placebo-controlled, parallel-group trial in five hospitals in Italy between 2000 and 2008 on adult (> 18 years) patients with eGFR of 40 mL/min per 1.73 m^2 or higher who were randomly assigned on a 1:1 ratio to 3 year treatment with two 20 mg intramuscular injections of octreotide-LAR (n = 40) or 0.9% sodium chloride solution (n = 39) every 28 d. The mean ± standard error of mean increase in TKV in the treatment group (220.1 ± 49.1 mL) was lower than in the placebo group (454.3 ± 80.8 mL) but the difference was not statistically significant. They reported four cases (10%) of cholelithiasis or acute cholecystitis in the octreotide-LAR group that were probably treatment-related.

Vasopressin 2 receptor antagonist: Blockade of vasopressin V2 receptor is thought to limit cyst growth, thereby delaying progressive renal dysfunction. Vasopressin antagonists and somatostatin analogues lower intracellular cAMP levels and though associated with limited clinical benefits, they have significant side effects[28]. Torres *et al*[57] conducted a large (1445 patients between 2007 and 2009) well-structured prospective study of Tolvaptan, a selective vasopressin 2 receptor antagonist in young patients (⩽ 50 years) with ADPKD with reasonably good kidney function (eGFR > 60 mL/min), and with MRI-measured TKV > 750 mL. They compared TKV, kidney function, albuminuria, kidney pain and vital signs. The TEMPO (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes) trial showed that tolvaptan was effective in slowing the expansion of kidney volume and deterioration of kidney function[58]. Tolvaptan has been reported to prolong the median age at ESRD onset by 6.5 years and increase life expectancy by 2.6 years. Even if the benefits of tolvaptan persist in the longer term, it would still not be cost effective treatment[59]. Tolvaptan has significant adverse effects including polyuria, nocturia, polydipsia and elevation of aminotransferase enzyme concentrations with the potential for acute liver failure. In the TEMPO 3:4 trial, 8.3% of patients in the treatment arm had severe tolvaptan-related aquaresis leading to drug discontinuation[28]. Appropriate patient selection is critical to optimize long-term benefits while minimizing adverse effects and hepatotoxic risk factors[4].

Combined drug treatment such as the use of low doses of rapamycin, tolvaptan, and AEterna-Zentaris

slows the progression of PKD with limited side effects, suggesting the use of combined therapies also in clinical trials[60]. Although not targeting the causative mechanisms of cyst formation and growth, the HALT-PKD study examined the effects of dual blockade of the RAAS and aggressive blood pressure control on the rate of progression of ADPKD[61]. In summarising the various trials of drug therapy for ADPKD, Myint *et al*[62] called for further well-designed and suitably powered trials of longer duration using new biomarkers or therapeutic agents with better tolerance are required.

Hypertension

Patch *et al*[63] undertook a cohort study of 2085 patients with ADPKD between 1991 and 2008 to determine the association between antihypertensive therapy and mortality in patients with ADPKD. The proportion on antihypertensive drugs increased from 32% in 1991 to 62% in 2008. Also, use of drugs acting on the RAAS increased from 7% of participants to 46% by 2008. These changes were associated with a reducing mortality. Effective BP control prevents an increase in LVM index and reduces urinary albumin excretion, indicating the relative importance of good BP control in slowing cardiac and renal organ damage in ADPKD[64]. RAAS inhibitors cause regression of LVH and play an important role in the cardiovascular risk management of ADPKD patients[34].

Chronic pain

Chronic pain defined as pain existing for > 4-6 wk, is a significant cause of morbidity in patients with ADPKD. Chronic pain in ADPKD patients is often severe, impacting physical activity and social relationships and frequently difficult to manage[65]. Analysis of 171 questionnaires completed by patients with polycystic kidney disease of varying levels of renal function showed the order of frequency of pain as: low back pain, abdominal pain, headache, chest pain and leg pain. The severity of pain, documented by the visual analogue scale was 4 to 5/10 in the majority of patients[66]. MRI will differentiate between mechanical low back pain caused by cyst enlargement from cyst rupture or infection. Also, the increased incidence of uric acid nephrolithiasis as a factor in producing renal colic must be considered when evaluating acute pain in the population at risk. If stone disease is suspected, then abdominal CT scan and/or ultrasound should be the method of investigation.

Approaches to chronic pain management must include measures that help patients to adapt to chronic pain thereby limiting its interference with their life style[67]. Management ranges from non pharmacologic therapy to high-dose opioid therapy and more invasive procedures, including surgical intervention. Celiac plexus neurolysis and intercostal nerve radiofrequency ablations offer temporary respite. Dorsal column neurostimulation is a more permanent step, affording superior analgesia with better QOL[65,68]. The use of open or laparoscopic cyst decortication procedures for control of pain and infection in those with preserved renal function does not result in further renal dysfunction[14].

ESRD/dialysis

The key issues relating to peritoneal dialysis in patients with ADPKD are: a higher incidence of abdominal wall hernias, the increased risk of diverticulitis; and peritoneal space problems due to enlarged kidneys[69]. However, the little evidence available showed no real difference between ADPKD and non ADPKD patients[69,70].

SURGICAL OPTIONS

Cyst procedures

Anecdotal report of successful intracystic infusion of ciprofloxacin that achieved a sufficiently high antibiotic level in infected renal cysts so as to completely eradicate *S. choleraesuis* in a 52-year-old male with ADPKD refractory renal cyst infection with multiple pyocysts[71] has highlighted a potential salvage therapy for refractory renal cyst infection especially when surgery is contraindicated. Transcatheter renal artery embolisation is performed to reduce kidney volume in ADPKD patients with nephromegaly and improve lung function by reducing the splinting effect on the diaphragm[36]. Open transperitoneal bilateral renal cyst reduction surgery in patients with symptomatic ADPKD has been shown to be a relatively safe and effective treatment for individuals in whom more conservative therapies have failed[72].

Cyst decortication is highly effective in the management of disease-related chronic pain for the majority of patients with ADPKD and may alleviate hypertension and preserve renal function[73]. The technique of retroperitoneoscopic decortication as described by Hemal *et al*[74] is preferred in the presence of infected cysts so as to prevent intraperitoneal contamination.

Transplantation

When patients with ADPKD are assessed for renal transplantation, the key issues relate to native nephrectomy, liver cysts, screening for intracranial aneurysms and living-related kidney donation. Prophylactic native nephrectomy is indicated in patients with a history of cyst infection or recurrent haemorrhage or to those in whom space must be made to implant the allograft[75]. Other issues include anaemia management, the potential benefits of select immunosuppressive agents, the role for combined kidney-liver transplantation and complications of ADPKD after transplantation[76].

Few studies have investigated whether the TKV and liver volume in patients with ADPKD decrease after renal transplantation. Yamamoto *et al*[77] analysed changes in the volume of native kidney (bilateral: n = 28; unilateral: n = 5) and liver (concomitant polycystic disease: n = 18) in 33 patients with ADPKD, who underwent renal transplantation. Volumetry was retrospectively conducted using simple CT scan data 6

mo before transplantation, at the time of transplantation, and one, three, and five years after transplantation. Kidney volumes were significantly reduced in all but one patient after renal transplantation, decreasing by 37.7% and 40.6% at 1 and 3 years, respectively. In contrast, 16 of 18 patients showed significant increase of liver volumes after renal transplantation with the mean rates of increase of 8.6% and 21.4% at 1 and 3 years, respectively. In the light of these findings, native nephrectomy would be unnecessary if the space for an allograft is available in the absence of infection, bleeding, or malignancy. When ADPKD is combined with polycystic liver disease, the possibility of intolerable symptoms caused by growing liver cysts should be considered[75,77].

Nephrectomy

More recent data suggests that about a fifth of ADPKD patients undergoing renal transplantation would require native unilateral or bilateral nephrectomy[78-80]. Brazda *et al*[81] reported a higher rate of native nephrectomy (35.4%) and advocated that if native nephrectomy is needed, it would be better before transplantation than after.

Indication/timing: As highlighted above, the indications for nephrectomy include pain/discomfort, space for transplantation, ongoing haematuria, recurrent infections, and gastrointestinal pressure symptoms (early satiety)[82,83]. Another argument in favour of nephrectomy in those with complex cysts is the risk of malignancy as exemplified by two cases of renal cell carcinomas in 157 ADPKD patients undergoping nephrectomy before or after transplantation - an incidence of 1.3%[79]. Fuller *et al*[78] evaluated the indications for and outcome of pre-transplant, concomitant and post-transplant native nephrectomy in patients with ESRD due to ADPKD. Between 1992 and 2002, 32 (18.7%) of 171 patients with ESRD due to ADPKD who received a kidney transplant underwent native nephrectomy - 25 bilateral and 7 unilateral. They observed that the predominant indication for native nephrectomy depended on its timing - haematuria, a renal mass and chronic pain in the pretransplant group; lack of space in the concurrent group; and urinary tract infection in the posttransplant group[78]. Bilateral nephrectomy performed either before or during transplantation has the advantage of removing future complications of ADPKD while not significantly increasing immediate general complications[80]. Nunes *et al*[84] studied 159 renal transplants in patients with ADPKD divided into two groups according to the need for a unilateral native nephrectomy owing to enlarged kidneys (n = 143) *vs* those not needing it at the time of transplantation (n = 16). They reported no differences in rates of delayed graft function, acute rejection and chronic allograft dysfunction.

Song *et al*[85] assessed the transplant outcome of ADPKD patients who underwent concurrent bilateral nephrectomies during kidney transplantation. Their study compared 31 patients undergoing concurrent bilateral nephrectomywith 32 patients without and reported a significantly longer operation time (300 ± 30.85 min *vs* 120 ± 20.78 min, $P < 0.01$), higher need for blood transfusion (4.31 ± 1.05 U *vs* 1.35 ± 0.23 U, $P < 0.01$) and higher rate of adjacent organ injury (22.58% *vs* 0%, $P < 0.01$) during operation in the concurrent bilateral nephrectomy group. This was hardly surprising.

Tyson *et al*[86] examined population level data on 2368 patients with ADPKD and performed unadjusted, multivariable and propensity score adjusted analyses of postoperative outcomes of 271 patients (11.4%) who underwent simultaneous kidney transplantation and bilateral native nephrectomy compared to bilateral native nephrectomy alone. They concluded that except for increased rates of intraoperative bleeding, blood transfusion and urological complications there were no significant differences in postoperative adverse outcomes[86]. In patients with ADPKD native nephrectomy of massively enlarged kidneys may be safely performed during the transplant procedure with no repercussions on the length of hospital stay, graft short- and long-term function and patient survival. Concomitant native nephrectomy of enlarged kidneys at the time of renal transplantation is reasonable and safe for patients with ESRD due to ADPKD[87,88]. It must be bourne in mind however, that native nephrectomy in ADPKD is a major undertaking associated with significant morbidity and mortality. Kirkman *et al*[82] reported that two of 20 patients in the bilateral nephrectomy pre-transplant group and one in the bilateral nephrectomy post-transplant group died in the immediate post-operative period.

Nephrectomy technique: Historically, nephrectomy for ADPKD was performed by an open technique. Eng *et al*[89] performed a study to compare outcomes (operative time, complications, transfusion requirement, and length of stay) in hand-assisted laparoscopic nephrectomy (n = 56) with open nephrectomy (n = 20). Overall complication rates were similar but patients undergoing open bilateral nephrectomy were more likely to receive transfusion, and the length of stay was longer in the open group [5.9 d *vs* 4.0 d for unilateral (P = 0.013) and 7.8 d *vs* 4.6 d for bilateral]. The most frequent complications associated with hand-assisted laparoscopic nephrectomy were incisional hernia at the hand-port site and thrombosis of arteriovenous fistulae. Compared to open bilateral nephrectomy, the laparoscopic approach resulted in significantly shorter hospital stay, decreased morbidity and quicker recovery. With an average weight of 3 kg, these were really only moderately large kidneys[90,91]. For patients considering renal transplantation, avoidance of transfusion is important to prevent sensitisation which limits access to compatible organs. Laparoscopic nephrectomy is technically safe and feasible in patients with ADPKD but progressive cyst aspiration is a critical step, facilitating the identification of vital structures and the creation of

enough abdominal cavity space to operate[90].

Nephrectomy/transplant outcome

Jacquet *et al*[92] reported the outcome of a longitudinal study on renal transplantation in patients with ADPKD comparing 534 ADPKD patients with 4779 non-ADPKD patients. This comprehensive French study performed using DIVAT (Donnees Informatisees et VAlidees en Transplantaion) demonstrated that renal transplantation is associated with better graft survival but patients had more thromboembolic and metabolic complications, and an increased incidence of hypertension. And from Italy, Mosconi *et al*[93] analysed the results of 1800 patients with ADPKD and 12505 ESRD patients from other causes during 2002-2010. Among patients with long term follow-up, ADPKD patients had better graft survival compared with other kidney diseases (86% *vs* 82% at 5 years; $P < 0.01$); and mortality was not different (92% *vs* 79% at 1 year). ADPKD is a risk factor for the development of new onset diabetes after transplantation (OR = 2.41, $P = 0.035$)[94].

Dinckan *et al*[88] compared the outcome of renal transplantation in ADPKD patients undergoing concurrent unilateral ($n = 38$) or bilateral ($n = 125$) native nephrectomy with 161 randomly selected controls. Despite additional surgery and a higher complication rate, the long-term results of patients with complications were not affected negatively and graft survival was similar in the two groups. Following bilateral native nephrectomy, hypertension control was better and the incidence of lower urinary tract infection was lower postoperatively[85]. Overall one year patient and graft survival were 94%-97% and 92%-96% respectively[81,88,95]. Surgical complications, which might be associated with simultaneous nephrectomy requiring re-operation, occurred in 12% of patients[95]. One wonders whether the outcome of the 38% who received kidneys from living donors might have been different if they had pre-transplant native nephrectomy.

RESEARCH POINTERS

Interventions to halt progression of ADPKD

The potential role of glucose metabolism in the pathogenesis of ADPKD may provide a new perspective for the understanding of the pathobiology of ADPKD and open potential new avenues for therapeutical interventions[96].

Treatment aimed at preventing or reducing cyst formation or slowing cyst growth is a reasonable strategy for prolonging useful kidney function in patients with ADPKD[23]. The findings of Caroli *et al*[56]'s study provide the background for large randomised controlled trials to test the protective effect of somatostatin analogues against deterioration in kidney function and progression to ESRD. Advances in research into molecular mechanisms of cystogenesis will help develop new targeted ADPKD therapies[28].

Meijer *et al*[97] have designed DIPAK 1 study (Developing Interventions to Halt Progression of ADPKD 1) to examine the efficacy of the somatostatin analogue lanreotide on preservation of renal function. The DIPAK 1 study is a multicenter, randomised controlled, clinical trial designed to show whether subcutaneous administration of lanreotide every 4 wk slows down disease progression in patients with ADPKD.

Vitamin D is increasingly being recognised for a number of other important physiological functions, including reducing blood pressure and proteinuria as well as kidney inflammation and fibrosis. Vitamin D deficiency is associated with proteinuria, increased mortality and may mediate the progression to kidney failure. Based on the prediction that cholecalciferol will attenuate hypertension, proteinuria and reduce the urinary excretion of a biomarker, monocyte chemoattractant protein-1 (MCP-1, a surrogate inflammatory marker of progression in ADPKD). Rangan *et al*[98] have designed a study to provide evidence as to whether a simple intervention such as vitamin D repletion, in either deficient or insufficient states, is a treatment to prevent kidney failure in ADPKD.

QOL with ADPKD

Particular emphasis needs to be placed on performing clinical trials with the goal of improving outcomes and QOL of patients with ADPKD[76].

OUTCOME

ADPKD patients have good graft and patient survival[13]. Haynes *et al*[99] performed a retrospective cohort study of all patients with ADPKD who received RRT between 1971 and 2000 at the Oxford Kidney Unit. Age at start of RRT and presence of a functioning transplant were associated with improved survival in unadjusted analyses. After adjustment for age the period of treatment also became a significant predictor of overall survival. Survival on RRT appears to have improved and exceeds that observed in the general population, such that RRT now provides almost two-thirds of the life expectancy of the general population, compared to about half in earlier decades.

Data were retrieved from three Danish national registries (1993-2008) on about 823 patients of whom 431 had died during the study period. A multivariate competing risk model comparing the two 8-year periods, adjusted for age at ESRD, gender and treatment modality, showed that deaths from cardiovascular disease decreased by 35% and deaths from cerebrovascular disease decreased by 69% from the first to the second time period[100].

LIMITATIONS

The absence of large RCT on various aspects of the disease and treatment, and the preponderance of case series and observational studies is a significant limitation. Though these reports are valuable, there

still remains considerable uncertainty and ambiguity in many aspects of ADPKD patient care as it relates to ESRD. To a large extent our knowledge is based on small numbers in various trial, single centre retrospective data and numerous review articles.

CONCLUSION

The outlook of patients with ADPKD is improving and is in fact much better than that for patients in ESRD due to other causes. This review highlights the need for a well-structured RCT as a first step towards trying newer interventions so as to develop updated clinical management guidelines.

REFERENCES

1 **Dell KM**. The spectrum of polycystic kidney disease in children. *Adv Chronic Kidney Dis* 2011; **18**: 339-347 [PMID: 21896375 DOI: 10.1053/j.ackd.2011.05.001]

2 **Romão EA**, Moysés Neto M, Teixeira SR, Muglia VF, Vieira-Neto OM, Dantas M. Renal and extrarenal manifestations of autosomal dominant polycystic kidney disease. *Braz J Med Biol Res* 2006; **39**: 533-538 [PMID: 16612477 DOI: 10.1590/S0100-879X2006000400014]

3 **Thong KM**, Ong AC. The natural history of autosomal dominant polycystic kidney disease: 30-year experience from a single centre. *QJM* 2013; **106**: 639-646 [PMID: 23587574 DOI: 10.1093/qjmed/hct082639-646]

4 **Baur BP**, Meaney CJ. Review of tolvaptan for autosomal dominant polycystic kidney disease. *Pharmacotherapy* 2014; **34**: 605-616 [PMID: 24706579 DOI: 10.1002/phar.1421]

5 **Torra R**. Autosomal dominant policystic kidney disease, more than a renal disease. *Minerva Endocrinol* 2014; **39**: 79-87 [PMID: 24736482]

6 **Yoshihara D**, Kugita M, Sasaki M, Horie S, Nakanishi K, Abe T, Aukema HM, Yamaguchi T, Nagao S. Telmisartan ameliorates fibrocystic liver disease in an orthologous rat model of human autosomal recessive polycystic kidney disease. *PLoS One* 2013; **8**: e81480 [PMID: 24324698 DOI: 10.1371/journal.pone.0081480]

7 **Suwabe T**, Ubara Y, Mise K, Kawada M, Hamanoue S, Sumida K, Hayami N, Hoshino J, Hiramatsu R, Yamanouchi M, Hasegawa E, Sawa N, Takaichi K. Quality of life of patients with ADPKD-Toranomon PKD QOL study: cross-sectional study. *BMC Nephrol* 2013; **14**: 179 [PMID: 23978051]

8 **Wüthrich RP**, Mei C. Pharmacological management of polycystic kidney disease. *Expert Opin Pharmacother* 2014; **15**: 1085-1095 [PMID: 24673552]

9 **Ars E**, Bernis C, Fraga G, Martínez V, Martins J, Ortiz A, Rodríguez-Pérez JC, Sans L, Torra R. Spanish guidelines for the management of autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant* 2014; **29** Suppl 4: iv95-i105 [PMID: 25165191 DOI: 10.1093/ndt/gfu186]

10 **Rozenfeld MN**, Ansari SA, Shaibani A, Russell EJ, Mohan P, Hurley MC. Should patients with autosomal dominant polycystic kidney disease be screened for cerebral aneurysms? *AJNR Am J Neuroradiol* 2014; **35**: 3-9 [PMID: 23292526 DOI: 10.3174/ajnr.A3437]

11 **Martínez V**, Comas J, Arcos E, Díaz JM, Muray S, Cabezuelo J, Ballarín J, Ars E, Torra R. Renal replacement therapy in ADPKD patients: a 25-year survey based on the Catalan registry. *BMC Nephrol* 2013; **14**: 186 [PMID: 24007508 DOI: 10.1186/1471-2369-14-186]

12 **Meijer E**, de Jong PE, Peters DJ, Gansevoort RT. Better understanding of ADPKD results in potential new treatment options: ready for the cure? *J Nephrol* 2008; **21**: 133-138 [PMID: 18446706]

13 **Errasti P**, Manrique J, Lavilla J, Rossich E, Hernandez A, Pujante D, Ndarabu A, García N, Purroy A. Autosomal-dominant polycystic kidney disease: high prevalence of graft loss for death-related malignancies and cardiovascular risk factors. *Transplant Proc* 2003; **35**: 1717-1719 [PMID: 12962769 DOI: 10.1016/S0041-1345(03)00619-5]

14 **Badani KK**, Hemal AK, Menon M. Autosomal dominant polycystic kidney disease and pain - a review of the disease from aetiology, evaluation, past surgical treatment options to current practice. *J Postgrad Med* 2004; **50**: 222-226 [PMID: 15377813]

15 **Orskov B**, Rømming Sørensen V, Feldt-Rasmussen B, Strandgaard S. Improved prognosis in patients with autosomal dominant polycystic kidney disease in Denmark. *Clin J Am Soc Nephrol* 2010; **5**: 2034-2039 [PMID: 20671227 DOI: 10.2215/CJN.01460210]

16 **Abbott KC**, Agodoa LY. Polycystic kidney disease at end-stage renal disease in the United States: patient characteristics and survival. *Clin Nephrol* 2002; **57**: 208-214 [PMID: 11924752 DOI: 10.5414/CNP57208]

17 **Helal I**, McFann K, Reed B, Yan XD, Schrier RW. Changing referral characteristics of patients with autosomal dominant polycystic kidney disease. *Am J Med* 2013; **126**: 832.e7-832.e11 [PMID: 23830538 DOI: 10.1016/j.amjmed.2012.12.018]

18 **Bonon A**, Mangolini A, Pinton P, Del Senno L, Aguiari G. Berberine slows cell growth in autosomal dominant polycystic kidney disease cells. *Biochem Biophys Res Commun* 2013; **441**: 668-674 [PMID: 24184483 DOI: 10.1016/j.bbrc.2013.10.076]

19 **Abdul-Majeed S**, Nauli SM. Polycystic diseases in visceral organs. *Obstet Gynecol Int* 2011; **2011**: 609370 [PMID: 22242024 DOI: 10.1155/2011/609370]

20 **Ratnam S**, Nauli SM. Hypertension in Autosomal Dominant Polycystic Kidney Disease: A Clinical and Basic Science Perspective. *Int J Nephrol Urol* 2010; **2**: 294-308 [PMID: 25364490]

21 **Kathem SH**, Mohieldin AM, Nauli SM. The Roles of Primary cilia in Polycystic Kidney Disease. *AIMS Mol Sci* 2014; **1**: 27-46 [PMID: 25599087 DOI: 10.3934/molsci.2013.1.27]

22 **Mochizuki T**, Tsuchiya K, Nitta K. Autosomal dominant polycystic kidney disease: recent advances in pathogenesis and potential therapies. *Clin Exp Nephrol* 2013; **17**: 317-326 [PMID: 23192769 DOI: 10.1007/s10157-012-0741-0]

23 **Grantham JJ**, Mulamalla S, Swenson-Fields KI. Why kidneys fail in autosomal dominant polycystic kidney disease. *Nat Rev Nephrol* 2011; **7**: 556-566 [PMID: 21862990 DOI: 10.1038/nrneph.2011.109]

24 **Su Z**, Wang X, Gao X, Liu Y, Pan C, Hu H, Beyer RP, Shi M, Zhou J, Zhang J, Serra AL, Wüthrich RP, Mei C. Excessive activation of the alternative complement pathway in autosomal dominant polycystic kidney disease. *J Intern Med* 2014; **276**: 470-485 [PMID: 24494798 DOI: 10.1111/joim.12214]

25 **Chapman AB**. Approaches to testing new treatments in autosomal dominant polycystic kidney disease: insights from the CRISP and HALT-PKD studies. *Clin J Am Soc Nephrol* 2008; **3**: 1197-1204 [PMID: 18579674 DOI: 10.2215/CJN.00060108]

26 **Srivastava A**, Patel N. Autosomal dominant polycystic kidney disease. *Am Fam Physician* 2014; **90**: 303-307 [PMID: 25251090]

27 **Luciano RL**, Dahl NK. Extra-renal manifestations of autosomal dominant polycystic kidney disease (ADPKD): considerations for routine screening and management. *Nephrol Dial Transplant* 2014; **29**: 247-254 [PMID: 24215018 DOI: 10.1093/ndt/gft437]

28 **Riella C**, Czarnecki PG, Steinman TI. Therapeutic advances in the treatment of polycystic kidney disease. *Nephron Clin Pract* 2014; **128**: 297-302 [PMID: 25573484 DOI: 10.1159/000368244]

29 **Pirson Y**. Extrarenal manifestations of autosomal dominant polycystic kidney disease. *Adv Chronic Kidney Dis* 2010; **17**: 173-180 [PMID: 20219620 DOI: 10.1053/j.ackd.2010.01.003]

30 **Hadimeri H**, Lamm C, Nyberg G. Coronary aneurysms in patients with autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 1998; **9**: 837-841 [PMID: 9596081]

31 **Itty CT**, Farshid A, Talaulikar G. Spontaneous coronary artery dissection in a woman with polycystic kidney disease. *Am J Kidney Dis* 2009; **53**: 518-521 [PMID: 18992981 DOI: 10.1053/j.ajkd.2008.08.027]

32 **Kang YR**, Ahn JH, Kim KH, Choi YM, Choi J, Park JR. Multiple cardiovascular manifestations in a patient with autosomal dominant polycystic kidney disease. *J Cardiovasc Ultrasound* 2014; **22**: 144-147 [PMID: 25309692 DOI: 10.4250/jcu.2014.22.3.144]

33 **Ecder T**. Cardiovascular complications in autosomal dominant polycystic kidney disease. *Curr Hypertens Rev* 2013; **9**: 2-11 [PMID: 23971638 DOI: 10.2174/1573402111309010002]

34 **Alam A**, Perrone RD. Left ventricular hypertrophy in ADPKD: changing demographics. *Curr Hypertens Rev* 2013; **9**: 27-31 [PMID: 23971641 DOI: 10.2174/1573402111309010005]

35 **Fukunaga N**, Yuzaki M, Nasu M, Okada Y. Dissecting aneurysm in a patient with autosomal dominant polycystic kidney disease. *Ann Thorac Cardiovasc Surg* 2012; **18**: 375-378 [PMID: 22293308 DOI: 10.5761/atcs.cr.11.01756]

36 **Yamakoshi S**, Ubara Y, Suwabe T, Hiramatsu R, Yamanouchi M, Hayami N, Sumida K, Hasegawa E, Hoshino J, Sawa N, Takaichi K, Kawabata M. Transcatheter renal artery embolization improves lung function in patients with autosomal dominant polycystic kidney disease on hemodialysis. *Clin Exp Nephrol* 2012; **16**: 773-778 [PMID: 22526485 DOI: 10.1007/s10157-012-0619-1]

37 **Idrizi A**, Barbullushi M, Koroshi A, Dibra M, Bolleku E, Bajrami V, Xhaferri X, Thereska N. Urinary tract infections in polycystic kidney disease. *Med Arh* 2011; **65**: 213-215 [PMID: 21950226 DOI: 10.5455/medarh.2011.65.213-21]

38 **Ayesa SL**, Gradinscak DJ, Schembri GP. (67)Ga SPECT/CT accurately localized recurrent hepatic cyst infection in patients with autosomal dominant polycystic kidney disease. *Clin Nucl Med* 2014; **39**: 625-628 [PMID: 24662650 DOI: 10.1097/RLU.0000000000000402]

39 **Rahbari-Oskoui F**, Mittal A, Mittal P, Chapman A. Renal relevant radiology: radiologic imaging in autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol* 2014; **9**: 406-415 [PMID: 24370765 DOI: 10.2215/CJN.08940813]

40 **Ellimoottil C**, Greco KA, Hart S, Patel T, Sheikh MM, Turk TM, Flanigan RC. New modalities for evaluation and surveillance of complex renal cysts. *J Urol* 2014; **192**: 1604-1611 [PMID: 25072181 DOI: 10.1016/j.juro.2014.07.099]

41 **Israel GM**, Hindman N, Bosniak MA. Evaluation of cystic renal masses: comparison of CT and MR imaging by using the Bosniak classification system. *Radiology* 2004; **231**: 365-371 [PMID: 15128983 DOI: 10.1148/radiol.2312031025]

42 **Kawano H**, Muto S, Ohmoto Y, Iwata F, Fujiki H, Mori T, Yan L, Horie S.Exploring urinary biomarkers in autosomal dominant polycystic kidney disease. *Clin Exp Nephrol* 2014 Dec 28; Epub ahead of print [PMID: 25543187 DOI: 10.1007/s10157-014-1078-7]

43 **Levey AS**, Pauker SG, Kassirer JP. Occult intracranial aneurysms in polycystic kidney disease. When is cerebral arteriography indicated? *N Engl J Med* 1983; **308**: 986-994 [PMID: 6835317 DOI: 10.1056/NEJM198304283081702]

44 **Butler WE**, Barker FG, Crowell RM. Patients with polycystic kidney disease would benefit from routine magnetic resonance angiographic screening for intracerebral aneurysms: a decision analysis. *Neurosurgery* 1996; **38**: 506-515; discussion 515-516 [PMID: 8837803 DOI: 10.1097/00006123-199603000-00018]

45 **Jiang T**, Wang P, Qian Y, Zheng X, Xiao L, Yu S, Liu S. A follow-up study of autosomal dominant polycystic kidney disease with intracranial aneurysms using 3.0 T three-dimensional time-of-flight magnetic resonance angiography. *Eur J Radiol* 2013; **82**: 1840-1845 [PMID: 23466029 DOI: 10.1016/j.ejrad.2013.01.024]

46 **Niemczyk M**, Pilecki T, Gradzik M, Bujko M, Niemczyk S, Pączek L. Blood pressure and intracranial aneurysms in autosomal dominant polycystic kidney disease. *Kidney Blood Press Res* 2014; **39**: 630-635 [PMID: 25571876 DOI: 10.1159/000368475]

47 **Chang MY**, Ong AC. Mechanism-based therapeutics for autosomal dominant polycystic kidney disease: recent progress and future prospects. *Nephron Clin Pract* 2012; **120**: c25-34; discussion c35 [PMID: 22205396 DOI: 10.1159/000334166]

48 **McCarty MF**, Barroso-Aranda J, Contreras F. Activation of AMP-activated kinase as a strategy for managing autosomal dominant polycystic kidney disease. *Med Hypotheses* 2009; **73**: 1008-1010 [PMID: 19570618 DOI: 10.1016/j.mehy.2009.05.043]

49 **He Q**, Lin C, Ji S, Chen J. Efficacy and safety of mTOR inhibitor therapy in patients with early-stage autosomal dominant polycystic kidney disease: a meta-analysis of randomized controlled trials. *Am J Med Sci* 2012; **344**: 491-497 [PMID: 22902868 DOI: 10.1097/MAJ.0b013e318256754f]

50 **Perico N**, Antiga L, Caroli A, Ruggenenti P, Fasolini G, Cafaro M, Ondei P, Rubis N, Diadei O, Gherardi G, Prandini S, Panozo A, Bravo RF, Carminati S, De Leon FR, Gaspari F, Cortinovis M, Motterlini N, Ene-Iordache B, Remuzzi A, Remuzzi G. Sirolimus therapy to halt the progression of ADPKD. *J Am Soc Nephrol* 2010; **21**: 1031-1040 [PMID: 20466742 DOI: 10.1681/ASN.2009121302]

51 **Xue C**, Dai B, Mei C. Long-term treatment with mammalian target of rapamycin inhibitor does not benefit patients with autosomal dominant polycystic kidney disease: a meta-analysis. *Nephron Clin Pract* 2013; **124**: 10-16 [PMID: 24022660 DOI: 10.1159/000354398]

52 **Liu YM**, Shao YQ, He Q. Sirolimus for treatment of autosomal-dominant polycystic kidney disease: a meta-analysis of randomized controlled trials. *Transplant Proc* 2014; **46**: 66-74 [PMID: 24507028 DOI: 10.1016/j.transproceed.2013.10.040]

53 **Braun WE**, Schold JD, Stephany BR, Spirko RA, Herts BR. Low-dose rapamycin (sirolimus) effects in autosomal dominant polycystic kidney disease: an open-label randomized controlled pilot study. *Clin J Am Soc Nephrol* 2014; **9**: 881-888 [PMID: 24721888 DOI: 10.2215/CJN.02650313]

54 **Ruggenenti P**, Remuzzi A, Ondei P, Fasolini G, Antiga L, Ene-Iordache B, Remuzzi G, Epstein FH. Safety and efficacy of long-acting somatostatin treatment in autosomal-dominant polycystic kidney disease. *Kidney Int* 2005; **68**: 206-216 [PMID: 15954910 DOI: 10.1111/j.1523-1755.2005.00395.x]

55 **Hogan MC**, Masyuk TV, Page LJ, Kubly VJ, Bergstralh EJ, Li X, Kim B, King BF, Glockner J, Holmes DR, Rossetti S, Harris PC, LaRusso NF, Torres VE. Randomized clinical trial of long-acting somatostatin for autosomal dominant polycystic kidney and liver disease. *J Am Soc Nephrol* 2010; **21**: 1052-1061 [PMID: 20431041 DOI: 10.1681/ASN.2009121291]

56 **Caroli A**, Perico N, Perna A, Antiga L, Brambilla P, Pisani A, Visciano B, Imbriaco M, Messa P, Cerutti R, Dugo M, Cancian L, Buongiorno E, De Pascalis A, Gaspari F, Carrara F, Rubis N, Prandini S, Remuzzi A, Remuzzi G, Ruggenenti P. Effect of longacting somatostatin analogue on kidney and cyst growth in autosomal dominant polycystic kidney disease (ALADIN): a randomised, placebo-controlled, multicentre trial. *Lancet* 2013; **382**: 1485-1495 [PMID: 23972263 DOI: 10.1016/S0140-6736(13)61407-5]

57 **Torres VE**, Meijer E, Bae KT, Chapman AB, Devuyst O, Gansevoort RT, Grantham JJ, Higashihara E, Perrone RD, Krasa HB, Ouyang JJ, Czerwiec FS. Rationale and design of the TEMPO (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and its Outcomes) 3-4 Study. *Am J Kidney Dis* 2011; **57**: 692-699 [PMID: 21333426 DOI: 10.1053/j.ajkd.2010.11.029]

58 **Torres VE**, Chapman AB, Devuyst O, Gansevoort RT, Grantham JJ, Higashihara E, Perrone RD, Krasa HB, Ouyang J, Czerwiec FS. Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl J Med* 2012; **367**: 2407-2418 [PMID: 23121377 DOI: 10.1056/NEJMoa1205511]

59 **Erickson KF**, Chertow GM, Goldhaber-Fiebert JD. Cost-effectiveness of tolvaptan in autosomal dominant polycystic kidney disease. *Ann Intern Med* 2013; **159**: 382-389 [PMID: 24042366 DOI: 10.7326/0003-4819-159-6-201309170-00004]

60 **Sabbatini M**, Russo L, Cappellaio F, Troncone G, Bellevicine C, De Falco V, Buonocore P, Riccio E, Bisesti V, Federico S, Pisani A. Effects of combined administration of rapamycin, tolvaptan, and AEZ-131 on the progression of polycystic disease in PCK rats. *Am J Physiol Renal Physiol* 2014; **306**: F1243-F1250 [PMID: 24647711 DOI: 10.1152/ajprenal.00694.2013]

61 **Chapman AB**, Torres VE, Perrone RD, Steinman TI, Bae KT, Miller JP, Miskulin DC, Rahbari Oskoui F, Masoumi A, Hogan MC, Winklhofer FT, Braun W, Thompson PA, Meyers CM, Kelleher C, Schrier RW. The HALT polycystic kidney disease trials: design and

implementation. *Clin J Am Soc Nephrol* 2010; **5**: 102-109 [PMID: 20089507 DOI: 10.2215/CJN.04310709]
62 **Myint TM**, Rangan GK, Webster AC. Treatments to slow progression of autosomal dominant polycystic kidney disease: systematic review and meta-analysis of randomized trials. *Nephrology* (Carlton) 2014; **19**: 217-226 [PMID: 24460701 DOI: 10.1111/nep.12211]
63 **Patch C**, Charlton J, Roderick PJ, Gulliford MC. Use of antihypertensive medications and mortality of patients with autosomal dominant polycystic kidney disease: a population-based study. *Am J Kidney Dis* 2011; **57**: 856-862 [PMID: 21458899 DOI: 10.1053/j.ajkd.2011.01.023]
64 **Zeltner R**, Poliak R, Stiasny B, Schmieder RE, Schulze BD. Renal and cardiac effects of antihypertensive treatment with ramipril vs metoprolol in autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant* 2008; **23**: 573-579 [PMID: 17984104 DOI: 10.1093/ndt/gfm731]
65 **Casteleijn NF**, Visser FW, Drenth JP, Gevers TJ, Groen GJ, Hogan MC, Gansevoort RT. A stepwise approach for effective management of chronic pain in autosomal-dominant polycystic kidney disease. *Nephrol Dial Transplant* 2014; **29** Suppl 4: iv142-iv153 [PMID: 25165181 DOI: 10.1093/ndt/gfu073]
66 **Bajwa ZH**, Sial KA, Malik AB, Steinman TI. Pain patterns in patients with polycystic kidney disease. *Kidney Int* 2004; **66**: 1561-1569 [PMID: 15458452 DOI: 10.1111/j.1523-1755.2004.00921.x]
67 **Bajwa ZH**, Gupta S, Warfield CA, Steinman TI. Pain management in polycystic kidney disease. *Kidney Int* 2001; **60**: 1631-1644 [PMID: 11703580 DOI: 10.1046/j.1523-1755.2001.00985.x]
68 **Walsh N**, Sarria JE. Management of chronic pain in a patient with autosomal dominant polycystic kidney disease by sequential celiac plexus blockade, radiofrequency ablation, and spinal cord stimulation. *Am J Kidney Dis* 2012; **59**: 858-861 [PMID: 22361041 DOI: 10.1053/j.ajkd.2011.12.018]
69 **Li L**, Szeto CC, Kwan BC, Chow KM, Leung CB, Kam-Tao Li P. Peritoneal dialysis as the first-line renal replacement therapy in patients with autosomal dominant polycystic kidney disease. *Am J Kidney Dis* 2011; **57**: 903-907 [PMID: 21458901 DOI: 10.1053/j.ajkd.2011.01.019]
70 **Hadimeri H**, Johansson AC, Haraldsson B, Nyberg G. CAPD in patients with autosomal dominant polycystic kidney disease. *Perit Dial Int* 1998; **18**: 429-432 [PMID: 10505567]
71 **Yang CC**, Chuang FR, Wu CH, Chen JB, Lee CH, Lee CT. Refractory Salmonella enterica serotype choleraesuis-related renal cyst infection in a patient with autosomal dominant polycystic kidney disease undergoing hemodialysis treated successfully with intracystic ciprofloxacin infusion. *Med Princ Pract* 2012; **21**: 576-578 [PMID: 22710499 DOI: 10.1159/000339199]
72 **Fleming TW**, Barry JM. Bilateral open transperitoneal cyst reduction surgery for autosomal dominant polycystic kidney disease. *J Urol* 1998; **159**: 44-47 [PMID: 9400433 DOI: 10.1016/S0022-5347(01)64007-2]
73 **Millar M**, Tanagho YS, Haseebuddin M, Clayman RV, Bhayani SB, Figenshau RS. Surgical cyst decortication in autosomal dominant polycystic kidney disease. *J Endourol* 2013; **27**: 528-534 [PMID: 23157176 DOI: 10.1089/end.2012.0529]
74 **Hemal AK**, Gupta NP, Rajeev TP, Aron M, Bhowmik D, Jain R. Retroperitoneoscopic management of infected cysts in adult polycystic kidney disease. *Urol Int* 1999; **62**: 40-43 [PMID: 10436431 DOI: 10.1159/000030354]
75 **Kanaan N**, Devuyst O, Pirson Y. Renal transplantation in autosomal dominant polycystic kidney disease. *Nat Rev Nephrol* 2014; **10**: 455-465 [PMID: 24935705 DOI: 10.1038/nrneph.2014.104]
76 **Alam A**, Perrone RD. Management of ESRD in patients with autosomal dominant polycystic kidney disease. *Adv Chronic Kidney Dis* 2010; **17**: 164-172 [PMID: 20219619 DOI: 10.1053/j.ackd.2009.12.006]
77 **Yamamoto T**, Watarai Y, Kobayashi T, Matsuda Y, Tsujita M, Hiramitsu T, Nanmoku K, Goto N, Katayama A, Tominaga Y, Uchida K. Kidney volume changes in patients with autosomal dominant polycystic kidney disease after renal transplantation. *Transplantation* 2012; **93**: 794-798 [PMID: 22491657 DOI: 10.1097/TP.0b013e318246f910]
78 **Fuller TF**, Brennan TV, Feng S, Kang SM, Stock PG, Freise CE. End stage polycystic kidney disease: indications and timing of native nephrectomy relative to kidney transplantation. *J Urol* 2005; **174**: 2284-2288 [PMID: 16280813 DOI: 10.1097/01.ju.0000181208.06507.aa]
79 **Patel P**, Horsfield C, Compton F, Taylor J, Koffman G, Olsburgh J. Native nephrectomy in transplant patients with autosomal dominant polycystic kidney disease. *Ann R Coll Surg Engl* 2011; **93**: 391-395 [PMID: 21943464 DOI: 10.1308/003588411X582690]
80 **Sulikowski T**, Tejchman K, Zietek Z, Rózański J, Domański L, Kamiński M, Sieńko J, Romanowski M, Nowacki M, Pabisiak K, Kaczmarczyk M, Ciechanowski K, Ciechanowicz A, Ostrowski M. Experience with autosomal dominant polycystic kidney disease in patients before and after renal transplantation: a 7-year observation. *Transplant Proc* 2009; **41**: 177-180 [PMID: 19249508 DOI: 10.1016/j.transproceed.2008.10.034]
81 **Brazda E**, Ofner D, Riedmann B, Spechtenhauser B, Margreiter R. The effect of nephrectomy on the outcome of renal transplantation in patients with polycystic kidney disease. *Ann Transplant* 1996; **1**: 15-18 [PMID: 9869924]
82 **Kirkman MA**, van Dellen D, Mehra S, Campbell BA, Tavakoli A, Pararajasingam R, Parrott NR, Riad HN, McWilliam L, Augustine T. Native nephrectomy for autosomal dominant polycystic kidney disease: before or after kidney transplantation? *BJU Int* 2011; **108**: 590-594 [PMID: 21166760 DOI: 10.1111/j.1464-410X.2010.09938.x]
83 **Król R**, Ziaja J, Cierniak T, Pawlicki J, Chudek J, Wiecek A, Cierpka L. Simultaneous transabdominal bilateral nephrectomy in potential kidney transplant recipients. *Transplant Proc* 2006; **38**: 28-30 [PMID: 16504655 DOI: 10.1016/j.transproceed.2005.12.099]
84 **Nunes P**, Mota A, Alves R, Figueiredo A, Parada B, Macário F, Rolo F. Simultaneous renal transplantation and native nephrectomy in patients with autosomal-dominant polycystic kidney disease. *Transplant Proc* 2007; **39**: 2483-2485 [PMID: 17954154 DOI: 10.1016/j.transproceed.2007.07.035]
85 **Song WL**, Zheng JM, Mo CB, Wang ZP, Fu YX, Feng G, Shen ZY. Kidney transplant for autosomal dominant polycystic kidney disease: the superiority of concurrent bilateral nephrectomy. *Urol Int* 2011; **87**: 54-58 [PMID: 21677416 DOI: 10.1159/000324603]
86 **Tyson MD**, Wisenbaugh ES, Andrews PE, Castle EP, Humphreys MR. Simultaneous kidney transplantation and bilateral native nephrectomy for polycystic kidney disease. *J Urol* 2013; **190**: 2170-2174 [PMID: 23727414 DOI: 10.1016/j.juro.2013.05.057]
87 **Tabibi A**, Simforoosh N, Abadpour P, Gholamrezaie HR, Nafar M. Concomitant nephrectomy of massively enlarged kidneys and renal transplantation in autosomal dominant polycystic kidney disease. *Transplant Proc* 2005; **37**: 2939-2940 [PMID: 16213267 DOI: 10.1016/j.transproceed.2005.07.053]
88 **Dinckan A**, Kocak H, Tekin A, Turkyilmaz S, Hadimioglu N, Ertug Z, Gunseren F, Ari E, Dinc B, Gurkan A, Yucel S. Concurrent unilateral or bilateral native nephrectomy in kidney transplant recipients. *Ann Transplant* 2013; **18**: 697-704 [PMID: 24356642 DOI: 10.12659/AOT.889377]
89 **Eng M**, Jones CM, Cannon RM, Marvin MR. Hand-assisted laparoscopic nephrectomy for polycystic kidney disease. *JSLS* 2013; **17**: 279-284 [PMID: 23925022 DOI: 10.4293/108680813X13654754535719]
90 **Seshadri PA**, Poulin EC, Pace D, Schlachta CM, Cadeddu MO, Mamazza J. Transperitoneal laparoscopic nephrectomy for giant polycystic kidneys: a case control study. *Urology* 2001; **58**: 23-27 [PMID: 11445473 DOI: 10.1016/S0090-4295(01)01005-6]
91 **Gill IS**, Kaouk JH, Hobart MG, Sung GT, Schweizer DK, Braun WE. Laparoscopic bilateral synchronous nephrectomy for autosomal dominant polycystic kidney disease: the initial experience. *J Urol* 2001; **165**: 1093-1098 [PMID: 11257645 DOI: 10.1016/S0022-5347(05)66435-X]
92 **Jacquet A**, Pallet N, Kessler M, Hourmant M, Garrigue V, Rostaing L, Kreis H, Legendre C, Mamzer-Bruneel MF. Outcomes of renal transplantation in patients with autosomal dominant polycystic kidney disease: a nationwide longitudinal study. *Transpl Int* 2011; **24**: 582-587

[PMID: 21352383 DOI: 10.1111/j.1432-2277.2011.01237.x]
93 **Mosconi G**, Persici E, Cuna V, Pedone M, Tonioli M, Conte D, Ricci A, Feliciangeli G, La Manna G, Nanni Costa A, Stefoni S. Renal transplant in patients with polycystic disease: the Italian experience. *Transplant Proc* 2013; **45**: 2635-2640 [PMID: 24034011 DOI: 10.1016/j.transproceed.2013.07.016]
94 **Hamer RA**, Chow CL, Ong AC, McKane WS. Polycystic kidney disease is a risk factor for new-onset diabetes after transplantation. *Transplantation* 2007; **83**: 36-40 [PMID: 17220788 DOI: 10.1097/01.tp.0000248759.37146.3d]
95 **Neeff HP**, Pisarski P, Tittelbach-Helmrich D, Karajanev K, Neumann HP, Hopt UT, Drognitz O. One hundred consecutive kidney transplantations with simultaneous ipsilateral nephrectomy in patients with autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant* 2013; **28**: 466-471 [PMID: 23042709 DOI: 10.1093/ndt/gfs118]
96 **Rowe I**, Boletta A. Defective metabolism in polycystic kidney disease: potential for therapy and open questions. *Nephrol Dial Transplant* 2014; **29**: 1480-1486 [PMID: 24459136 DOI: 10.1093/ndt/gft521]
97 **Meijer E**, Drenth JP, d'Agnolo H, Casteleijn NF, de Fijter JW, Gevers TJ, Kappert P, Peters DJ, Salih M, Soonawala D, Spithoven EM, Torres VE, Visser FW, Wetzels JF, Zietse R, Gansevoort RT. Rationale and design of the DIPAK 1 study: a randomized controlled clinical trial assessing the efficacy of lanreotide to Halt disease progression in autosomal dominant polycystic kidney disease. *Am J Kidney Dis* 2014; **63**: 446-455 [PMID: 24342522 DOI: 10.1053/j.ajkd.2013.10.011]
98 **Rangan GK**, Harris DC. Rationale and design of an observational study to determine the effects of cholecalciferol on hypertension, proteinuria and urinary MCP-1 in ADPKD. *Curr Hypertens Rev* 2013; **9**: 115-120 [PMID: 23971693 DOI: 10.2174/15734021113099990006]
99 **Haynes R**, Kheradmand F, Winearls CG. Survival after starting renal replacement treatment in patients with autosomal dominant polycystic kidney disease: a single-centre 40-year study. *Nephron Clin Pract* 2012; **120**: c42-c47 [PMID: 22205054 DOI: 10.1159/000334429]
100 **Orskov B**, Sørensen VR, Feldt-Rasmussen B, Strandgaard S. Changes in causes of death and risk of cancer in Danish patients with autosomal dominant polycystic kidney disease and end-stage renal disease. *Nephrol Dial Transplant* 2012; **27**: 1607-1613 [PMID: 21873624 DOI: 10.1093/ndt/gfr46]

P- Reviewer: Akyuz F, Paraskevas KI, Shou ZF **S- Editor**: Gong XM
L- Editor: A **E- Editor**: Wu HL

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com