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Review

A Report on Nephropathic Cystinosis in Iran- A Scoping Review

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Keywords. Nephropathic cystinosis; Cystine diseases; Cysteamine; Lysosomal storage diseases; Morbidity

Cystinosis is a rare lysosomal disease affecting all organs. The outcome and the quality of life varies depending on the early diagnosis, patient adherence to medication, and regular follow up. There is lack of enough evidence about cystinosis patients in Iran. In this review, we are going to find the incidence and prevalence, the age at diagnosis, clinical presentation, the comorbidities, and the outcome of disease in Iranian children. We searched all available database of Iran published between January 1994 and January 2023. The search was filtered for the Iranian population. Totally 1125 cystinosis patients over 37 years (between 1985 to 2023) was identified. The estimated incidence rate was 1.03 per 100000 live births. The pooled prevalence was 28.3 (95%CI:14.9- 46) per 1000000 populations. Median age at presentation, diagnosis, and occurrence of end stage kidney disease were 0.73, 1.5, and 8.3 years, respectively. The most frequent presentation that led to evaluation was failure to thrive (94%). Ophthalmic exam and bone marrow aspiration were the mostly used methods for diagnosis. The most common detected mutation was c.681G4A/c.681G4A. The cysteine level represent that more than half of the cases did not receive correct dosage of medication. Almost 8.7% of cystinosis patients reached adulthood. Launching to transition protocol is mandatory for surviving to adulthood. There were scant data in regard to extrarenal outcomes, systemic and ophthalmic medications side effects, longitudinal ophthalmic involvement reports, and the quality of life.

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INTRODUCTION

Cystinosis is an inherited autosomal recessive condition that affects the cystine lysosomal transport protein. It is an orphan disease involving primarily kidney and other organs, and is induced by mutation in CTNS gene on 17p13q.[1] The incidence is almost 1-2 of 100,000 live births. The outcome and the quality of life varies depending on the early diagnosis and good compliance of the patients.[2,3] The disease is categorized into infantile, juvenile. and adult forms, according to the age at presentation and its severity. The diagnosis is based on clinical manifestation, detection of cysteine on cornea, cystine levels in leukocytes, and is confirmed by genetic study for the detection of CTNS gene that encode for carrier of cystinosin in lysosome.[2] Infantile type is characterized by growth retardation and Fanconi syndrome resulting in kidney failure.[4] The aim of this study was to find the incidence, prevalence, clinical presentation, adherence and the outcomes of patients with cystinosis in Iran.

MATERIALS AND METHODS

Protocols and Registration**:** The scope review is registered with the International Prospective Register of Systematic Scope Reviews (PROSPERO), Review Registration number: PROSPERO, 2020 CRD42020143174 Available from:

https://www.crd.york.ac.uk/prospero/display_record.php?ID = CRD42020143174 [5]

Search Strategies

We explored the following search database: PubMed, EMBASE, OVID, SCOPUS, Web of Sciences, health. barakatkns.com, MagIran, SID, irandoc.ac.ir, thesis.research.ac.ir between January 1994 and January 2023. PICO of systematic scope review was used to screen the articles. The MeSH keywords were used.

The search was filtered for the Iranian population with no limitation of age, published in English or Persian languages. In order to find the missed articles, we did hand-searching to identify pertinent cross references and data collected from annual Cystinosis Patient Day. Furthermore, the title of unpublished medical thesis searched among universities database.)http://thesis.research.ac.ir(

Study Selection: All studies on Iranian cystinosis patients who were diagnosed through clinical and laboratory findings and/or detection of cystine crystals deposition in the cornea or bone marrow, elevated cystine levels in leukocytes, or verified by genetic study regardless of age were included. All observational studies including cross –sectional, case series, cohort, case-control were evaluated by STORBE checklist (https://www.strobe-statement.org/checklists/) and the risk of bias modified by Hoy *et al*.[6] Experimental studies on animal models and narrative reviews, and articles about idiopathic tubular acidosis were excluded. The setting was hospital, outpatient, and annual Cystinosis Patient Day that the majority of cystinosis cases living around Iran would be invited to be gathered in an awareness educational seminar meanwhile to be assessed by specialists.

Keywords used were Cystinosis, diabetes insipidus, failure to thrive, Fanconi syndrome, hypothyroidism, photophobia, renal failure, renal transplant, Renal tubular acidosis, rickets.

Inclusion criteria are all cases with cystinosis (infantile, juvenile, adult). Main outcomes were the percentage of infantile, juvenile, or adult types. Additional outcomes were percentage of each organ involvement, the outcome of patients (died, kidney replacement therapy (KRT), and the age of presentation and diagnosis.

Data Extraction

Two authors independently extracted data from studies using a pre-specified sheet in Microsoft Excel 2010 as follows: The study population, center, type of study, period of study, sample size, patient demographic information (age, sex), technique of diagnosis, length of follow up, outcomes, medications, adequacy of treatment, cystine level, detected CTNS gene. The quality and the risk of bias of papers were assessed by STORBE and by Hoy *et al.* respectively. Disagreements were resolved by discussion between the two reviewers and in the case of no conclusion, the study was excluded.

Statistical Analysis

We reported the categorical variables as frequency (percentage), the mean or median of the continuous variables with 95% confidence intervals.

We utilized EndNote X7.4 to handle the evidence and analyzing the result of systematic search and Microsoft Excel 2010 to preparing data extraction sheet. We conjointly used MedCalc Statistical Software version 15.8 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2015) and IBM SPSS Statistics 23.0.

RESULTS

Study screening and selection

Figure 1 depicted the literature survey, the number of banished abstracts and the final number of articles included for assessment. Table 1 represented the summary of the included studies.

Prevalence and Incidence. Of 38 articles (including thesis (n = 16) and conference proceedings(n = 5)), reported from 1985 to 2023 with 1125 cystinosis population, 24 studies were about cystinosis, and the rest of studies were about chronic kidney disease and kidney replacement therapy (n = 12), and one study was about tubulopathy. According to the latest reported numbers of cystinosis patients in Iran, the estimated incidence rate was 1.03 per 100,000 live births. The pooled prevalence was 28.3 (95%CI:15- 46) per 1000000 populations.[7]

The frequency of different types. The most

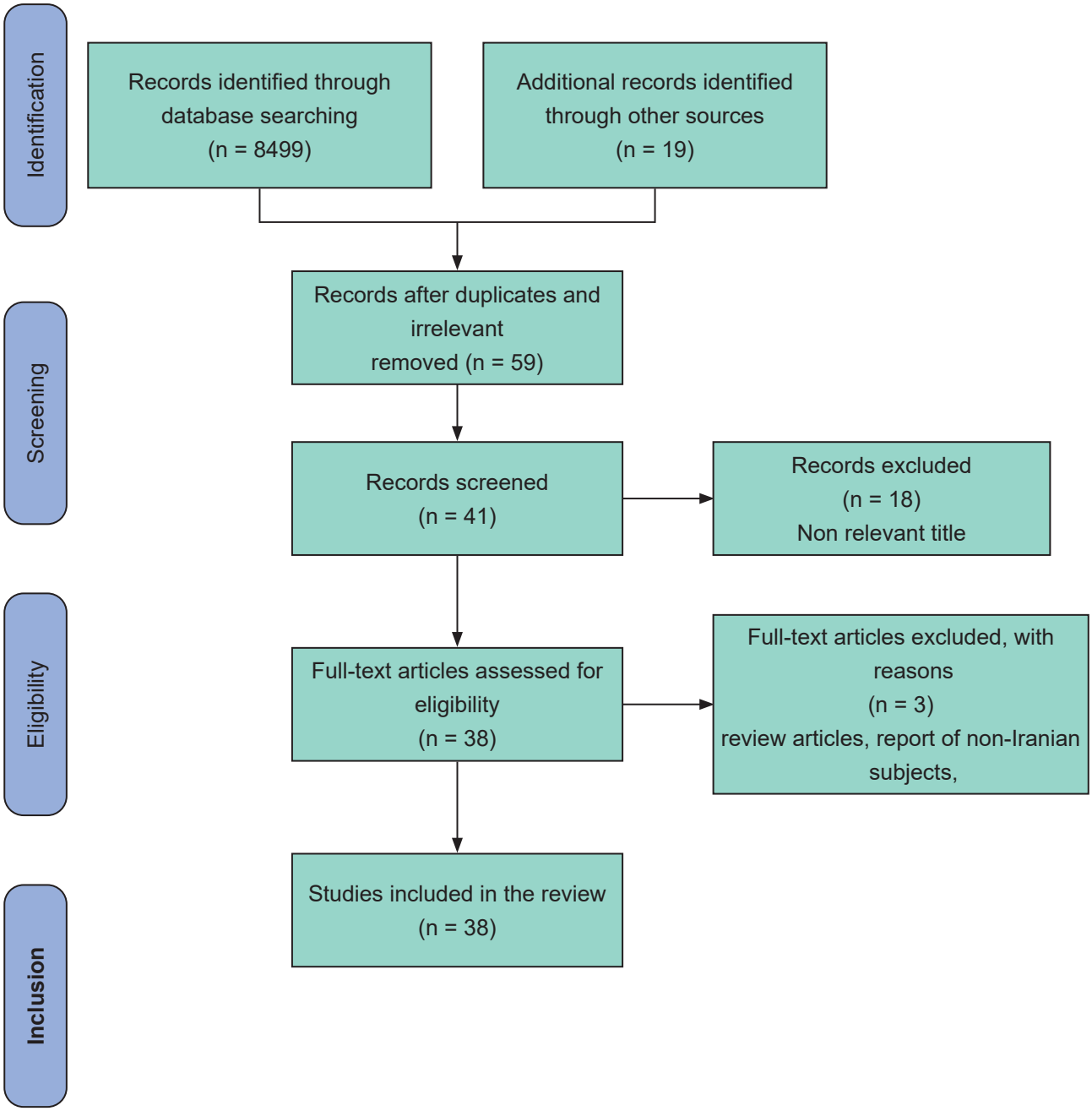

Figure 1. Flowchart of Selection of Relevant Studies about Cystinosis in Iran.

frequent type is infantile type. There is a gap of knowledge about the two other types of juvenile[7] and ophthalmic forms. Individuals with juvenile or late-onset NC usually have normal growth pattern[8] with proteinuria or nephrotic syndrome and normal corneal exams during their earlier life. Even normal annual ophthalmic exams,[9] and low level of leukocyte cystine levels[10] might postponed the diagnosis.

Demography. The median age at presentation was 0.73 years (95%CI: 0.08-8.04) while the age at diagnosis was 1.5 years (95% CI: 0.66-3.58). We have divided the data into two time periods: before and after 2015, based on the availability of cystine level measurement in Iran and increased awareness through annual patient day meetings.[11] The mean age of presentation documented from 0.96 (0.68 SD) to 0.37 years (0.31 SD), moreover some cases were diagnosed earlier 1.64(0.79 SD) vs. 0.37 (0.4SD) years. About 48% of cases were

Table 1. Summary of Extracted Data

Author, Year	Publication year	Study design	Population	period study	region	N	Clinical	Age(yr)	Gender	Method of diagnosis	Outcome	GENE. detected	STORBE/ Bias
Ahmadzadeh A. 2009[34]	2001-2010	cohort	CKD	1997-2007	Ahwaz	9	UA	diagnosis-0.66,	UA	UA	CKD=9		Good-Fair/ Moderate
Ansari Sh, 2013[35]	2011-2019	case report	Cystinosis	2012	Tehran	1	FTT 1, Polyuria, polydipsia 1 Rickets 1, Fanconi syndrome 1	report1.5,	M-1	Oph-1, BMA-0, Genetic-UA	UA		Good-Fair/ Moderate
Basiratnia, M, 2014[11]	2011-2019	observational	patient day	2012-2014	Shiraz	21	UA	UA	UA	UA	ESRD-12		Poor/High
Behdad B, 2014[36]	2011-2019	case report	cystinosis	2014	Tehran	1	UA	onset-0.76; diagnosis-1.14, report-9.10,	F-1	Oph-1,	kTX-1, Died-1,		Good.Fair/ moderate
Daneshgari, A, 1999[37]	=<2000	case report	transplant	1999-2000	Tehran	4	FTT 4, Polyuria, polydipsia 4 Fanconi syndrome 4	UA	F-1, M-3	Oph-1, BMA-4,	kTX-4,	UA	Good.Fair/ moderate
Derakhshan A, 2004[38]	2001-2010	cross sectional	CKD	1993-2000	Shiraz	3	UA	UA	UA	UA	ESRD-8		Poor/ moderate
Ghazaie F, 2017[39]	2011-2019	cross sectional	genetic. cystinosis	2014-2016	Tehran	28	FTT 28, Polyuria, polydipsia 28 Rickets 28, Fanconi syndrome 28 .	UA	F-12, M-16	Oph-28, Genetic-28	UA	c.257_258delCT (p.Ser86PhefsTer38) in exon 6 ;	Good.Fair/ Low
Gholami Yarahmadi S, 2022[21]	>=2020	case report	cystinosis	2022	Tehran	2	FTT 2, Polyuria, polydipsia 2 Rickets 1, Fanconi syndrome 2	report-8.5, ESRD-3	F-2	Oph-2, Genetic-2	ESRD-2, kTX-2,	c.257_258delCT (p.Ser86PhefsTer38), c.323delA (p.Q108RfsTer10)	Good.Fair/ Low
Hooman N, 2009[40]	2001-2010	cohort	CKD-PD	1993-2006	Iran	5	UA	onset- 0.33; diagnosis-1, ESRD-8	UA	UA	ESRD-5(PD)		Good.Fair/ Low
Hooman N, 2017[41]	2011-2019	obserational	tubulopathy	2013	Iran	130	UA	diagnosis-1.93, report-23.89, ESRD-11	UA	UA	UA		Good.Fair/ Low
Hoseini R, 2019[42]	2011-2019	cross sectional	transplant	1985-2012	Tehran	21	UA	ESRD-3	F-16, M-5	UA	ESRD-6(HD), kTX-21		Good.Fair/ Low
Hosseini S, R, 2008[43]	2001-2010	cross sectional	cystinosis	1997-1998	Tehran	21	FTT 18. Polyuria, polydipsia 12 Rickets 16, Fanconi syndrome 12 hypothyroidism 4	UA	F-13, M-8	UA	UA		Good.Fair/ Low

Table 1. Continued

Author, Year	Publication year	Study design	Population	period study	region	N	Clinical	Age(yr)	Gender	Method of diagnosis	Outcome	GENE. detected	STORBE/ Bias
Hosseini S, 2018[15]	2011-2019	cross sectional	WBC. cystine-conference	2015-2017	Iran	308	UA	UA	F-146, M-162	UA	UA		Good.Fair/ Moderate
Imanzadeh F, 2003[44]	2001-2010	case report	cystinosis	2003	Tehran	1	FTT 1, Polyuria, polydipsia 1 hypothyroidism 1		M-1	BMA-1	UA		Good.Fair/ Moderate
Jahangiri F, 2017[45]	2011-2019	cohort	CKD-PD	1993-2012	Tehran	1	UA	diagnosis-1.5, ESRD-9	UA	UA	UA		Good.Fair/ Low
Madani K, 2001[46]	2001-2010	cross sectional	CKD	1991-1999	Tehran	11	UA	UA	UA	UA	ESRD-11		Good.Fair/ Low
Madani, A, 2003[47]	2001-2010	cross sectional	cystinosis	2003	Tehran	15	FTT 15, Polyuria, polydipsia 15 Rickets 13, Fanconi syndrome 6 splenomegaly 1, cardiomyopathy 1 myopathy 1	report-6.33,	F-8, M-7	Oph-15, BMA-15	Native K-7, ESRD-7(PD)		Good.Fair/ Low
Madani, A, 2004[46]	2001-2010	cohort	CKD-HD	1989-2002	Tehran	10	UA	onset- 0.8(1.5), diagnosis-3.54,	UA	UA	ESRD-10(HD)		Good.Fair/ Low
Mirdehghan M, 2003[48]	2001-2010	case series	cystinosis	1995-2000	Ahwaz	10	FTT 10, Polyuria, polydipsia 7 Rickets 10, Fanconi syndrome 10 hypothyroidism 2	onset-0.66(0.25-1.5), diagnosis-1.8,	F-6, M-4	UA	Died-4		Good.Fair/ Low
Mirzaie, N, 2011[49]	2011-2019	case series	transplant	1996-2011	Tehran	14	UA	onset-0.94, diagnosis-2.5, ESRD-4	F-11, M-3	Oph-14	ESRD-2(HD)	UA	Good.Fair/ Low
Moarefian, S, 2013[50]	2011-2019	cross sectional	cystinosis	2013	Tehran	22	FTT 22, Polyuria, polydipsia 12 Fanconi syndrome 22 hypothyroidism 9, myopathy 7	UA	F-15, M-7	Oph-4, BMA-22	Native K-8, ESRD-4, kTX-2	UA	Good.Fair/ Low
Mortazavi FS, 2013[51]	2011-2019	cross sectional	CKD	1999-2009	Tabriz	5	UA	report-1, ESRD-13	F-1, M-4	UA	UA	UA	Good.Fair/ Moderate
Mortazavi FS, 2013[52]	2011-2019	cross sectional	cystinosis	2001-2011	Tabriz	10	FTT 10, Polyuria, polydipsia 10 Rickets 10.Fanconi syndrome 10 hypothyroidism 10	diagnosis-2,	F-5, M-5	Oph-10	UA	UA	Good-Fair/ Low

Table 1. Continued

Author, Year	Publication year	Study design	Population	period study	region	N	Clinical	Age(yr)	Gender	Method of diagnosis	Outcome	GENE. detected	STORBE/ Bias
Najafi M, 2019[28]	2011-2019	case report	cystinosis	2019	Mashhad	2	FTT 2, Polyuria, polydipsia 1 Fanconi syndrome 1	onset-0.33 diagnosis-0.66, report-1,	F-1, M-1	Genetic-1	ESRD-1, kTX-1, Died-1	exon 10 of the CTNS gene to intron 2/3 of TRPV1, encompassing CARKL/SHP	Good.Fair/ Low
Nakhaie Sh, 2009[53]	2001-2010	cohort	cystinosis	1996-2005	Tehran	23	FTT 18, Polyuria, polydipsia 10 hepatomegaly 8, splenomegaly 5	diagnosis-1, report-5.99,	F-15, M-8	UA	Native K-7, ESRD-14(HD-3, PD-6), kTX-5, Died-2, LTFU-0	UA	Good-Fair/ Low
Nakhaie Sh, 2022[7]	>=2020	case series	cystinosis	2022	Iran-218//19	19	FTT 15, Polyuria, polydipsia 13 Rickets 1, Fanconi syndrome 2 hepatomegaly 4, splenomegaly 4	report-15,	F-11, M-8	Oph-11, BMA-2, Genetic-2	Native K-2, ESRD-17(HD-3), kTX-14, Died-2,	UA	GoodFair/ Low
Nemati, F, 1998[54]	=<2000	case series	cystinosis	1998-1999	Tehran	15	FTT 15, Polyuria, polydipsia 15 Rickets 15, Fanconi syndrome 15	report-8,	UA	UA	kTX-1, Died-1, LTFU-7,	UA	Good . Fair/ Moderate
Nikibakhsh AA, 2013[55]	2011-2019	cohort	CKD-PD	2005-2011	Urmia	3	UA	report-8,	F-0, M-3	UA	ESRD-3(PD), Died-1		Good . Fair/ Moderate
Pourahmadi S, 2001[56]	2001-2010	case report	cystinosis	2001	Mashhad	3	FTT 3, Polyuria, polydipsia 3 Rickets 3, Fanconi syndrome 2 hypothyroidism 1	report-5.99,	F-1, M-2	Oph-3	UA	UA	Good.Fair/ Moderate
Rezaie F, 2018[19]	2011-2019	observational	Cystinosis-conference	2018	Iran	185	UA	onset- 0.08	UA	UA	UA		Good.Fair/ Moderate
Sadeghipour F, 2017[29]	2011-2019	cross sectional	genetic. cystinosis	2017	Shiraz	20	Rickets 11, hypothyroidism 10	onset- 0.7; diagnosis-1.23, report-9.10,	F-5, M-15	Oph-19, Genetic-20	kTX-5,	c.681G>A; E227E	Good .Fair/ Low
Sarbaz-Hoseini, Z, 2014[57]	2011-2019	cross sectional	Cystinosis-thesis, patient day	1991-2011	Tehran, Iran	97	hepatomegaly 31, splenomegaly 31, myopathy 5	age diagnosis-1.25, repor-6.73,	F-45, M-50	Oph-94	Native K-33, ESRD-27 Died-13	UA	Good. Fair/ Low

Table 1. Continued

Author, Year	Publication year	Study design	Population	period study	region	N	Clinical	Age(yr)	Gender	Method of diagnosis	Outcome	GENE. detected	STORBE/ Bias
Shah-rahman, F, 2018[58]	2011-2019	cross sectional	cystinosis-thesis	2008-2017	Mashad	20	FTT 18, Polyuria, polydipsia 16 Fanconi syndrome 17 hypothyroidism 5	onset-2.3; report- 6.5,	F-9, M-11	Oph-20	ESRD-1(PD) kTx-4, Died-1	UA	Good. Fair/ Low
Shahkarami S, 2013[31]	2011-2019	case series	genetic. cystinosis	2013	Ahwaz	25	FTT 25, Polyuria, polydipsia 21 Rickets 22, Fanconi syndrome 25	report-4,	F-11, M-14	Oph-25, Genetic-11	UA		GoodFaire/ Low
Sharifian M, 2008[59]	2001-2010	cohort	transplant	1995-2006	Tehran	15	FTT 15, hypothyroidism 5.	diagnosis-1.5,	F-8, M-7	Oph-3	ESRD-6(HD-5, PD-1) kTx-15,	UA	GoodFair/ Low
Sharifian M, 2011[20]	2011-2019	cross sectional	cystinosis	1993-2010	Tehran-Ahwaz	44	FTT 44, Polyuria, polydipsia 30 Rickets 31, Fanconi syndrome 35	UA	F-24, M-20	Oph-44	ESRD-7(HD), kTX-16, Died-8, LTFU-21	UA	Good. Fair/ Low
Tajodini M, 2017[60]	2011-2019	case report	cystinosis	2017	Tehran	1	UA	UA	F=1	UA	kTX-1,	UA	Good, Fair/ Low
Saleki F, 2022[30]	2020	Case report	Cystinosis	2020	Tehran	2	FTT-2, Polydipsia-2, Fanconi syndrome -2, Rikets-2	Report-9, 10yr	F=2	Genetic-2	UA	c.257_258delCT (p.Ser86PhefsTer38) in exon 6// c.323delA (p.Q108RfsTer10)	Good.Fair /Low

FTT= Failure to Thrive, F=Female, M=Male, UA= unavailable, Oph= Ophthalmic Exam, BMA= Bone marrow aspiration, KTX= kidney transplantation, LTFU= Lost to Follow up, ESRD= End stage Renal disease, HD= hemodialysis, PD= peritoneal dialysis

male (95% CI = 42.8 – 54.3), and 52% were female (95% CI = 46.8 – 58.6).

Gap of Knowledge. Data are limited due to the ages associated with elevated creatinine levels and development of end-stage kidney disease (ESKD).

Presentation. The earliest symptoms of index patients were inadequate weight and height gain (failure to thrive) accompanied by irritability due to excessive thirst and heavy diaper. According to the extracted input, the frequency of manifestations in decreasing order were failure to thrive 94% (95% CI = 89 – 94), polyuria-polydipsia 78.3% (95%CI = 66.6-88), Fanconi syndrome 79% (95% CI = 61 – 92), and rickets 77.4% (95%CI = 57.6-92%). Severe genu valgum requiring hemi-epiphysiodesis at the age of 10 years by average was reported in 14 cases.[12]

Gap of knowledge. No information exists on the severity of FTT at diagnosis and the longitudinal monitoring of growth.

Comorbidities. The concurrent abnormalities were vesicoureteral reflux reported in 15.3% (95%CI = 5.7- 30.7), and urinary tract infection reported in 23.6% (95% CI = 8.5-43.4%) of cases. Twenty five percent of cases had restrictive or obstructive lung disease in spirometry with normal chest x-ray.[13] Other accompanying signs were hepatomegaly and/or splenomegaly 31.25% (95% CI = 23.9 – 39), cardiomyopathy 39.5% (95% CI = 2.6 - 95.5), myopathy 13.4% (95% CI = 2.05 – 32.7), and hearing loss 6.8% (95%CI = 1.8-16.8).

A neurologic assessment of forty cases revealed that 25% had history of seizures, 15% had tension type headache, and distal muscle weakness was detected in 5% of individuals with cystinosis.[14]

Other rare manifestations of cystinosis that reported as case report or case series were bilateral Duane syndrome with pseudotumor cerebri (n = 1), exophthalmia (n = 1), blindness (n = 2), optic atrophy (n = 1), aortic dissection (n = 1), portal hypertension(n = 1), polycystic kidney disease, glomerular sclerosis, and nephrotic syndrome reported in four cases.

Gap of knowledge. There is no data regarding central nervous system involvement, cognition, neuropathy, longitudinal assessment of muscle strength, or endocrine and exocrine symptoms.

Diagnostic tools. In addition to clinical features,[4] a review of evidence in Iran indicated that the confirmation of cystinosis is based on the detection of cystine crystals deposition in the cornea in 84.5% of cases (95% CI = 68.5 - 95.5), cystine crystals deposition in bone marrow in 80.3% of patients (95% CI = 41.7-99.7), measurement of cystine levels in leukocytes, and finally a genetic study 75.6% (95%CI = 22-99). The proportion of homozygote inheritance was 67.8% (I^2 = 69%; 95%CI = 49-86), compound heterozygote was 15% (95%CI = 7.8-25), and heterozygote was 13% (95%CI = 1.4-33) The mutation of gene c.681G4A/c.681G4A was the most commonly mutation detected with proportion of 45%(95%CI = 30-59.8). The two other more frequent gene mutations were c.779C > T; p.T260I and c.261T > A; p.F87L.

Leukocyte cystine level measurement has been started since 2015 by using liquid Chromatography-Tandem mass spectrometry.[15] The first measurement of leukocyte cysteine level in 238 children undergoing therapy revealed that 70% had values over 0.2 nmol 1⁄2 cystine/mg protein with a median of 0.36 (range 0-6.65), and 45% had levels beyond 0.4 nmol 1⁄2 cystine/mg protein.

Gap of Knowledge. No data regarding the severity of anterior segment, posterior segment, visual acuity, optic tomography is available prior to initiation of cysteamine eye drops and in each scheduled visit, according to proposed approach.[16] There is lack of evidence regarding the close monitoring of cysteamine HCl level and the kidney and extra- kidney involvement.

Treatment. The affected patients need dietary management, supportive, and specific therapy. Supportive therapeutic measures consist of the management of fluid, electrolyte, and metabolic acidosis imbalance. Other medications such as indomethacin for reducing polyuria, and Angiotensin II receptor blockers (ARBs) or Angiotensin-converting enzyme inhibitors (ACEIs) to eliminate proteinuria. Supplements such as L-carnitine, and hormones replacement such as levothyroxine and recombinant growth hormone might be necessary, if indicated.[4,17]

Cysteamine-depleting medications (both systemic and topical) are the cornerstone of treatment.[18] Immediate release Cysteamine bitartrate should be administered with a dose of 1.30 g/m2 /day, with a maximum of 1.95 g/m2 /day divided to every 6 hours. A survey declared that almost 42% (95%CI = 27.6-57.5%) of the cases did not received the medication with appropriate dosage.[19] The local

application of cysteamine hydrochloride eye drops is indispensable to reduce cysteine deposition in the cornea due to its inadequate vascularization. Generic local eye drops are utilized by patients in Iran, but their efficacy or adverse effects are not documented so far.

Gap of Knowledge. Few studies reported the frequency, dosage, adherence, monitoring, and adverse effects of medications utilized including levothyroxine,[20] L-carnitine, growth hormone,[20,21] Cysteamine bitartarate , and bicitrate solution.[22]

Outcome. There is limited data on cystinosis patients who survived to adulthood in Iran. Nineteen of 218 cases (8.7%) were older than 18 years. The oldest survivor was 34 years old. Nakhaie *et al.* focused on some gastrointestinal manifestation of a cohort of cystinosis cases reached adulthood. and did not report the other extra renal morbidities.[7] One quarter of them transferred to adult nephrologists.

End-stage kidney disease occurred in 68.34% (95%CI: 51.5- 83) of patients at the mean(range) age of 8.3 years (3-13 yrs). The frequency of receiving kidney transplant was 62% (95%CI:10-24). Acute rejection was reported in 28.9% (95%CI = 15.5-44.6%) of transplanted cases. Graft lost was reported in 19.6% (95%CI = 10.2-31.3%) of patients which was due to renal vein thrombosis, chronic glomerulopathy, and non-functioning graft. Almost 16.5% (95%CI:10-24) of index cases died.

Gap of Knowledge. There is no information regarding the variations in the outcome of kidney and extra-renal organs by time. There is no evidence regarding which complications precede or follow in these cases.

Quality of life. There is no information pertaining to adulthood, transition, education, marriage, pregnancy, occupation, and quality of life, the challenges of availability of medications, family burden, cost of living, and compliance in patients with cystinosis so far.

DISCUSSION

This scoping review assists to remark that some inquiries about cystinosis in Iran stand on available evidence; consequently, abundant queries are still necessary. Although the estimated incidence rate was comparable to that reported in the literature,[2] the mean age (years) of diagnosis lessened form 1.64 before 2015 to 0.94 afterward. However, there was a lack of input to assess its impact on kidney function.

A cohort of 450 nephropathic cystinosis patients over more than three decades concluded that early diagnosis and adequate dosage of cysteine depleting medication would significantly improve kidney function and linear growth.[23]

The earliest manifestation of cystinosis is Fanconi syndrome that usually appear at 4-6 months of age. Nevertheless, the corneal deposition could be visible in untreated patients at age 16 months.[1] We found that the most common presentations of cystinosis patients were failure to thrive, polyuria, polydipsia, Fanconi syndrome, and rickets at the median age of eight months. There is evidence that better kidney outcome is strongly depended on early diagnosis and treatment,[23] high index of suspicion is demanded when measurement of cysteine level in WBC or genetic study could not be done. In addition to clinical manifestation and family history, traditionally, corneal exams and bone marrow aspirations are used to confirm the diagnosis.[24] Genetic study is expensive and is not financially affordable for many families. The measurement of leukocyte cysteine levels can be conducted just at a single private laboratory in Iran, rendering the analysis mostly inaccessible throughout the country. Moreover, there are pitfalls of leukocyte cysteine level measurement in some circumstances.[10] Cysteine deposition starts in utero, subsequently newborn screening is suggested in some countries.[25,26]

The most genetic mutation in CTNS gene is large 57-kb deletion in Europe, its incidence is rare in the East Mediterranean and Middle East.[27] Only one patient in this review had 57-kb deletion.[28] The most frequent gene mutation was c.681G > A, the same as Egypt, Turkey and Middle East.[29-31] That demonstrated variability of genetic mutation in various parts of the world.

The diagnosis and management of cystinosis require a multidisciplinary approach that needs interaction, cooperation and awareness of the disease and its complications to improve the quality of life, health. Fertility in females are normal but hypogonadism and oligospermia in males have been reported.[32,33] Although 8% of Iranian patients with cystinosis are above 18 years old, there is scant information about involvement of other organs. There is no information about their education,

quality of life, socioeconomic status, occupation, marital status, etc. in Iran.

Ophthalmic involvement is a major criterion for diagnosis of infantile and ophthalmic cystinosis. More than 84% of children had ocular Regular prescription of local cysteamine HCL eye drop to improve clinical manifestation by reducing the precipitation of cysteine on cornea. There was no report of compliance of children in utilizing the Iranian made ophthalmic eye drop (cysteamine HCL), its side effects, the cystinosis corneal scoring system at diagnosis, on follow up, and its efficacy, or late complications. There is a need for closer interaction between nephrologists and ophthalmologists for reporting the eye involvement more precisely.

The study limitations were heterogeneity of studies, overlap in research years, lack of longitudinal data, and the incidence prevalence rates might be overestimated. Despite improving the life expectancy, there is no transition protocols for those who survived to adulthood. There were rare evidences about extrarenal involvement of cystinosis and their outcomes, the compliance and accessibility of medications, their side effects, longitudinal corneal cystinosis scoring, and the quality of life, occupation, and education of the involved patients.

CONCLUSION

This systematic scoping review explores that there are gaps of knowledge in many aspects that require starting a cystinosis registry and documenting the follow-up to improve the outcome and the quality of life.

CONFLICT OF INTEREST

None.

AUTHORS CONTRIBUTION

All authors have contributed to the conceptualization of the study, critically reviewing the articles, data extraction.

STUDY FUNDING

None.

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