

# Cystinosis: renal glomerular and renal tubular function in relation to compliance with cystine-depleting therapy

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## Abstract

**Background and objectives** Nephropathic cystinosis is a lysosomal storage disorder characterized by renal tubular Fanconi syndrome in infancy and glomerular damage leading to renal failure at ~10 years of age. Therapy with the cystine-depleting agent cysteamine postpones renal failure, but the degree of compliance with this treatment has not been correlated with preservation of kidney function.

**Methods** We assessed leucocyte cystine depletion by cysteamine and created the composite compliance score that incorporates the extent of leucocyte cystine depletion, as well as duration of cysteamine treatment, into a single integer. Age at renal failure was used to gauge preservation of renal function, and the Fanconi syndrome index (FSI), a measure of aminoaciduria, was used to assess renal tubular Fanconi syndrome. **Results** Age at renal failure varied directly and linearly with the composite compliance score ( $y=0.3x+8.8$ ;  $R^2=0.61$ ). The slope indicated that for every year of excellent cystine depletion, nearly 1 year of renal function was preserved. Age at renal failure correlated roughly with mean leucocyte cystine level, but not with mean cysteamine dosage. There was no correlation between the FSI and the composite compliance score.

**Conclusions** Greater compliance with oral cysteamine therapy yields greater preservation of renal glomerular, but not tubular, function. Oral cysteamine therapy should be given at the maximum tolerated dose, within the recommended limits.

**Keywords** Nephropathic cystinosis · Cystine · Fanconi syndrome · Cysteamine · End-stage renal disease

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## Introduction

Nephropathic cystinosis (NC; OMIM #219800) is a lysosomal storage disease that results from defective transport of the amino acid cystine out of lysosomes [1–3]; the subsequent accumulation of cystine leads to multiorgan dysfunction [4]. Individuals with cystinosis carry biallelic mutations in *CTNS*, resulting in deficiency of cystinosin, the integral membrane protein responsible for cystine egress from lysosomes [5, 6].

In the natural history of cystinosis, the first cells manifesting a defect are the renal proximal tubule cells responsible for reabsorbing small molecules. Impairment of this function causes renal Fanconi syndrome (FS), and affected infants display massive polyuria, aminoaciduria, proteinuria, and electrolyte and mineral losses at 6–12 months of age [1, 2, 7]. In fact, cystinosis is the most frequent cause of inherited renal Fanconi syndrome [8]. At the same time, renal glomerular cells undergo progressive damage leading inexorably to end-stage renal disease (ESRD), generally by 10 years of age [9]. Nephropathic cystinosis is responsible for approximately 5 % of all ESRD [10, 11], and in the United States accounts for approximately 1.4 % of children on dialysis and 2 % of pediatric kidney transplants [12]. In cystinosis, renal replacement therapy cures the kidney disease, but continued cystine accumulation in other organs and tissues results in corneal crystals, hypothyroidism, a distal vacuolar myopathy, diabetes mellitus, and other complications in early adulthood. The diagnosis of cystinosis is suspected based upon infantile-onset renal Fanconi syndrome and the presence of cystine crystals on slit-lamp examination of the cornea [4]. The diagnosis can be confirmed by measuring increased levels of cystine in circulating polymorphonuclear leucocytes; these cells, as well as cultured fibroblasts, contain 50–100-fold normal levels of cystine in affected individuals [13].

Beyond symptomatic therapy for renal Fanconi syndrome and other complications, the treatment of choice for

nephropathic cystinosis is the cystine-depleting free thiol, cysteamine [14]. This drug, available on a research basis since 1978 and approved by the FDA as Cystagon (cysteamine bitartrate) in 1994 and as Procysbi (delayed release cysteamine bitartrate) in 2013, has dramatically changed the course of cystinosis from a fatal disease to a chronic, treatable disorder. At optimal doses, cysteamine can reduce cell cystine levels by 80–90 % [13]. It has proven efficacy in preventing renal glomerular damage and postponing ESRD and the need for kidney transplant [13, 15, 16]. Although established renal damage in cystinosis is irreversible, early intervention with cysteamine therapy reduces the rate of glomerular deterioration [16].

In all these studies, leucocyte cystine depletion was employed as a surrogate for parenchymal cystine depletion and was used to determine dosing. However, the relationship between treatment compliance, as gauged by the extent of leucocyte cystine depletion, and the duration of preserved renal function was not analyzed. Furthermore, the question of whether the renal FS improved with cysteamine treatment was not addressed. Hence, we now retrospectively examine three decades of NIH cystinosis patient data, determining the relationship between age at end-stage renal disease and the degree of compliance with cysteamine therapy. We also plotted the severity of renal Fanconi syndrome against compliance with cysteamine therapy.

## Methods

### Patients

The diagnosis of nephropathic cystinosis was based upon consistent clinical and laboratory findings, including the presence of corneal crystals, and an elevated leucocyte cystine content. All patients were enrolled in a clinical research protocol, “Natural History Study of the Use of Cysteamine in the Treatment of Cystinosis”, approved by the NICHD and NHGRI Institutional Review Boards at the National Institutes of Health. Patients and/or their parents gave written, informed consent. Clinical and laboratory data of 245 cystinosis patients were evaluated by retrospective chart analysis.

### Measures of renal disease

For this study, ESRD was defined as a level of renal function requiring dialysis or renal transplant. To quantify the severity of the Fanconi syndrome, the Fanconi syndrome index of aminoaciduria (FSI) was calculated. Amino acids were measured in 24-h urine collections using a 4151 Alpha Plus analyzer (LKB-Biochrom, Cambridge, United Kingdom) with five lithium buffers. Analysis was performed in the same time frame as the leucocyte cystine measurements. The FSI was

calculated as the daily urinary excretion of 21 selected amino acids (aspartic acid, hydroxyproline, threonine, serine, asparagine, glutamic acid, glutamine, proline, glycine, alanine, valine, half-cystine, methionine, isoleucine, leucine, tyrosine, phenylalanine, ornithine, lysine, histidine, and arginine), and expressed as  $\mu\text{moles/kg body weight/day}$ . Normal mean  $\pm$  SD values are  $94 \pm 45$ ; typical values for patients with renal tubular Fanconi syndrome are  $1,085 \pm 725$  [17].

### Leucocyte cystine measurements

From 1975 through approximately 2006, leucocyte cystine levels were measured using the cystine-binding protein assay [18]; since 2006, cystine content was assayed at the University of California-San Diego Cystine Determination Lab using LC/MS. For normal individuals, the leucocyte cystine is  $\leq 0.2$  nmol half-cystine/mg protein; nephropathic cystinosis patients generally have levels of 5–23 nmol half-cystine/mg protein [2]. A target value for cystine-depleting therapy is  $\leq 1.0$  nmol half-cystine/mg protein. The mean of all the leucocyte cystine levels obtained within a year was used to determine the Compliance Score for that year (see below).

### Composite compliance score

In order to correlate renal glomerular and tubular functions with compliance, a single numerical measure of compliance had to be assigned to each patient. This measure incorporated both the level of leucocyte cystine depletion and the duration of cystine-depleting therapy.

To begin, a numerical value of compliance, based upon leucocyte cystine values, was assigned to each year of age. Analysis of each patient began at year 1, defined as ages 0–1; year 2 was defined as age 1–2, etc. The numerical value for each year was determined using the following scoring system:

- A score of “0” was assigned if the patient’s average leucocyte cystine level was  $\geq 3.0$  nmol half-cystine/mg protein on cysteamine therapy, or if the patient was not treated with cysteamine.
- A score of “1” was assigned if the average leucocyte cystine level was  $\geq 2.0$  and  $< 3.0$  nmol half-cystine/mg protein.
- A score of “2” was assigned if the average leucocyte cystine level was  $\geq 1.0$  and  $< 2.0$  nmol half-cystine/mg protein.
- A score of “3” was assigned if the leucocyte cystine level was  $< 1.0$  nmol half-cystine/mg protein.

For every year of life prior to ESRD, these numbers were added to create a total (composite) score for each patient. Accordingly, patients with higher composite scores had overall better compliance with treatment (and lower leucocyte

cystine levels) and patients with lower composite scores (or “0”) had poor compliance or no compliance with treatment.

Some patients had missing data. For patients who had <3 years between recorded leucocyte cystine levels, values for the missing years were extrapolated from the values of the flanking years. That is, the values for the missing years were taken to be the average of the measurements recorded for the previous year and the year following the missing years. Patients with  $\geq 3$  consecutive years of missing data were excluded from analysis.

#### Statistical analyses

Linear regression analysis was based on the least squares approach, with determination of correlation coefficients [19].

## Results

All nephropathic cystinosis patients ( $n=245$ ) seen at the NIH Clinical Center between 1975 and 2005 were initially considered. Of these, 74 were neither transplanted nor in renal failure; they were excluded from analysis because the time of ESRD was an outcome measure. An additional 24 patients who had a gap of  $\geq 3$  years without recorded leucocyte cystine levels were also excluded because their levels of compliance could not be reliably scored. This left 147 patients for analysis; their mean age was 28 years with a range of 11–48 years.

Ninety-four of these patients had received essentially no cystine-depleting therapy. The remaining 53 patients received some cysteamine, and for each patient, the mean leucocyte cystine concentration was determined from the time of the first NIH visit to the time of renal failure. This involved 1,855 cystine determinations (mean  $35 \pm 3$  (SEM) per patient; range, 2–82). The mean leucocyte cystine values themselves ranged from 0.61 to 11.04 nmol half-cystine/mg protein, averaging  $2.35 \pm 0.26$  (SEM). Age at renal failure varied inversely with mean leucocyte cystine value, with a great deal of scatter (Fig. 1). The slope was  $-0.78$ , meaning that for every increase in the mean leucocyte cystine value of 1 nmol half-cystine/mg protein, approximately 9 months of renal function were lost.

Mean leucocyte cystine values did not take into account duration of cystine treatment. For this, we employed a composite compliance score, incorporating both the extent and duration of cystine depletion. The 94 patients who received virtually no cysteamine had a composite compliance score of 0. Their mean age at ESRD was  $10.3 \pm 0.3$  (SEM) years; 87 of the 94 reached ESRD before 16 years of age.

The 53 who had received some cysteamine entered ESRD at a mean age of  $15.4 \pm 0.7$  (SEM) years; only 27 of the 53 reached ESRD before 16 years of age. For the 53 patients with a composite compliance score  $>0$ , we plotted the age at ESRD

(range, 5–25 years) against the composite compliance score (range, 2–56). Age at ESRD varied directly with compliance, with a slope of 0.30 years per unit of compliance and a correlation coefficient of 0.61 (Fig. 2a).

We also grouped the 53 patients by composite compliance scores of 0–10, 10–20, 20–30, 30–40, and 40–56. The mean age at ESRD for the five groups varied linearly with the mean composite compliance score for each group; the correlation coefficient was 0.997 (Fig. 2b).

Data were available to determine the mean cysteamine dosage (in mg/kg/day) for 52 of the 53 patients who received cysteamine. For this assessment, we did not employ data for patients once they reached 40 kg, as these per-kg dosages were inordinately low. Using this data set, there was no correlation between age at ESRD and mean cysteamine dosage in mg/kg/day (Fig. 3).

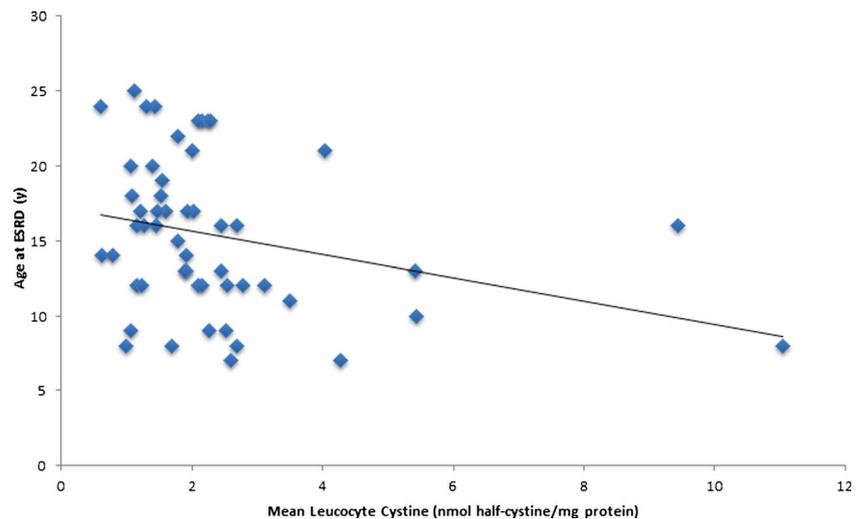
For 37 patients, the mean FSI could be calculated based upon 24-h urine collections. For these individuals, the mean FSI did not correlate with the composite compliance score (Fig. 4).

## Discussion

In nephropathic cystinosis, lysosomal cystine accumulation damages different tissues at different rates, perhaps by enhancing apoptosis [20]. The kidney is one of the earliest organs to be destroyed, perhaps because of its robust proteolysis producing large quantities of lysosomal cystine, or because of its relative inability to create newly differentiated parenchymal cells. In any event, the renal phenotype of cystinosis consists of the overlap of early renal tubular Fanconi syndrome and progressive loss of glomerular function [16, 21]. There is significant variability in the onset of these complications, considered to be related to the amount of residual cystine transporting capacity retained by the mutant cystinosis protein. In addition, modifier genes and environmental factors such as systemic hypertension, urinary tract infections, diet, drugs, and reduced creatinine production by wasted muscles, likely influence the progression of chronic renal failure in cystinosis patients, which has been documented by longitudinal studies [9, 22]. While most cystinosis children lose renal function at 9–10 years of age, some require dialysis or transplant as early as 2–4 years of age [23].

For all nephropathic cystinosis patients, early and diligent cystine-depleting therapy with oral cysteamine helps preserve renal glomerular function. Cysteamine depletes lysosomal cystine by reacting with cystine to form the mixed disulfide of half cystine (cysteine) and cysteamine [24]; this compound exits lysosomes via a transport system for cationic amino acids [25]. The usual cysteamine dosage is 60–90 mg/kg / day or  $1.35\text{--}1.90\text{ g/m}^2\text{/day}$ , divided every 6 h [4], and the goal is to keep leucocyte cystine levels below 1 nmol/half-cystine/

**Fig. 1** Age at end-stage renal disease (ESRD) plotted against mean leucocyte cystine level for 53 cystinosis patients treated with oral cysteamine. The line follows the equation  $y = -0.78x + 17.2$  ( $R^2 = 0.08$ )



mg protein. Cystine levels are obtained 5–6 h after a dose to ensure that this level of depletion is maintained throughout the day. Low cystine levels are widely accepted as evidence of both compliance and efficacy [4, 16]. Because cysteamine has beneficial effects on so many organ systems in cystinosis [26], it should be prescribed for all affected individuals, regardless of age and transplantation status [27]. However, compliance with cysteamine therapy is often compromised, largely because of the unpleasant taste and smell, nausea, and other gastrointestinal discomforts.

The efficacy of oral cysteamine in preserving renal glomerular function has been demonstrated in several controlled clinical trials. In the first study [13], creatinine clearance was found to be higher in a group of children who had been treated with cysteamine than in an historical control group (38.5 vs. 29.7 ml per minute per 1.73 m<sup>2</sup>). In a second NIH study, patients well treated with cysteamine fared better than those less well treated or not treated at all [15]. Moreover, because human kidneys normally grow and acquire glomerular function through 3 years of age, early intervention with cysteamine therapy vastly reduces the rate of glomerular deterioration [15]. Finally, Gahl et al. defined a new measure of renal function, the predicted reciprocal serum creatinine at age 10 years (PRC10). This parameter was based upon the linear relationship between reciprocal serum creatinine and age, and incorporated age, serum creatinine, and rate of renal deterioration into a single term. For cystinosis patients, the PRC10 was lower in those receiving cysteamine than in those not treated with cysteamine [28].

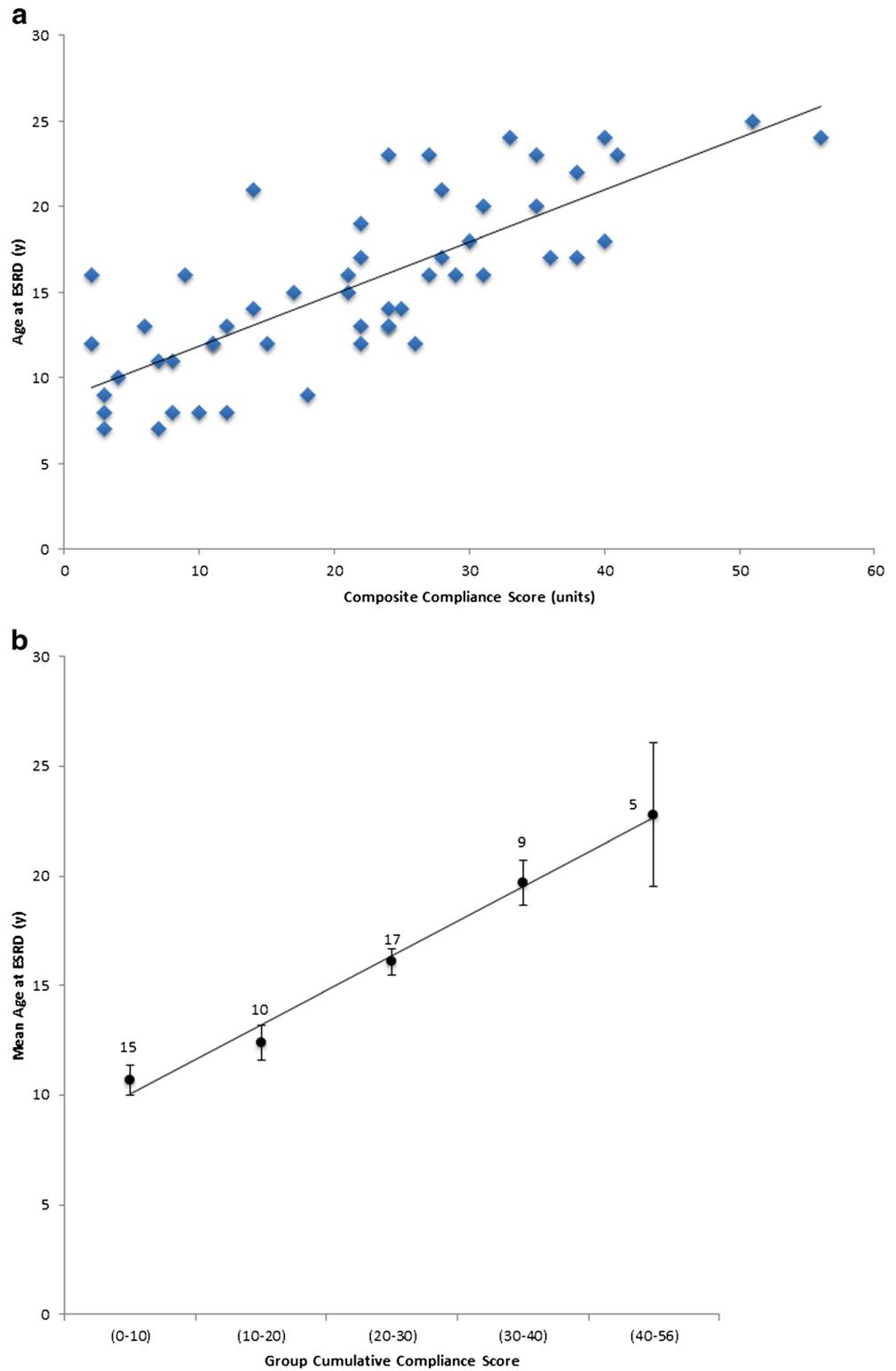
None of these studies, however, examined the relationship between preservation of renal glomerular function and compliance with cysteamine treatment using quantitative parameters and a subjective function. To address this, we created a measure of compliance that reflected both the level of cystine depletion and the duration of depletion. To accomplish this, we assigned a numerical value to each year of compliance

prior to renal failure, and gave the most positive values to the lowest leucocyte cystines. Thus, long-term depletion would be rewarded with a high compliance score. Conversely, no compliance, regardless of the duration of follow-up, would yield a score of zero. The dependent variable, age at ESRD, was an intuitively meaningful measure of preservation of renal function.

The result was the equation  $y = 0.30x + 8.8$  (Fig. 2a). The y-intercept of 8.8 years serves as an extrapolation of data on treated patients to estimate the age at ESRD for patients never treated with cysteamine (i.e., composite compliance score of 0). This age is consistent with the data of the European Dialysis and Transplant Association Registry, which reported a median age for ESRD in children with untreated cystinosis of 9.5 years [9]. However, both ages (8.8 and 9.5 years) are less than 10.3 years, the mean value for our 94 patients with composite compliance scores of 0. This likely occurred because some children with a composite compliance score of “0” were not completely untreated but received some therapy without a reduction of leucocyte cystine sufficient to achieve a positive composite compliance score.

The other parameter of interest in this equation is the slope, i.e., 0.30 years (of kidney preservation) per unit of compliance. Note that excellent compliance, signified by leucocyte depletion to  $\leq 1$  nmol half-cystine/mg protein, corresponds to a score of 3.0 composite compliance score units over the course of a year. The slope, then, translates into  $3.0 \times 0.3 = 0.9$  years of preservation of renal glomerular function, meaning that optimal cystine depletion achieved nearly a year-for-year salvage of remaining kidney function. Age at ESRD also varied roughly with the extent of leucocyte cystine depletion (Fig. 1) but not with the mean daily dose of cysteamine (Fig. 3). This may be because the severity of cystinosis varies significantly, so that a severely affected patient needs a higher per-kg dose of cysteamine to achieve the same level of cystine depletion. In addition, patients said to be receiving a high dose

**Fig. 2** Relationship between age at end-stage renal disease (ESRD) and composite compliance score for cysteamine therapy. **a** Scattergram for 53 patients with composite compliance scores >0. The best straight line follows the equation  $y=0.30x + 8.82$  ( $R^2=0.61$ ). **b** Plot of mean age at ESRD vs. mean composite compliance score for groups of cystinosis patients with composite compliance score units of 0–10, 10–20, 20–30, 30–40, and 40–56. Vertical and horizontal bars give SEM. The number above each point gives the number of patients in that group. When the five group means for ESRD and composite compliance score are plotted, the best straight line follows the equation  $y=0.31x + 8.7$  ( $R^2=0.997$ )

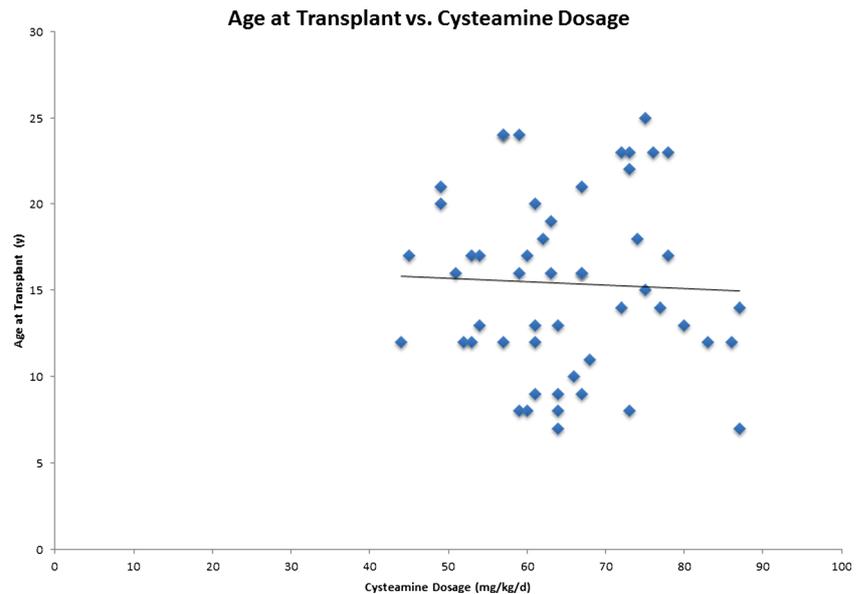


of cysteamine may not be complying with their prescribed dosage.

Renal tubular cells differ from glomerular cells in their morphology, and they appear more susceptible to the damage caused by cystine accumulation. Renal tubular Fanconi

syndrome is one of the first manifestations of nephropathic cystinosis, and is characterized by renal losses of nutrients, minerals, electrolytes, and other small molecules, including amino acids. In patients with Fanconi syndrome such as those with cystinosis, renal amino acid losses are 6–16-fold normal

**Fig. 3** Age at end-stage renal disease (ESRD) plotted against mean cysteamine dose. There was no correlation; the best straight line follows the equation  $y = -0.0194x + 16.647$  ( $R^2 = 0.0016$ )



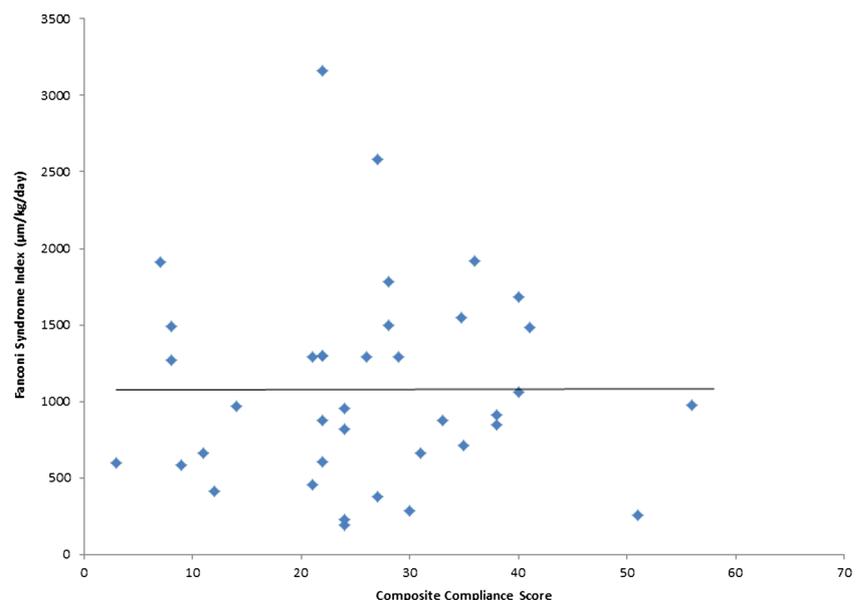
[17, 29], and mean fractional excretions of amino acids range from 0.10 for arginine to 0.71 for histidine [30]. Daily excretion of specific amino acids, quantified by the Fanconi syndrome index, provides a good measure of the severity of the Fanconi syndrome, because amino acid excretion is not substantially influenced by dietary intake or supplements.

In contrast to the positive correlation between age at ESRD and compliance with cysteamine treatment, the severity of renal Fanconi syndrome did not vary with the composite compliance score (Fig. 4). Only anecdotal information is available on this topic [31], but our data confirm the general impression that renal tubular damage is extensive and irreversible by the time of diagnosis and intervention with cysteamine therapy, estimated at approximately 14 months of age.

It remains to be determined if cystine depletion initiated shortly after birth can salvage a substantial amount of reabsorptive capacity [32].

It has been conclusively demonstrated that oral cysteamine therapy lowers the cystine content of circulating leucocytes and parenchymal cells, helps to maintain renal glomerular function, preserves thyroid function, and prevents distal myopathy, diabetes mellitus, and other complications of cystinosis. Based upon the analysis of three decades of NIH data, we have now shown that, in cystinosis, the extent of preservation of renal glomerular function, but not tubular function, varies with the extent and duration of leucocyte cystine depletion. We conclude that cystinosis patients should be prescribed cysteamine up to the maximum tolerated dose,

**Fig. 4** Relationship between Fanconi syndrome index (FSI) and composite compliance score for cysteamine therapy. No correlation was present; i.e., regardless of the level of compliance, there was no reduction in the FSI



as long as it does not exceed 90 mg/kg or 1.9 g/m<sup>2</sup> per day. In addition, our data, collected on patients exclusively receiving Cystagon<sup>R</sup> as their source of cysteamine, can be compared in the future to data collected on patients receiving Procysbi<sup>R</sup> to deplete their cystine. Parameters to follow would be mean composite compliance score, mean age at ESRD, and the relationship between the two.

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