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Much has changed since the launching in the US of the End-Stage Renal Disease (ESRD) Program under Medicare on July 1, 1973, a unique entitlement program based solely on the presence of a clinical condition. Dialysis, initially a privilege for a select few, has exploded since then to become a multi-billion dollar industry today, with over 600,000 patients on dialysis in the US, and over 1.6 million worldwide.

The first patient on chronic hemodialysis was 39-year-old American Clyde Shields who had glomerulonephritis; he survived for 11 years. Today, the elderly population has the fastest growing ESRD rate, with often a large burden of comorbidities and very high mortality rates. Close to half of patients older than 75 years of age have some degree of chronic kidney disease (CKD), many of whom are at increased risk of cardiovascular disease and death. It is then very timely that this year’s theme for World Kidney Day, which occurred on March 13, 2014, was “CKD and aging.”

On the other end of the age spectrum, the obesity epidemic has led to an increase in the rate of hypertension in the pediatric population. The metabolic syndrome/obesity epidemic is also likely responsible for the dramatic increase in nephrolithiasis rate. Previously largely regarded as a benign condition, nephrolithiasis is associated with huge costs of care and increased risk of acute kidney injury and CKD.

My contribution, “The Elderly Patient with Low eGFR: Beyond the Numbers,” presents many considerations in the care of older adults with low renal function, with the goal of promoting individualized care based on shared decision making.

In “Anemia and Bone Disease of Chronic Kidney Disease: Pathogenesis, Diagnosis, and Management,” DOUGLAS SHEMIN, MD, reviews the pathogenesis and diagnosis of anemia and bone disease in CKD, and summarizes recent consensus guidelines for treatment.

In “Ambulatory Blood Pressure Monitoring in Children: A Safe and Effective Diagnostic and Screening Tool for the Diagnosis of Hypertension in Children,” ROBIN KREMSDORF, MD, and M. KHURRAM FAIZAN, MD, review the technique of ABPM and its value in the work-up of children with elevated blood pressure.

In “The Growing Prevalence of Kidney Stones and Opportunities for Prevention,” KATHERINE RICHMAN, MD, JOHN O’BELL, MD, and GYAN PAREEK, MD, offer an updated review on nephrolithiasis with an emphasis on prevention through a multidisciplinary approach.

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The Elderly Patient with Low eGFR: Beyond the Numbers
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ABSTRACT
Chronic Kidney Disease (CKD) is widely prevalent in the elderly population. The recent "Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline on the Evaluation and Management of CKD" builds on the previous Kidney Disease Outcomes Quality Initiative (KDOQI) guideline and addresses many of its gaps. However, older adults with CKD have unique characteristics that may not be addressed by general guidelines. This review presents many of the challenges and considerations in the care of elderly patients with CKD, with the ultimate goal of promoting an individualized management plan based on shared decision-making.

KEYWORDS: chronic kidney disease, elderly, prognosis, conservative management, shared decision-making

INTRODUCTION
The introduction of the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines by the National Kidney Foundation (NKF) in 2002 established the classification of chronic kidney disease (CKD) based on glomerular filtration rate (GFR) or realistically, estimated GFR (eGFR) [1]. Applying this classification to the NHANES 1999-2004 cohort, it was estimated that 16.8% of the US general population has CKD. The prevalence was much higher, 39.4%, in those aged 60 and older, most of whom have early stages of CKD [2]. This raised concern that CKD may be over diagnosed, especially in the elderly without albuminuria, since some decrease in eGFR may simply represent normal kidney aging. The Kidney Disease: Improving Global Outcomes (KDIGO), now independent from NKF, published new CKD guidelines in early 2013. Among the numerous updates were the addition of albuminuria - a major prognosis modifier - into the classification by GFR, the division of CKD stage 3 into 3a and 3b, focus on CKD outcomes, guidance on specialist referral and promotion of multidisciplinary CKD chronic care models, including the ability to provide conservative (non-dialytic) management [CM] [3]. Age, however, was not incorporated into CKD classification and the issue of kidney senescence versus disease still stirs debate [4]. While the referral rate for CKD has increased significantly since 2002, there continues to be a surprising lack of guideline awareness among many non-specialists. Older patient age, among other factors, tends to decrease the odds of referral [5]. Certainly, not all elderly with CKD may benefit from specialist care, but many would. Older adults have unique characteristics. The following sections will review several key considerations relevant to the care of older patients with low eGFR.

DIAGNOSTIC CHALLENGES:
KIDNEY SENESCENCE OR DISEASE?

Kidney Senescence: selected attributes
Most anatomical and histological changes attributed to kidney aging stem from cross-sectional studies such as autopsies and biopsies. The number of glomeruli is determined prenatally and varies widely from 330,000 to 1,100,000 among adults. Renal mass generally starts decreasing around the 4th decade of life, which may also be seen radiographically and corresponds mostly to cortical loss. Histological changes on light microscopy are generally termed “nephrosclerosis” and include glomerulosclerosis, arteriosclerosis, tubular atrophy and interstitial fibrosis [6]. In a large cohort of living donors at the Mayo Clinic, the prevalence of nephrosclerosis varied from 2.7% at ages 18–29 to 75% at ages 70–77 [7].

Functionally, there are very few longitudinal studies looking at decline in GFR. Perhaps the most notable is the Baltimore Longitudinal Study of Aging, where 254 “normal” adults of ages 22–97 were followed with serial [5–14x] creatinine clearance [CrCl] measurements from 1958–1981. Overall, there was an average decline in measured CrCl [mCrCl] of 0.75 mL/min/year but there were 3 patterns: a group with slow decline in serial mCrCl, a group with faster decline and a group with no change to a small improvement[8]. This led some to believe that renal functional decline with age is not universal. However, it is important to note that diabetics were not excluded if they had no proteinuria (diabetes may be associated with an initial increase in GFR due to hyperfiltration) and CrCl measurement itself is not without flaws. Nonetheless, it has been widely quoted since that “GFR” decreases at an average rate [0.75–1 mL/min/1.73m2/year] in healthy aging.

Living donors, being especially well screened, are typically a good representation of “healthy” older adults, although some may have treated hypertension. The Mayo Clinic cohort mentioned above offers some additional notable observations [cross-sectional]: GFR overall declined by age;
none of the 1203 donors (max age 77) had a measured GFR (mGFR) < 60 mL/min/1.73m² [using iothalamate], there was no correlation between mGFR and nephrosclerosis; the only characteristics associated with nephrosclerosis independent of age and sex in this healthy population were urine albumin, nocturnal blood pressure, and treated hypertension; finally, 5% would have had CKD by eGFR, but had normal mGFR and no nephrosclerosis [7].

**Measuring Kidney Function in the Elderly**

Based on the above, a hypothetical healthy 90-year-old woman with no comorbidities, starting off with a GFR of 100 mL/min/1.73m² and losing GFR after age 30 at an annual rate of 0.75, would have a GFR of 55 mL/min/1.73m² that could be attributed to aging and not “disease.” However, measuring GFR using exogenous substances (inulin) is not practical or readily available in many places and is replaced in clinical practice by estimates (eGFR). Most labs automatically report eGFR using the 4-variable MDRD or the more recent CKD-EPI equation. The latter is slightly more accurate [9]. While these equations are very practical and useful for epidemiological studies, it is important to remember that no matter which one is used, the difference between eGFR and mGFR can be substantial, in some cases more than 30 mL/min/1.73m². The incorporation of cystatin C may improve the accuracy of eGFR [10] but is costly and not widely used yet. Measured creatinine clearance (mCrCl) is another option but it is cumbersome for many elderly and errors in collection are common. It may not necessarily be more accurate than eGFR, since it typically overestimates mGFR by a variable degree, which gets worse as GFR decreases, due to an increase in creatinine secretion by the proximal tubules and extra renal degradation. Surprisingly however, one study found that mCrCl underestimates mGFR in the elderly [11]. Still, it may be useful in extremes of weight, amputees, vegetarians and those taking creatine supplements [12], as all of these factors are not taken into account in eGFR equations.

**Senescence or disease: does it matter?**

**Hard outcomes in the elderly with low eGFR**

Studies in nephrology have traditionally focused on hard outcomes such as mortality and End-Stage-Renal-Disease (ESRD). From an epidemiological standpoint, an association between moderately low eGFR (stage 3a) and poor outcomes such as mortality and End-Stage-Renal-Disease (ESRD) in the elderly was attenuated but the absolute mortality was higher. Age did not affect ESRD risk [13]. Population-level associations however, may not necessarily apply to an individual patient. For example, the above meta-analysis also showed increased mortality at very high eGFR values in patients >55y, likely reflecting the influence of patients with muscle wasting [due to malnutrition or other comorbidities] [13]. Does that mean that a healthy and active 65-year-old individual with eGFR 100 mL/min/1.73m² is at risk? Probably not. The same concept goes for an older adult with eGFR 50 mL/min/1.73m². The new KDIGO CKD classification system does not distinguish between age groups [3]. The author agrees with this decision, with the acknowledgment that no guideline is designed to be a substitute for individual judgment.

**THERAPEUTIC CHALLENGES IN THE CARE OF ELDERLY PATIENTS WITH CKD AND THE ROLE OF THE NEPHROLOGIST**

**General referral guidelines**

The KDIGO guidelines suggest a list of criteria for referral to a nephrologist. These include: Acute kidney injury (AKI), CKD stage 4-5, significant albuminuria or proteinuria, progressive CKD, RBC casts, unexplained hematuria, refractory hypertension, persistent serum potassium abnormalities, recurrent and extensive nephrolithiasis and hereditary kidney diseases [3]. Some of the benefits of early versus late referral include: reduced mortality and hospitalization, better uptake of peritoneal dialysis and earlier placement of dialysis access [14]. Patients with early stages of CKD often can be managed by their primary care providers (PCP).

Traditional facets of typical CKD care, some of which may be done by PCPs, may include treatment aimed at delaying progression, managing complications such as anemia, bone-mineral disorders, hyperkalemia, metabolic acidosis, blood pressure and glycemic control, correct dosing of medications, preparing for ESRD and other interventions aimed at cardiovascular risk reduction.

**Beyond the guidelines**

Regardless of whether reduced eGFR is attributed to aging or CKD, the older adult with low eGFR presents unique challenges. Many interventions are often of unproven benefit and sometimes harmful in the elderly. Outcomes of particular interest to the elderly, such as maintaining independence and quality of life (QOL), are often lacking in many clinical trials. Older adults with limited life expectancy may not live long enough to realize the benefits of certain therapies. Guidelines are inherently incapable of addressing individual situations and may conflict with recommendations aimed at another comorbidity. It is up to the provider to reconcile guidelines with patient preferences and to individualize therapy after judging risk/benefit ratio. For example, in an 85-year-old frail hypertensive woman with CKD and frequent falls, it may be unsafe to aim for a blood pressure of 130/80 mmHg. In a similar patient who has hyperphosphatemia, the increased pill burden of phosphate binders may
outweigh the potential long-term benefits.

In an interesting survey of provider decision-making, the strongest factor that influenced PCP decision to refer older adults with CKD was the expectation that the nephrologist will discuss goals of care. Initiation of dialysis per se was not a factor [15]. Decades after its introduction, dialysis therapy has boomed and has automatically been assumed to prolong life. However, the elderly population with ESRD often has poor outcomes and very high mortality rates [16]. CM may be a better alternative for some of them. The nephrologist’s role includes assessing, educating and counseling elderly CKD patients and their caregivers to determine the best course of action in the event of ESRD. Estimation of CKD prognosis and understanding outcomes of renal replacement therapy (DT) versus CM (including outcomes that may be relevant to the patient, other than mortality) is crucial for proper “shared decision-making” to occur.

Who progresses to ESRD?

In a very large VA cohort (n = 209,622) with CKD stages 3-5 followed for a mean of 3.2 years, risk of death was higher than risk of treated ESRD in adults >65-84 years of age for eGFR >15 mL/min/1.73 m2. For adults >85 years age, mortality always exceeded risk of treated ESRD. There was not enough information to identify patients who had indications for DT but elected not to start it [17]. Complementing this information, a large community-based CKD cohort from Alberta, Canada (n=1,813,824) was studied retrospectively with a median follow up of 4.4 years. Among those 75 years of age and older, the rate of untreated ESRD was significantly higher (2-10 fold) than the rate of treated ESRD, while the opposite was observed in younger adults. Possible reasons for this include a competing risk of death in older adults, lower rate of uremic symptoms or less acceptance to RRT and transplantation. Still, the rate of combined treated and untreated ESRD was elevated in the elderly [18]. According to USRDS data, the elderly show the highest ESRD incidence and prevalence rates [16].

Using the rate of eGFR decline to predict ESRD is intuitive. However, what constitutes rapid progression is controversial. Data from the Alberta Kidney Disease Network show a graded increase in treated ESRD risk of approximately 2-fold for each 1 mL/min/1.73m2/year increase in eGFR decline slope. Albuminuria is also a major risk factor although changes in albuminuria over time require more studies [3].

However, CKD progression is often non-linear. Acute kidney injury (AKI) can significantly alter the course of CKD. A meta-analysis (n=5529 patients) showed that patients 65 and older with AKI were 28% (95% CI 1.01 - 1.55, p<0.05) less likely to recover renal function than younger ones [19]. In a US cohort of 233,803 hospitalized elderly patients who survived to discharge, the adjusted hazard ratio for developing ESRD was 41.2 (95% CI 34.6 to 49.1) for patients with AKI and CKD relative to those without kidney disease, compared to 8.4 (95% CI 7.4 to 9.6) for patients with CKD and without AKI [20]. There is growing interest in predictive models for CKD progression to ESRD. For example, Tangri et al. developed and validated a predictive model of kidney failure from 2 large Canadian cohorts with CKD stage 3-5 [21]. It is available online and in mobile applications such as QxMD. Drawz et al. developed and validated a 1-year predictive model from 2 VA cohorts, which was comparable to Tangri’s model in the validation cohort (C-index 0.823 vs 0.780 respectively) [22]. While the utility of these models needs to be evaluated prospectively, they may be useful in the shared decision-making process. Caution is warranted however, when using them (if at all) in populations with different characteristics than the original cohorts.

Survival with or without DT

While older adults can have favorable outcomes after kidney transplantation, the reality is that only very few get this opportunity – 3.4% of ESRD patients 70 or older, 0.5% of patients 80 and older [23]. This topic is beyond the scope of this review.

In the absence of randomized controlled trials of CM versus DT, retrospective studies offer important insights. In a UK cohort of elderly ESRD patients (n = 129), DT provided better survival (measured from when eGFR <15) compared to CM (12 months of multidisciplinary treatment - MDT). However, patients with high comorbidity scores, especially ischemic heart disease, did not have better survival on DT compared to CM [24]. In a larger UK cohort (n = 844), DT only provided a marginal, non-statistically significant survival advantage of 4 months (measured from a putative eGFR in CM patients) when adjusted for age >75, comorbidity and diabetes [25]. From a different perspective, another UK observational study of 202 elderly patients showed an advantage of DT compared to CM [37.8 versus 13.9 months]. However, DT patients had significantly more hospital days and CM patients were more likely to die at home. When accounting for hospital days and time spent on dialysis (whole day for many patients), the difference in “hospital/dialysis free” survival shrinks between the 2 groups to just a few months [26].

There is also interest in predictive mortality models for incident and prevalent dialysis patients. For example, Cohen et al. developed and validated a prognostic tool to estimate 6-month mortality in prevalent dialysis patients in the US [27]. It is available online and in some mobile applications.

Tamura et al. provide a useful framework for individualizing decisions in elderly ESRD patients by considering life expectancy, risks and benefits of competing treatments (including “number needed to treat” comparisons) and patient preferences. They apply it to choice of dialysis modality, choice of dialysis vascular access and referral for transplantation [28]. Using a predictive model to calculate life expectancy would come in handy when following such framework.
Other important outcomes and considerations

Frailty (and geriatric syndromes in general) is very common in elderly CKD patients. Prevalence dramatically increases with CKD stage and is associated with increased mortality [29]. In a US cohort (n=2275), 78.8% of ESRD patients > 80 years of age met criteria for frailty and had more than 2-fold increase in mortality [30]. Nursing home incident ESRD residents (n=3702) were studied linking USRDS data with Minimum Data Set–Activities of Daily Living (MDS–ADL) scores. Patients experienced a sharp decline in functional status in the first 3 months after dialysis initiation. At 1 year, 58% had died and only 13% had maintained their functional status [31]. Similarly, initiation of dialysis had a negative effect on independent living in a community of patients > 80 years old [32].

Functional status of ESRD patients managed by CM was preserved until the last month before death in a UK single center study [33]. Symptoms in the last month can be significant and may require an integrated multidisciplinary palliative care approach [34].

QOL was assessed in a single UK center in a cohort of patients with ESRD treated with RRT versus CM (n = 170, mean age >70, follow up 3 years). CM patients were older, more dependent, had higher comorbidities, poorer physical health and more anxiety at baseline. Mental health, depression symptoms and global satisfaction with life were similar in all modality groups at baseline. SF-36 and anxiety scores changed little during follow-up in both groups. Satisfaction with life scores decreased significantly after dialysis initiation and did not subsequently recover, but did not change over time in the CM group [35].

Shared Decision Making

Discussing all the elements above and aligning CKD management with the patient’s goals of care is at the heart of patient-centered medicine. An interesting Australian survey in CKD 3-5 patients (n=105 completed) aimed to assess factors influencing patient choice of ESRD treatment. Patients were more likely to chose RRT over CM if it increases life expectancy, if it can be done during the day or evening versus day only and if subsidized transport was available. They were more likely to chose CM if RRT meant more hospital days and more restrictions on travel. Patients would trade off 7 months of life expectancy to reduce hospital visits and 15 months of life expectancy to increase ability to travel [36]. Unfortunately, elderly patients are often marginalized in the decision to undergo RRT and are left with many misconceptions.


US Concerns and challenges

Most of the data on CM coming from other countries, there are concerns that its implementation in the US is challenging due to “uneven access to palliative care across health care systems, a shortage of palliative-care physicians, limited training of US nephrologists in these areas, and poor reimbursement for these and other cognitive services” [37]. Furthermore, patient choices and goals of care may not agree with the growing number of imposed reportable and penalizable “quality measures,” many of which are of questionable utility, especially in the vulnerable elderly. This introduces conflict of interest when practices may be faced with financial penalties.

However, the US healthcare system is constantly evolving. The interest in patient-centered medical homes is extending into patient-centered neighborhoods, with the promise, if done correctly and with fair incentives, of addressing many of these concerns [38, 39].

The dramatic increase in dialysis rates in the US seems to be substantially slowing down recently, suggesting later dialysis starts and greater use of CM [40].

On an international level, KDOQI convened a “Controversies Conference on Supportive/Palliative Care in CKD” in December of 2013 in Mexico, which can be reviewed online [http://kdoqig.org/home/conferences/supportivcare/].

CONCLUSION

The elderly population with CKD is growing fast and often has poor outcomes. Guidelines provide guidance as to the management of CKD but older adults present unique diagnostic and therapeutic challenges that go beyond simple numerical targets. Collaboration between primary providers and nephrologists, often within larger multidisciplinary teams may optimize the care of these individuals through better counseling and a process of shared decision-making. Many may be better served by CM. Obstacles are numerous but can gradually be overcome by the concerted efforts of all the involved parties.

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Disclosures 

None

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Anemia and Bone Disease of Chronic Kidney Disease: Pathogenesis, Diagnosis, and Management

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ABSTRACT
Anemia and metabolic bone disease accompany chronic kidney disease (CKD), and worsen as CKD progresses. It is likely that both processes contribute to the increased morbidity and mortality seen in CKD. This paper briefly reviews the pathogenesis and diagnosis of anemia and bone disease in CKD, and summarizes recent consensus guidelines for treatment.

KEYWORDS: Chronic kidney disease, anemia, hyperparathyroidism

INTRODUCTION
Chronic kidney disease (CKD) affects 10–15% of adults in the United States, is a group of disorders characterized by a progressive decline in the glomerular filtration and renal excretion of low molecular weight solutes. The severity of CKD is measured by the estimated glomerular filtration rate (eGFR), derived from the serum creatinine (SCr) level, and demographic criteria: age, sex, and ethnicity. The normal eGFR is over 120 ml/min; as CKD worsens, the eGFR declines. The current classification of CKD was introduced in 2002 by the National Kidney Foundation (NKF) and subsequently adopted by the international group, Kidney Disease Improving Global Outcomes (KDIGO). The cause of CKD may be diabetes mellitus, hypertension, polycystic disease, chronic glomerulonephritis or other causes, but regardless of diagnosis, the NKF/KDIGO classification defines stage III as an eGFR of 30–60 ml/min, stage IV as an eGFR of 15–30 ml/min, and stage V CKD as an eGFR below 15 ml/min.

Many large observational studies demonstrate that cardiovascular morbidity and mortality increase as the stage advances. Recently, it has been shown that albuminuria ( > 30 mg/gram creatinine/24 hour urine), independently of the eGFR predicts morbidity and mortality. Patients with CKD are at highest risk of all cause mortality if their eGFR is < 15 ml/min and urinary albumin excretion is > 300 mg/gram creatinine, but in all age groups, mortality risk increases below an eGFR of 60 ml/min.

CKD involves many pathophysiologic abnormalities: fluid overload, hypertension, accelerated atherosclerosis, inflammation, malnutrition, metabolic acidosis, hyperkalemia, anemia, and metabolic bone disease and it is difficult to ascribe the increased mortality risk to one or even a few causes. As part of a broad approach, these abnormalities can be evaluated and treated, thereby potentially decreasing the mortality risk. Reviewing the treatment of all of these processes is beyond the scope of a short paper. But two abnormalities associated with the decreased renal synthetic function of CKD: anemia, due to decreased production of erythropoietin, and bone disease, due to decreased production of calcitriol, decreased excretion of phosphorus, and increased synthesis of parathyroid hormone (PTH), may present early in CKD. They are relatively easy to diagnose and treat, and provide an opportunity to the primary care provider to potentially decrease some risks associated with CKD. This paper will review the diagnosis and management of anemia and bone disease due to CKD.

Anemia
Anemia, defined as a Hgb < 11.0 g/dL, is common in CKD and worsens as the CKD stage increases: data from a large observational study showed an anemia prevalence of 1.3 % in stage III, 5.2% in stage IV, and 44.1% in stage V CKD; once patients progress to dialysis, it exceeds 90%. The cause of anemia is multifactorial, including deficiencies of vitamin B12 or folate, defective intestinal absorption of iron due to the presence of hepcidin, occult bleeding due to a qualitative defect in platelet function, hemolysis, or bone marrow disease. But the likely greatest contributor relates to CKD itself: a defect in erythropoietin (EPO) production.

EPO is a 165 amino acid protein, which stimulates bone marrow receptors to produce red cell precursors and promote their differentiation into mature erythrocytes. EPO is primarily synthesized in kidney cells, so progressive loss of kidney function leads to decreased EPO production. EPO production normally can be increased thousandfold in response to tissue hypoxia in a process mediated by hypoxia inducible factor 1, and loss of this augmentation occurs in CKD. These abnormalities are present in all causes of CKD, with some exceptions: polycystic disease, for example, may be associated with normal or high EPO production.

Until the mid to late 1980s, the only therapy for the anemia of CKD was vitamin and iron supplementation and blood transfusions. Besides depleting the blood supply, over-reliance on transfusions caused increase in hepatitis B and C in CKD patients, iron overload, and development of antibodies, increasing sensitization to potential renal transplants.
The gene for EPO production was cloned in 1985; immediately, EPO production began, and soon, many clinical trials showed that administration of exogenous EPO increased the Hgb in patients at all stages of CKD, and decreased transfusion dependence. Also, most clinical trials showed that administration of EPO and its structural analogue, darbepoetin (with a longer half life) tends to improve subjective symptoms (fatigue, exercise tolerance, sexual dysfunction, cognitive function, and depression) in CKD in treated patients compared to controls. These findings, along with suggestions that cardiovascular morbidity and mortality was decreased with EPO treatment, and Medicare payment for erythropoietin in dialysis patients on dialysis, led to virtually universal EPO treatment of the anemia in dialysis patients and common treatment at earlier stages of CKD.

But the Hgb target to which EPO therapy should be directed was not well established. Three large, randomized, placebo controlled trials, published between 2006 and 2009 addressed this issue. The trials all randomized anemic patients with CKD to either a high or low Hgb target by varying the dose of EPO or darbepoetin. The Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study randomized patients to Hgb normalization (mean achieved Hgb 13.5 g/dL) or partial correction (mean achieved Hgb 11.3) and found that normalization of the Hgb was associated with a statistically greater rate of a composite outcome of cardiovascular death or morbidity. The Cardiovascular Risk Reduction by Early Anemia treatment with Epoetin beta (CREATE) trial randomized patients to full anemia correction (target Hgb 13 -15 g/dL) or partial correction (target Hgb 10.5–11.5 g/dL). There was a non-statistically significant trend towards a higher incidence of cardiovascular events in the full correction group. Finally, the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) trial compared targeting a Hgb of 13 g/dL with darbepoetin to placebo in CKD patients with diabetes, and found treatment to a higher Hgb target was not associated with a cardiovascular benefit, and was associated with a higher risk of stroke, and cancer associated mortality.

The results of these trials have greatly influenced treatment of CKD associated anemia with EPO or darbepoetin. In 2011, The Food and Drug Administration [FDA] released an advisory statement that the target Hgb level in CKD patients should no longer be 10–12 g/dL, but should be replaced by a program of using the lowest possible EPO or darbepoetin dose necessary to avoid transfusions. The FDA later specified that although that treatment of CKD associated anemia should be individualized, dosing of EPO or darbepoetin in an anemic patient with CKD should be decreased once the Hgb level exceeds 11.0. The FDA guidelines were endorsed by the KDIGO advisory group in 2012 and the American advisory group KDOQI (Kidney Disease Outcomes Quality Initiative) in 2013.

**Bone Disease**

Bone disease in CKD results from abnormalities of metabolism of two ions: phosphorus and calcium, and two hormones: 1,25 vitamin D (calcitriol) and PTH. Phosphorus in the diet is absorbed in the gastrointestinal tract, has a molecular weight of 31 daltons and is water soluble, is filtered by the kidney and its excretion decreases, and the serum level rises, as the eGFR decreases in CKD. The increase in the phosphorus level decreases the concentration of ionized and albumin bound calcium, as a greater proportion of calcium is bound to phosphorus. Renal hydroxylation of 25-vitamin D to its active form [calcitriol] also decreases as a result of progressive CKD. The presence of calcitriol is necessary for absorption of dietary calcium, and decreasing calcitriol, in addition to the high phosphorus level, leads to a drop in the serum calcium concentration.

The decrease in the serum calcium level stimulates calcium sensing receptors in the parathyroid gland to increase transcription and synthesis of PTH. High serum phosphorus and low calcitriol level also independently increase release of PTH. The high PTH, which may be present as early in CKD as an eGFR of 40 ml/min, increases as CKD progresses. Most laboratories in the United States use an intact PTH [i-PTH] assay, which measures both the biologically active PTH molecule and renally excreted inactive fragments, so as GFR worsens, the high intact PTH is due, in part, to this artifactual effect. In a patient with normal renal function, the elevated PTH would correct the low calcium and high phosphorus levels by increasing renal tubular reabsorption of calcium and decreasing reabsorption of phosphorus, but this fails to occur as CKD progresses. So the metabolic bone abnormalities of CKD include hyperphosphatemia (phosphorus level > 5.5 mg/dL), hypocalcemia, a low circulating calcitriol level, and a high level of PTH.

Sustained elevation of the PTH causes two major problems in CKD. PTH regulates bone mineral content, and elevation of the PTH increases osteoblastic, and more importantly, osteoclastic activity, leading to decreased bone mineralization and growth, and an increased risk of fractures. In addition, release of calcium and phosphorus from bone can lead to deposition of calcium and phosphorus in soft tissue and blood vessels, contributing to accelerated atherosclerosis and arterial stiffening. There is an incremental relationship between elevation of the PTH level and cardiovascular morbidity and mortality. Low circulating levels of calcitriol are also associated with increased mortality. A high phosphorus level is clearly identified with mortality in CKD patients treated with maintenance dialysis and there is now new evidence suggesting a relationship between elevation of the serum phosphorus and mortality in individuals with less advanced CKD.

Therapies for the metabolic bone abnormalities of CKD are aimed at correcting the abnormal levels of calcium, phosphorus, calcitriol, and PTH, and hopefully decreasing the effects of bone abnormalities on mortality. Unfortunately,
most of the data on these therapies are present in retrospective, observational, or short-term prospective trials. But, similar to guidelines on treatment of anemia in CKD, two main consortiums of experts, the KDIGO group, in 2009, and the KDOQI group in 2010, have established guidelines for the evaluation and treatment of metabolic bone disease in CKD, and the guidelines are largely in agreement.²⁻²⁰

In stage III CKD, both groups recommend measuring the calcium and phosphorus every 6–12 months, and the PTH level once, with follow-up levels depending on the circumstance. In stage IV CKD, they recommend calcium and phosphorus levels every 3–6 months and PTH levels every 6–12 months, and in stage V CKD, calcium and phosphorus measurements every 1–3 months, and PTH levels every 3–6 months. In all CKD stages, the 25-vitamin D level should be measured at least once, with follow-up levels depending on the circumstance.

In all CKD stages, if 25–vitamin D deficiency [< 30 ng/ml] is detected, patients should be given nutritional vitamin D [ergocalciferol]. Because of decreased hydroxylation of 25-OH vitamin D in advanced CKD, some experts suggest administration of calcitriol instead.²¹ In CKD stages III–V, the calcium and the phosphorus level should be maintained in the reference range, [for phosphorus, 2.7–4.6 mg/dL in stage III–IV, and 3.5–5.5 in stage V CKD]. Although earlier position papers suggested tight control of the PTH level, KDIGO and KDOQI suggest maintaining the PTH level at 2–9 times the upper limit of normal of the reference range; this works out to be 150–600 pg/ml.

The details of achieving these targets are not specified, but usually involve a combination of vitamin D, dietary phosphorus restriction, and phosphorus binders. As above, ergocalciferol, 50,000 to 100,000 IU per week, with substitution of calcitriol, 0.25 mcg daily as renal function worsens, should be prescribed to vitamin D deficient patients; calcitriol will also independently decrease the PTH level. However vitamin D products will increase the phosphorus level, by increasing gastrointestinal phosphorus absorption. Dietary phosphorus restriction [5–10 mg/kg/day, compared to a usual phosphorus intake of 15–20 mg/kg/day] is the first step. Phosphate restriction may entail protein restriction, so this may require the involvement of a dietitian to avoid malnutrition. Ingestion of plant-based proteins leads to less hyperphosphatemia than ingestion of animal based proteins.²²

If dietary restriction fails to control the phosphorus level, phosphate binders, which prevent gastrointestinal phosphorus absorption, should be used, and there is some evidence that phosphorus binders improve morbidity and mortality in CKD.²³

Phosphorus binders are calcium-based [calcium carbonate, calcium acetate] or non-calcium based [sevelamer, or lanthanum]. All phosphorus binders will lower the serum phosphorus. There is no proven superiority of one class or agent over another.²⁴ Calcium containing agents, have, in small observational studies, been linked with a greater degree of vascular calcification,²⁵ and they should be avoided in patients with hypercalcemia.

CONCLUSION

Anemia and bone disease commonly occur as consequences of CKD, become more severe as CKD progresses, and contribute to the increased morbidity and mortality seen in CKD. Both abnormalities can be relatively easily diagnosed. The specifics of treatment are subject to some debate, but initial treatment, as summarized above, can readily be administered by a primary care physician.

References


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Ambulatory Blood Pressure Monitoring in Children: A Safe and Effective Diagnostic and Screening Tool for the Diagnosis of Hypertension in Children

ROBIN KREMSDORF, MD; M. KHURRAM FAIZAN, MD, FAAP

INTRODUCTION
Hypertension is becoming an increasingly recognized health problem in children. The obesity epidemic has led to a greater frequency of hypertension diagnosis in children. In adults, hypertension is a leading cause of preventable death, heart attack, stroke, and kidney disease. For all patients, the goal of identifying and treating hypertension is to prevent end-organ damage and reduce mortality.

DEFINITION OF HYPERTENSION IN CHILDREN
The definition and classification of pediatric hypertension was put forth in The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents published in 2004. Using demographic data from approximately 64,000 children including NHANES surveys from 1999–2000, definitions of pediatric hypertension and prehypertension were published for children ages 1-17 years, using height percentiles of 5th, 25th, 50th, 75th, 90th and 95th respectively. Hypertension in children is defined as average Systolic and/or Diastolic BP that is > 95th percentile for gender, age and height on > 3 occasions. Prehypertension in children is defined as average Systolic or Diastolic blood pressures that are > 90th percentile but < 95th percentile. The term White Coat Hypertension is used when a child has blood pressures that are > 95th percentile in the clinic or office but < 90th percentile when measured outside of a clinical setting. Ambulatory Blood Pressure Monitoring (ABPM) is usually required to make this diagnosis. In addition to defining hypertension cut-offs, the Fourth Report also provided valuable guidelines for the measurement of blood pressure in the pediatric population (Tables 1 & 2).

AMBULATORY BLOOD PRESSURE MONITORING (ABPM)
Ambulatory Blood Pressure Monitoring (ABPM) refers to a non-invasive procedure in which a portable blood pressure device, worn by a patient, periodically records BP over a specified period of time, usually 24 hours. ABPM is an important tool in evaluating pediatric hypertension. The information obtained during an ABPM study offers a more detailed and nuanced profile of an individual’s blood pressure than can be gathered from a series of clinic measurements. It allows for assessment of White Coat Hypertension. It measures the average systolic and diastolic blood pressure during both wakefulness and sleep. It measures the proportion of time that the systolic and diastolic blood pressure is abnormally high. The proportion of time above normal is referred to as the blood pressure load. Each of these components of blood pressure contributes to understanding the particular cardiovascular and renal risk of an individual patient. Among children and adults, abnormalities of ambulatory blood pressure predict the development of hypertensive end-organ damage, specifically left ventricular hypertrophy. Among adults, ambulatory blood pressure predicts cardiovascular events better than clinic blood pressures.

During an ABPM procedure the patient has a blood

<table>
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<tr>
<th>Table 1. Measurement of BP in Children.</th>
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<tr>
<td>Children &gt;3 years old who are seen in a medical setting should have their BP measured</td>
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<tr>
<td>The preferred method of BP measurement is auscultation</td>
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<tr>
<td>Correct measurement requires a cuff that is appropriate to the size of the child’s upper arm</td>
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<tr>
<td>Elevated BP must be confirmed on repeated visits before characterizing a child as having hypertension</td>
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<tr>
<td>Measurements obtained by oscillometric devices that are greater than 90th percentile should be repeated by auscultation</td>
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<th>Table 2. Conditions under which Children Under 3 Years Old Should Have BP Measured.</th>
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<tr>
<td>History of Prematurity, very low birth weight, or other neonatal complication requiring intensive care</td>
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<tr>
<td>Congenital heart disease (repaired or non-repaired)</td>
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<tr>
<td>Recurrent urinary tract infections, hematuria, or proteinuria</td>
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<tr>
<td>Known renal disease or urologic malformations</td>
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<tr>
<td>Family history of congenital renal disease</td>
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<tr>
<td>Solid-organ transplant</td>
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<tr>
<td>Malignancy or bone marrow transplant</td>
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<tr>
<td>Treatment with drugs known to raise BP</td>
</tr>
<tr>
<td>Other systemic illnesses associated with hypertension (neurofibromatosis, tuberous sclerosis, etc)</td>
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<td>Evidence of elevated intracranial pressure</td>
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pressure cuff placed by a nephrology nurse who measures the arm circumference to determine appropriate cuff size. The patient wears the cuff and a small electronic device which can be worn on a belt or in a pocket. The device prompts the cuff to inflate every 20 minutes during the day and every 30 minutes at night to measure blood pressure and also records the blood pressure readings. Patients are advised to avoid heavy physical activity during the study, because this raises blood pressure and can therefore cloud interpretation of the results. The patient wears the monitor for 24 hours. The monitor is then returned to the nephrology clinic and the readings are downloaded for analysis. The nephrologist reviews these results with the patient and family during a clinic visit.

ABPM is the best way to distinguish true hypertension from white coat hypertension. White coat hypertension exists when the blood pressure is elevated in a medical setting, but normal when a patient is in their usual environment. Some case series indicate that 30% of children with elevated clinic blood pressure actually have white coat hypertension. It is imperative that these children understand their true cardiovascular risk, and that they be spared from unnecessary medical therapy. Children with white coat hypertension are also at increased risk for true hypertension and cardiovascular disease compared to their peers.4 For these children, ongoing blood pressure monitoring [sometimes with annual ABPM] may be necessary.

Blood pressure normally declines during sleep. This is referred to as the “nocturnal dip.” Blunted dipping is when the mean systolic or diastolic blood pressure declines by <10% during sleep. This occurs in association with renal disease, poor sleep quality, and the use of glucocorticoids. It is more common among African-Americans.5 Blunted dipping is commonly seen in patients with diabetes.6 Adolescent diabetic patients with blunt dipping are more likely to develop microalbuminuria than adolescent diabetic patients with normal ABPM profiles.5 When blunted dipping is present, nocturnal administration of anti-hypertensive medication can restore a normal dip.

ABPM can be used to distinguish primary from secondary causes of hypertension in children. Awake diastolic blood pressure load >25% or asleep systolic blood pressure load >50% are both highly specific for diagnosing secondary hypertension in children.6 Children with secondary hypertension require a much more detailed evaluation to determine the cause of their blood pressure elevation than children with primary hypertension.

In the research setting, ABPM is frequently used to evaluate the effects of anti-hypertensive therapy. The use of ambulatory blood pressure [as opposed to casual blood pressure] offers to opportunity to evaluate duration of action of medications and assess patient compliance. It also allows measurement of changes in blood pressure variability and nocturnal dipping. Placebo medication has negligible effect on ambulatory blood pressure.3

The goal of all treatment of pediatric hypertension is to reduce cardiovascular risk. As such, accurate understanding of a child’s blood pressure is especially important for those whose cardiovascular risk is already increased. Masked hypertension is the phenomenon of elevated ambulatory blood pressure when clinic blood pressure is normal. In the CKID study, a cohort study of pediatric chronic kidney disease, children with masked hypertension had increased risk of left ventricular hypertrophy compared to those with normal ambulatory blood pressure.7 Children with diabetes, renal disease, dyslipidemia, or obesity are all at increased cardiovascular risk. Ambulatory blood pressure monitoring can be a useful tool in evaluating and screening for this risk.

**PEDIATRIC HYPERTENSION AND ABPM PROGRAM AT HASBRO CHILDREN’S HOSPITAL**

Pediatric Ambulatory Blood Pressure Monitoring has been available at the Pediatric Nephrology and Hypertension clinic at Hasbro Children’s Hospital in Providence since 2007. Twenty-four hour ambulatory blood pressure measurement is performed using programmable portable oscillometric devices (Spacelabs Healthcare). The program is supported by a team comprising of pediatric nephrologists, a clinical nurse and a pediatric nutritionist. All children undergo ambulatory blood pressure monitoring for a 24-hour period. Patients also undergo screening with a random urine sodium to estimate their dietary salt intake as well a urinary microalbumin measurement to assess cardiovascular and endothelial injury risk. Demographic data including weight, height and BMI is obtained on all children. A detailed family, dietary and physical activity history is obtained to assess lifestyle risk and genetic risk factors. Children identified with metabolic syndrome and obesity are provided extensive nutritional and lifestyle counseling and undergo follow-up ABPM studies. Children fulfilling criteria for hypertension are evaluated for secondary causes of hypertension. Indications for drug therapy as recommended by the Fourth Report1 are shown in Table 3.

As of June 2013, 606 successful ABPM studies have been performed at Hasbro Children’s Hospital. Twenty-eight percent of children were found to be clinically hypertensive on ABPM study by definitions put forth by the Fourth Report.3 Seven percent of children fulfilled criteria for white coat hypertension. Sixty-five percent of children had a normal 24-hour average blood pressure. Since the latter group was referred to the Pediatric Hypertension clinic on the basis of elevated

<table>
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<th>Table 3. Indications for Pharmacologic Therapy for Treatment of Hypertension.</th>
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<td>Persistent hypertension despite non-pharmacologic measures</td>
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<tr>
<td>Symptomatic hypertension</td>
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<tr>
<td>Secondary hypertension</td>
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<tr>
<td>Evidence of hypertensive target organ damage</td>
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<td>Diabetes (Type 1 and 2)</td>
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office blood pressures, these patients fulfill the diagnostic criteria for White Coat Hypertension. The fact that almost two-thirds of the children referred to our clinic for suspected hypertension turn out to have normal 24-hour ABPM studies [White Coat Hypertension] greatly underscores the importance of this modality as a screening and diagnostic tool.

The economic importance of using ABPM for the diagnosis of hypertension in children cannot be understated. Numerous studies have validated the primary use of ABPM for the diagnosis of hypertension in both children and adults as a cost-effective, safe and accurate tool. In addition, to providing cost savings, ABPM can avoid pain and anxiety in children from unnecessary and invasive tests ordered for work-up of hypertension. Judicious use of ABPM can reduce both physician and parental anxiety and increase productivity by reducing time lost from work and school. Standardized use of ABPM eliminates misdiagnosis of clinic hypertension from improper measurement technique, incorrect cuff size, patient anxiety and inter-observer variability since these are very common sources of erroneous blood pressure measurements in children.

CONCLUSION
Ambulatory blood pressure monitoring has been validated as a safe, painless, non-invasive and scientifically valid diagnostic and screening tool for the diagnosis of hypertension in both children and adults. Our experience indicates a high incidence of White Coat Hypertension in children referred for evaluation of suspected hypertension. When available, ABPM can provide significant economic benefit by reducing unnecessary workup as well as avoid patient and parental anxiety related to misdiagnosis of this important clinical condition. As the incidence of elevated blood pressure in children continues to rise, ABPM should be considered in all children at risk for developing hypertension so that appropriate preventive and therapeutic strategies can be implemented in early life to avoid long term morbidity and mortality related to this important clinical diagnosis.

References

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The Growing Prevalence of Kidney Stones and Opportunities for Prevention

KATHERINE RICHMAN, MD; JOHN O’BELL, MD; GYAN PAREEK, MD

ABSTRACT
The prevalence of kidney stones is climbing in the United States. Several investigators have demonstrated an association between metabolic syndrome and kidney stones and some have proposed a causal link. Risk factors for nephrolithiasis can be identified with a 24-hour urine collection and preventive measures can be customized to meet the needs of individual patients. Dietary and pharmacologic interventions are available to address urinary risk factors such as inadequate urine volume, hypercalcuria, hyperoxaluria, hyperuricosuria and hypocitraturia. Given that morbidity and healthcare costs associated with nephrolithiasis are on the rise, deterring stone formation is increasingly important. Multidisciplinary clinics that foster collaboration between urologists, nephrologists and dieticians offer patients effective prevention and treatment strategies.

KEYWORDS: kidney stones, nephrolithiasis, metabolic syndrome, risk factors

INTRODUCTION
The prevalence of nephrolithiasis in the United States is increasing [1, 2]. Patients with kidney stones often have a benign course, but life-threatening complications like acute kidney injury and infection can arise. Moreover, the financial burden from medical expenditures and lost productivity is substantial. By one estimate, more than 4 billion dollars were spent treating nephrolithiasis in the year 2000 and since that time costs have been steadily rising [3]. Healthcare providers practicing preventive care should be mindful of risk factors for nephrolithiasis and implement risk-reduction therapy when possible.

EPIDEMIOLOGY
In 1994, the National Health and Nutrition Examination Survey (NHANES) reported a kidney stone disease prevalence of 5.2%. More recent NHANES data, from 2007-2010, revealed an overall prevalence of 8.8%[1]. The prevalence of stones among men increased from 6.3% to 10.6% and from 4.1% to 7.1% among women. Nephrolithiasis continues to be most common in white individuals but the prevalence has increased by 150% (from 1.7% to 4.5%) in African Americans [1]. NHANES data also shows a 91% rise in emergency department (ED) visits for kidney stones since the 1990s. In 1992-1994, 178 per 100,000 ED visits were coded for nephrolithiasis. By 2004-2006 ED visits for stones had increased to 340 per 100,000[2]. ED visits for stones increased by 70% in men and by 128% in women, which is consistent with other observations that the gender gap in stone patients is narrowing [1, 2].

Data from Rhode Island Hospital (RIH) mirrors national data. In 2004, the RIH emergency department (ED) reported 111 cases of kidney stones. By 2013, ED visits coded for nephrolithiasis had grown to 695. As the prevalence of stones increases and medical expenditures mount, the need to focus on prevention intensifies.

Calcium oxalate and calcium phosphate calculi account for more than 80% of kidney stones. Less common stone types include uric acid, magnesium ammonium phosphate (struvite) and cysteine stones. Prevention and treatment strategies vary according to the stone composition. The remainder of this discussion will focus primarily on calcium stones.

RISK FACTORS
The growing prevalence of diabetes and metabolic syndrome and the rise in the number of patients with kidney stones may be more than a coincidence. Multiple studies have demonstrated a heightened risk of nephrolithiasis in patients with metabolic syndrome [4-6]. According to NHANES 3 data from 1988 to 1994, having just two metabolic syndrome traits (abdominal obesity, hypertension, hypertriglyceridemia, low high-density lipoprotein, impaired glucose tolerance) was associated with a significant increase in self-reported kidney stone disease. Study participants with 4 or 5 traits were twice as likely to report kidney stones as those with no features of metabolic syndrome [5].

More recent data from Korea identified hypertension and metabolic syndrome as independent risk factors for radiographically-proven kidney stones. Patients with hypertension had an odds ratio of 1.47 for nephrolithiasis, while those with metabolic syndrome had an odds ratio of 1.25 [6]. Obesity, weight gain, fasting glucose ≥ 100, and glycated hemoglobin ≥ 6.5% have also been associated with an increased risk of stone formation [7, 8]. Although calcium oxalate stones remain the most common stone type in patients with metabolic syndrome, there has been a
substantial increase in the frequency of uric acid nephrolithiasis as well, which appears to be correlated with insulin resistance [9, 10].

While bariatric surgery is increasingly used to treat the morbidity associated with obesity, patients who have undergone Roux-en-Y gastric bypass are at higher risk for nephrolithiasis than obese controls [11]. Hyperoxaluria and hypocitraturia, two urinary risk factors for stone formation, have been observed in nearly half of patients post gastric bypass [12]. Malabsorption of fatty acids results in saponification of calcium which decreases calcium-oxalate complex formation in the gut. In turn, more oxalate is available for absorption from the intestine and is ultimately excreted in the urine [12].

Other medical conditions that confer an increased risk of kidney stones include hyperparathyroidism, renal tubular acidosis, recurrent urinary tract infections, inflammatory bowel disease and medullary sponge kidney [13].

PREVENTION

Patients presenting with nephrolithiasis for the first time have a 50% chance of recurrence by 10 years [13]. In order to prevent recurrence, a detailed medical history and basic metabolic evaluation should be completed in all patients with nephrolithiasis. Available calculi should be analyzed. Serum calcium, phosphorous, potassium, bicarbonate, blood urea nitrogen, creatinine, uric acid and a basic urinalysis should be checked. Abnormalities such as hypercalcemia suggestive of hyperparathyroidism, or low serum bicarbonate consistent with a metabolic acidosis should be thoroughly explored. Recurrent kidney stones, bilateral or multiple stones, age younger than 25, solitary kidney, diabetes or a strong family history of nephrolithiasis should prompt a 24-hour urine collection to identify specific urinary risk factors [13].

Kidney stone formation occurs when the urine is supersaturated with dietary minerals such as calcium, oxalate and phosphate. Crystals precipitate from solution and aggregate to form stones. A 24-hour urine collection that measures volume, sodium, calcium, phosphorous, oxalate, uric acid, pH and citrate identifies risk factors for supersaturation and stone formation [14]. Knowing the type of stone formed by a patient is important in determining preventive measures, but urinary risk factors may vary among patients with the same type of stone. An intervention that is effective in one patient with calcium oxalate stones may not be effective in another patient with the same stone type. For example, not all patients with calcium oxalate stones have hyperoxaluria and prescribing a low oxalate diet is not always necessary.

At least two 24-hour urine collections should be done to confirm risk factors. Collections should not be done within three months of passing a stone. Testing should be done on an outpatient basis when the patient is free to maintain a typical self-selected diet. Using the results of the 24-hour urine collection, the clinician can customize preventive strategies to meet the needs of the individual patient [14]. Once interventions are made, the urine collection should be repeated to make sure that the prescribed therapy is effective in attenuating risk factors.

URINARY RISK FACTORS AND PREVENTIVE STRATEGIES

Inadequate Urine Volume

The cornerstone of preventing stone formation is avoiding supersaturation of the urine with a stone-forming substance. Thus all stone formers are advised to maintain dilute urine. Drinking enough to maintain urine output of at least 2 to 2.5 liters per day could cut the risk of stone recurrence in half [15].

Although increasing fluid intake is a relatively low-cost intervention and has few adverse effects, barriers to utilization do exist. Some patients report not liking the taste of water and forgetting to drink. Other patients are highly motivated to prevent stone recurrence but are unable to void frequently because of occupational demands and workplace restrictions [16].

Increasing intake of any low-calorie fluid is generally recommended. A recent prospective study of 194,095 health professionals found that participants who consumed one or more servings of sugar-sweetened cola per day were 23% more likely to develop stones than those who consumed less than one serving per week. Consuming sugar-sweetened non-cola carried a 33% higher risk of nephrolithiasis. Conversely, daily caffeinated coffee intake appeared to decrease the risk of stones by 26%. Decaffeinated coffee, tea, wine, beer and orange juice were also associated with a lower risk of nephrolithiasis [17].

Hypercalcuria

Hypercalcuria is usually idiopathic but can be the result of hyperparathyroidism. Parathyroid hormone levels should be checked in patients with electrolyte abnormalities like hypercalcemia and hypophosphatemia. Dietary calcium restriction is unnecessary and may, in fact, increase the risk of calcium stone formation [18]. In a prospective study of more than 78,000 women, the average daily dietary calcium intake was 39 mg lower in women who developed kidney stones than in those who did not. On the other hand, average sodium intake was 60 mg higher in stone formers [19]. Italian men, with recurrent calcium oxalate stones and hypercalcuria, randomized to a normal-calcium, low-salt and low-animal-protein diet had a relative risk of stone recurrence of 0.49 compared to men placed on a low-calcium diet [18].

Limiting sodium intake to 2300 mg per day is recommended to decrease urinary calcium and stone risk [20]. Thiazide diuretics also reduce urinary calcium and a recent systematic review of six randomized controlled trials found moderate-strength evidence that thiazide diuretics are...
effective in lowering the likelihood of stone recurrence. Hydrochlorothiazide, chlorthalidone and indapamide seemed to be equally effective [15]. Dosing has not been well studied, but quantification of urinary calcium with repeat 24-hour collections can be used to titrate therapy.

**Hyperuricosuria**

A low calcium diet might augment the risk of nephrolithiasis by increasing free oxalate in the gut. Enhanced oxalate absorption could ultimately lead to hyperuricosuria, thereby increasing stone risk. Although evidence is lacking for the efficacy of a low oxalate diet in stone prevention, restricting oxalate-rich foods like spinach, nuts and chocolate in patients with hyperuricosuria is generally recommended [21]. High doses of vitamin C amplify oxalate excretion and should be avoided [22]. As previously noted, bariatric surgery or small bowel disorders like Crohn’s disease can result in fatty acid malabsorption and hyperuricosuria. Restriction of dietary fat and oxalate and increasing calcium intake with meals may attenuate the risk of calcium oxalate stones in patients with malabsorption [20].

**Hypocitraturia**

Citrate chelates calcium in the urine and inhibits formation of calculi. Chronic diarrhea, renal tubular acidosis and diets high in animal-protein may all be accompanied by a decrease in urinary citrate and a higher risk of stone formation [23]. Urinary citrate can be increased via pharmacologic or dietary intervention. A number of investigations, including four small randomized controlled trials, have shown a decrease in stone recurrence with citrate supplementation, usually given in the form of potassium citrate [15]. For patients who are unable to tolerate pharmacologic therapy or prefer dietary intervention, consuming 4 ounces of lemon juice diluted in water or 32 oz of sugar-free lemonade daily results in a significant increase in urinary citrate [24].

When citrate is used in patients with a history of calcium phosphate stones the urine pH should be monitored closely. Citrate alkalizes the urine which can be advantageous in preventing uric acid and cysteine stones but promotes the formation of calcium phosphate stones.

**Hyperoxaluria**

Hyperoxaluria is associated with both uric acid stones and calcium stones. Uric acid decreases calcium oxalate solubility and encourages stone formation. A high purine diet often underlies hyperuricosuria but myeloproliferative disorders and uricosuric drugs are other possible etiologies [20]. Decreasing intake of animal protein may be of benefit and a few randomized controlled trials suggest that allopurinol decreases the risk of calcium oxalate stones [15].

**TREATMENT**

When prevention fails and calculi form, urologic intervention may be required. Approximately 10–20% of symptomatic stones do not pass spontaneously [20]. Most stones smaller than 5 mm will pass freely while calculi >10 mm usually require intervention [13]. According to the American Urological Association’s treatment guidelines, shock-wave lithotripsy and ureteroscopy are first-line procedures for stone removal. For larger stones (>1.5 cm) minimally invasive percutaneous surgery may be required through a 1 cm incision in the flank. Uncommonly, open surgical methods may be necessary to render a patient stone-free.

Multi-disciplinary clinics that combine the services of urologists, nephrologists and dieticians provide an effective approach to prevention and management. Hosking coined the term, “stone clinic effect” after demonstrating a significant decrease in stone recurrence in patients who had visited a clinic and received basic instruction on dietary modification and fluid intake [25]. When calculi form despite preventive efforts, regular surveillance in a stone clinic fosters timely intervention and can minimize morbidity.

**CONCLUSION**

The incidence of kidney stones is on the rise but preventive measures can be deployed. A 24-hour urine collection can determine risk factors for stone formation and be used to customize preventive strategies for individual patients. Maintaining dilute urine is an important prophylactic measure for any stone type. Hypercalcuria, hyperuricosuria, hypocitraturia, and hyperuricosurias are urinary risk factors for calcium-containing calculi, the most common type of stone. Dietary and pharmacologic measures can be taken to address these risk factors. Primary care providers and specialists have an opportunity to decrease morbidity and health care costs by working with patients to design individualized prevention strategies.

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