

Clinical features and outcomes of 98 children and adults with dense deposit disease

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Abstract

Background Dense deposit disease (DDD) is an ultra-rare renal disease.

Methods In the study reported here, 98 patients and their families participated in a descriptive patient-centered survey using an online research format. Reports were completed by patients (38%) or their parents (62%). Age at diagnosis ranged from 1.9 to 38.9 years (mean 14 years).

Results The majority of patients presented with proteinuria and hematuria; 50% had hypertension and edema. Steroids were commonly prescribed, although their use was not evidence-based. One-half of the patients with DDD for 10 years progressed to end-stage renal disease (ESRD), with young females having the greatest risk for renal failure. Of first allografts, 45% failed within 5 years, most frequently due to recurrent disease (70%). Type 1 diabetes (T1D) was present in over 16% of families, which represents a 116-fold increase in incidence compared with the general population ($p < 0.001$).

Conclusions Based on these findings, we suggest that initiatives are needed to explore the high incidence of T1D in family members of DDD patients and the greater risk for progression to ESRD in young females with DDD. These efforts must be supported by sufficient numbers of patients to establish evidence-based practice guidelines for disease management. An international collaborative research survey should be implemented to encourage broad access and participation.

Keywords Dense deposit disease · MPGN type II · Patient Information Survey

Introduction

Dense deposit disease (DDD), previously known as membranoproliferative glomerulonephritis type 2 (MPGN type 2), is an ultra-rare renal disease characterized by dense deposits in the lamina densa of the glomerular basement membrane (GBM). The rarity of this disease makes it difficult for clinicians to establish evidence-based clinical practices for its management. In addition, early studies typically grouped DDD with MPGN types 1 and 3, making it difficult to determine an accurate incidence rate for DDD and impossible to establish best practice guidelines [1–4]. Although basic science research over the past decade has increased our understanding of the genetics and pathophysiology of DDD [3, 5], epidemiological information about the disease course, medical history, medications, and clinical presentation has not been collected on large numbers of patients, emphasizing the need for population-based studies.

The purpose of this paper is to report the results of a survey of 98 DDD patients. Specifically, descriptive

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information is provided on family/patient medical disease history, history of DDD, medications, course of DDD/progression to end-stage renal disease (ESRD), and history of dialysis and transplantation. This self-reported information provides a broad picture of the disease-related experiences of DDD patients. It is the most comprehensive epidemiological article on DDD, both in terms of the scope of the survey and the number of participants. We believe that by describing the experiences of DDD patients, this paper will provide clinicians, patients, and families with an insight into this ultra-rare disease that can facilitate informed healthcare decision-making.

Background

Dense deposit disease is a glomerular disease characterized by electron-dense deposits (EDD) in the lamina densa of the GBM [1, 4]. These deposits arise secondary to dysregulation of the alternative pathway of the complement cascade. Dysregulation occurs at the level of the C3 convertase and involves a variety of factors, such as C3 nephritic factors (C3Nefs), genetic mutations in complement genes, and autoantibodies to complement proteins, such as complement factor H (fH) [2]. Although previously called MPGN type 2, suggesting a similarity with MPGN types 1 and 3, DDD is not an immune-complex disease (MPGN types 1 and 3 are), and the lesions are not primarily membranoproliferative [3, 6]. These distinctions have led to the adoption of DDD as a more appropriate name for this disease [3, 4]. Recent studies focused only on DDD show that the incidence is between two to three persons per million general population, making DDD rare even amongst the most rarest of diseases [7]. The National Organization for Rare Disorders (NORD; see <http://rarediseases.org>), for example, defines a rare disease as one that affects fewer than 200,000 people in the USA or 1 in 1,500 people [8].

DDD is most often diagnosed in children between the ages of 5 and 15 years and does not show a sex bias [4]. Although light microscopy and immunofluorescence findings can be suggestive of the diagnosis, electron microscopy (EM) is required and will show ribbon-like dense deposits in the GBM [3, 6]. The presence of C3Nefs in the serum is supportive of the diagnosis, although it is not conclusive [5]. Non-specific symptoms of renal insufficiency, such as hypertension, hematuria, proteinuria, and nephrotic syndrome, are frequently present in DDD patients. Acquired partial lipodystrophy (APL) and drusen (tiny yellow or white accumulations of extracellular material that build up in Bruch's membrane of the eye) are associated with DDD [9–11]. The treatment of DDD is unsatisfactory and only

nonspecific, the goals of which are to control blood pressure, reduce proteinuria, correct electrolyte imbalances, correct anemia, and address growth and other health issues created by declining or failed renal function [4]. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II type 1 receptor blockers (ARBs) are commonly prescribed for DDD patients, and although immunosuppression with steroids, specifically prednisone, has been advocated for over 30 years for all types of MPGN and many other renal diseases, there is no evidence for its benefit in DDD [5].

There are no disease-specific treatments for DDD although plasma infusion or exchange to provide intact fH and remove C3Nefs has been used [4, 5]. There are also a few centers around the world using the anti-complement drug eculizumab to treat small groups of DDD patients, but the outcome of this treatment has not yet been reported [12]. Based on the pathophysiology of DDD, successful treatment would be predicted to normalize activity of the alternative complement pathway, suggesting that serum C3 levels may be a biomarker of disease activity [4].

Roughly 50% of DDD patients progress to ESRD and require dialysis within 10 years of diagnosis [13, 14]. Various studies have suggested the factors predictive for progression to renal failure include younger age at diagnosis, specific variants of renal pathology, elevated serum creatinine levels and proteinuria at diagnosis, initial presentation with nephrotic and nephritic syndromes, and >20% chronic renal damage on initial biopsy [1, 3, 14–16]. The first factor is noteworthy because Nasr and colleagues [1] have reported that DDD patients diagnosed at >60 years of age have a higher incidence of renal failure, a point neither we nor other investigators have been able to confirm [4, 17]. Progression to ESRD necessitates renal replacement therapy by dialysis or transplantation. Unfortunately, approximately 50% of transplant recipients lose their allografts within 5 years of transplantation, making recurrence of DDD and graft failure a significant issue for DDD patients [16, 18–20].

As a chronic disease, DDD has a significant impact on the entire family, especially if renal failure develops. The aim of the study reported here was to use a patient-driven database to describe the medical experiences of DDD patients to facilitate and optimize their clinical care.

Methods

Participants

Individuals with DDD and their immediate families participated in a secured online research survey (Membranoproliferative

Glomerulonephritis–Database Baseline Survey) via the website <https://mpgn.nursing.uiowa.edu/>. Invitations to participate were extended through contact with health professionals, publications, and websites such as KIDNEEDS (<http://www.healthcare.uiowa.edu/kidneeds>), a research foundation that provides information on DDD. Information and consent were available on the front page of the Membranoproliferative Glomerulonephritis–Database Baseline Survey. After indicating consent, subjects received passwords to access the research survey. The University of Iowa Human Subject Review Board approved this study.

The Membranoproliferative Glomerulonephritis Database Baseline Survey included DDD patients as well as patients with MPGN types 1 and 3. All DDD patients had a diagnosis verified by biopsy that included EM findings. Patients biopsied prior to 1990 and those who could not provide a pathologic report diagnostic of DDD were not included in the study. Four patients initially diagnosed with DDD based on a primary biopsy were diagnosed with a different disease on a subsequent biopsy and were also excluded. Thirty-eight percent (38%) of surveys were completed by patients and 62% were completed by parents or guardians. There was no age limit for participation.

Instruments

The research team developed the original survey to gather information on patients with DDD and MPGN types 1 and 3. Detailed information on content validity and reliability testing has been published [17], and in this report, we have focused exclusively on DDD patients.

The survey was designed to describe how DDD patients and their families perceive their disease experiences. A revised version of the self-reported survey, with expanded disease categories for health history, lists of medications, and potential treatments, was completed in 2009 with the support of the University of Iowa Information Technology Services. The on-line survey meets the security standards of the University of Iowa and is linked to a highly secured relational database. Data are stored in a Microsoft SQL (Standard query language) server with a functioning relational database schema, which provides efficient data access and storage. Details of the development process will be published separately. Research team members with access to the SQL database can perform simple queries to answer research questions.

The survey consisted of 140 items divided across eight sections: patient information; family/patient health history; history of MPGN; medications; course of MPGN; history of dialysis; history of transplant; conclusion. Throughout the questionnaire, participants respond to closed questions but are also provided with open fields to allow them to contribute additional information.

Procedures

The research team did not send out invitations to participate in the survey. Rather, DDD patients or immediate family members initially contacted researchers by e-mail, phone, or mail to express an interest in the survey. Following completion of the online consent form, if patients had a diagnosis of DDD or MPGN Types 1 and 3, they were e-mailed a computer-generated password to gain access to the survey, which they usually completed online. A paper copy of the questionnaire was available for persons who preferred to complete a paper copy of the survey. If a paper survey was completed, data were entered into the database by a research team member. All responses were confidential, with individual subject codes applied to each survey. Access to the names connected to each coded survey was available only to researcher team members. Access to the online database was secured, password protected, and limited to only a few individuals on the research team.

Data analysis

Data, which were downloaded from the SQL server onto a Microsoft Excel spreadsheet, were analyzed using the Statistical Package for Social Science (SPSS for Windows 17; SPSS, Chicago, IL). The chi-square test was used to compare differences between groups. The two-sample *Z* test for proportions and one-tailed significant test were used to evaluate the effects of gender and disease duration on progression to renal failure. The Kaplan–Meier survival analysis was used to estimate survival time of native kidneys from date of diagnosis.

Results

Participants

Ninety-eight surveys were completed at the time of data capture (March 2010). Of the patients who responded, 56% ($n=55$) reported their sex as female and 86% ($n=84$) reported their ethnicity as ‘White/Caucasian’. Other reported races included American Indian (3), Hispanic (5), and mixed (4). The mean age at diagnosis was 14 years (male, mean 14.2 years; female, mean 13.9 years). For purposes of evaluating the effect of age-at-diagnosis, we compared the ≤ 12 -year-old group (‘younger population’; $n=60$; range 1.9–13.0 years) to the ≥ 13 -year-old group (‘older population’; $n=38$; range 13.1–38.9 years) as this breakpoint approximates puberty. Of the patients, 70% were diagnosed with DDD before age 15 years.

Patient/family medical/disease history

Disease histories were obtained on DDD patients and their parents and siblings. Information was also collected on extended family members, including grandparents, aunts, uncles, and cousins. Four of the listed health conditions were reported as co-morbidities by more than five individuals with DDD: fH polymorphism ($n=10$), depression ($n=9$), drusen ($n=7$), and hypothyroidism ($n=5$). APL, which has been reported as an autoimmune disease associated with DDD [17], was reported in four DDD patients, two of whom had progressed to ESRD. In three of these patients, the diagnosis of APL anteceded the diagnosis of DDD.

Medical diseases reported by more than ten families are listed in Table 1. Autoimmune diseases were found most commonly. It is noteworthy that 16 families reported family members with type 1 diabetes (T1D) and in seven families two or more blood-related family members carried this diagnosis. Based on data from the Center for Disease Control, the expected prevalence of T1D in the general population is approximately 1.4 per 1,000 U.S. families, suggesting that the diagnosis of DDD is associated with a nearly 116-fold increase in the familial rate of T1D ($p<0.001$).

History of DDD

Table 2 shows the symptoms that prompted the healthcare referral ultimately leading to the diagnosis of DDD. The

Table 1 Diseases reported in the medical history of more than ten families (total $n=98$)

Diseases	<i>n</i>	Percentage
Autoimmune		
Type 1 diabetes	16	16.3
Autoimmune hypothyroidism	21	21.4
Autoimmune rheumatoid arthritis	24	24.5
Dermatology		
Eczema	26	26.5
Unexplained rashes	11	11.2
Psoriasis	11	11.2
Gastrointestinal		
Irritable bowel syndrome	12	12.2
Genetic		
DDD-associated Factor H polymorphism	10	10.2
Mental health		
Depression	33	33.7
Ophthalmology		
Age-related macular degeneration	11	11.2
Glaucoma	10	10.2

DDD, Dense deposit disease

primary symptoms were hematuria (42.9%) and peripheral (37.8%) and facial (31.6%) edema. About one-fifth of DDD patients (21.4%) did not suspect a problem and in this group, signs of kidney disease were detected as part of a routine annual examination. Nausea, vomiting, and fever prompted more visits than did proteinuria and hypertension, although at presentation, 90% of DDD patients had proteinuria, 84% had hematuria, 54% had hypertension, and 40% were edematous. The number of symptoms identified by physicians at diagnosis was greater than the number of symptoms recognized by patients prior to their healthcare referral. In particular, hematuria ($X^2=35.125$, $p<0.001$), proteinuria ($X^2=103.753$, $p<0.001$), and hypertension ($X^2=36.550$, $p<0.001$) were more likely to be identified by physicians than by patients and/or their families (Table 2).

Medications

Prescribed medications are listed in Table 3. The most commonly used medications were ACE inhibitors and oral prednisone (ACE: $n=76$, 77.6%; prednisone use: every other day 55.1%, once daily 35.7%).

Progression to renal failure

Thirty-five (35.7%) DDD patients had progressed to ESRD: 22 of 55 females (40.0%) and 13 of 43 males (30.2%) (Table 4). There was no statistically significant effect of gender or of age-at-diagnosis, each separately, on the development of renal failure (RF) in the total group. However, in the ‘younger population’, a greater percentage of females than males were on dialysis (females: 50%, $n=17/34$; males: 27%, $n=7/26$; $Z=1.808$, $p=0.036$) (Table 4). RF was also more common among DDD patients diagnosed for >10 years: 10 of 19 (53%) patients with DDD >10 years versus 25 of 79 (32%) patients with DDD <10 years (two-sample Z test for proportions $Z=1.714$, $p=0.044$) (Table 4).

Renal survival time was calculated as the time from diagnosis to ESRD and was defined as a continuous variable. Figure 1 shows the Kaplan–Meier survival estimates for the renal survival time of all participants. Thirty-five DDD patients were in renal failure (35.7%). By using the 63 DDD patients with native kidney function as censored data to estimate the renal survival time of DDD patients, the median survival time to renal failure was calculated to be 10.4 years (standard error 1.401, 95% confidence interval 7.5–13.0 years). Major drops in the survival curve were observed during the first 5 years following diagnosis. For example, 2.5 and 5.0 years after diagnosis, the chance of progression to renal failure approximates 25 and 33%, respectively.

Table 2 Symptoms present at initial presentation and symptoms identified when diagnosing DDD

Symptoms present at initial presentation and symptoms identified when diagnosing DDD	Prompted visit		Diagnosed by physician ^a	
	<i>n</i>	Percentage	<i>n</i>	Percentage
Blood in urine	42	42.9	82	83.7
Protein in urine	18	18.4	89	90.8
High fever	16	16.3	19	19.4
Nausea and vomiting	19	19.4	24	24.5
Hypertension	13	13.3	53	54.1
Drusen on retina	3	3.1	4	4.1
Puffiness around eyes, face	31	31.6	38	38.8
Puffiness feet, hands, or legs	37	37.8	39	39.8
No symptom noted by participants; found on routine exam	-	-	21	21.4

^aPatients would have reported macroscopic hematuria and proteinuria. It was not possible to confirm which techniques these doctors used to diagnosed hematuria and proteinuria; DDD, Dense deposit disease

Dialysis and transplantation

The characteristics of the 35 DDD patients with RF are presented in Table 5. Thirty-four patients were on dialysis at some time (hemodialysis: *n*=17, 48.6%; peritoneal dialysis: *n*=17, 48.6%), and 22 patients (62.8%) had a

Table 3 Medications taken to treat DDD prior to transplant (*n*=98)

Medication	<i>n</i>	Percentage
Antihypertensives		
ACE Inhibitors	76	77.6
ARB/CCB	6	6.1
Non-ACE Inhibitors (excluding ARB/CCB)	13	13.3
Steroids		
Oral prednisone (alternate day)	54	55.1
Oral prednisone (every day)	35	35.7
Methylprednisolone	9	9.2
IV steroids	8	8.2
Diuretics	47	48.0
Anticoagulants		
Heparin	9	9.2
Aspirin	7	7.1
Plasma therapy		
Plasmapheresis	4	4.1
Plasma infusion	3	3.1
Immunosuppressives		
Mycophenolate mofetil (MMF)	4	4.1
Cyclosporin	3	3.1
Tacrolimus	3	3.1
Cyclophosphamide	4	4.1
Rituximab	1	1.0
Total	98	100.0

ACE, angiotensin-converting enzyme; ARB, angiotension renin blockers; CCB, calciumchannel blockers; IV, intravenous; DDD, Dense deposit disease

kidney transplantation either once (*n*=16, 45.7%) or twice (*n*=6, 17.1%). The mean time to first transplant from the time of diagnosis was 4.91 years (standard deviation3). One patient had a preemptive transplantation to avoid dialysis. Of the 28 total kidney transplant events (including 6 who had 2 transplants) among 22 recipients, ten grafts were lost, all which were the first transplant. All losses occurred during the first 5 years following transplantation ($X^2 = 7.368, p = 0.007$). Of the ten grafts lost, seven (70%) were lost due to recurrent disease. Of the allografts functioning for >5 years (*n*=9), survival time ranged from 5.1 to 10.2 years.

Discussion

The goal of this study was to describe the experiences and histories of 98 DDD patients and their families. In so doing, we believe a number of salient findings have emerged that are of importance to healthcare providers. First, and most striking, was the observation that over 16% of families reported at least one family member with T1D. Although Srikanta et al. and Didzar et al. [21, 22] also noted an association between T1D and MPGN, both of these papers describe only case reports linking immune-complex MPGN and T1D. This distinction is important as DDD is NOT an immune-complex MPGN [22]. To the best of our knowledge, therefore, our report is the first to note the association of DDD with T1D. It may be relevant that both T1D and DDD are inflammatory autoimmune diseases as commonalities in genetic predispositions may exist. For example, it has been known for more than three decades that alleles of the major histocompatibility complex contribute to susceptibility to autoimmunity, and with the availability of next-generation sequencing technologies, shared DDD–T1D HLA genotypes should be studied at high resolution to provide insight into this association [23, 24].

Table 4 Analysis of factors associated with the development of renal failure^a

General factors	Specific factors	RF	No RF	Total	<i>p</i>
Age at diagnosis	<13 years	24 (40.0%)	36 (60.0%)	60 (61.2%)	
	≥13 years	11 (28.9%)	27 (71.1%)	38 (39.7%)	
Duration of the disease	<10 years	25 (31.6%)	54 (68.4%)	79 (80.6%)	0.044
	≥10 years	10 (52.6%)	9 (47.4%)	19 (19.4%)	
Gender	Female	22 (40.0%)	33 (60.0%)	55 (56.12%)	
	Male	13 (30.2%)	30 (69.8%)	43 (43.9%)	
	Total	35 (35.7%)	63 (64.3%)		
	Gender	RF	No RF	Total	<i>p</i>
Age at diagnosis: <13 years	Female	17 (50.0%)	17(50.0%)	34 (56.7%)	0.036
	Male	7 (26.9%)	19 (73.1%)	26 (43.3%)	
	Total	24 (40.0%)	36 (60.0%)	60 (100.0%)	

RF, Renal failure

Data are presented as the number of DDD patients, with the percentage of total DDD patients ($n=98$) given in parenthesis

^aNo other signs and/or symptoms were associated with progression to RF at $p<0.05$

Early detection, monitoring, and treatment of the complications of chronic kidney disease (CKD), including hypertension, proteinuria, phosphorus, and calcium dysregulation, and anemia are essential to delay progression to ESRD. Of the 21% of DDD patients in whom renal disease was diagnosed during a routine physical exam, most had proteinuria. Although childhood proteinuria is not rare, if it is persistent or associated with other symptoms of renal disease, such as gross hematuria, hypertension, or persistent hypocomplementemia, a renal biopsy is indicated [25].

ACE inhibitors and prednisone were the most frequently prescribed medications. ACE inhibitors are used to treat hypertension and proteinuria and offer renal-sparing properties in advanced nephropathy beyond benefits that might be expected by a reduction in blood pressure [26, 27].

Prednisone was one of the first drugs used to treat DDD and a number of other inflammatory renal diseases. It is still commonly used to stabilize nephritic/nephrotic range disease [25, 28], although its use in DDD is not evidence-based [5, 7]. If prednisone is used, side effects should be carefully monitored, especially in children [5, 7, 28, 29].

Of the patients diagnosed with DDD for >10 years, 10 of 19 (53%) had progressed to ESRD, a number similar to that reported by several other groups [7, 14, 30]. Of note, we found that DDD in younger patients is more aggressive and that as a group, progression to ESRD is highest in young females. These age-related differences in progression to renal failure may reflect changes in innate immunity that occur with age. For example, innate immune responses may be less robust in older patients, the consequence of which may be a less effective response to a pathogenic insult [31]. Additional research is required to identify why young girls are more likely to develop renal failure [31–33].

Of the 35 DDD patients with RF, 22 underwent transplantation, among whom six had two grafts. All ten graft failures of the first transplants (45%) occurred within 5 years of surgery, a finding consistent with data reported by Braun and colleagues, who reported a 50% loss rate in a group of 75 pediatric patients within 5 years of surgery [20]. Recurrent disease was reported to be the primary cause graft failure in 70% of our patients.

Numerous studies have concluded that preemptive transplant is the renal replacement therapy that offers patients the best survival chances and quality of life [29, 34–37]. Only one person in our survey underwent a preemptive transplant, receiving a living-related donor kidney. Despite information to support preemptive transplantation as the better health option for patients with CKD stage 5, the number of preemptive transplants in the USA is

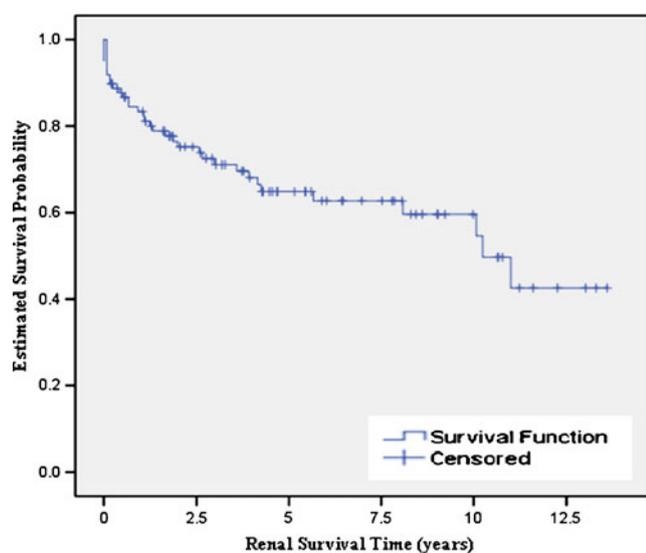


Fig. 1 Kaplan–Meier survival estimates for renal survival time

Table 5 Information on individuals with renal failure ($n=35$) who progressed to dialysis and/or kidney transplantation

Variable	Variable	<i>n</i>	Percentage	
Gender	Female	22	62.9	
	Male	13	37.1	
Number of transplantations	0	13	37.1	
	1	16	45.7	
	2	6	17.1	
	Mean	Standard deviation	Range	
Current age (years) ($n=35$)	20.8	10.5	3.7–52.2	
Age at diagnosis (years)	12.9	8.7	1.9–38.1	
Duration of disease (years)	7.8	5.2	1.2–18.0	
Time to first kidney transplantation (years) ($n=22$)	4.9	3.3	0.8–12.8	
Native kidney survival time (years)	2.4	3.1	0.0–11.0	
	Renal survival time (years)			
Age at diagnosis	<13 years ($n=24$, 68.57%)	2.08	2.70	0.00–10.1
	≥ 13 years ($n=11$, 31.43%)	3.06	3.94	0.00–11.0

relatively low (15% in the U.S. Renal Data System 2009 report [38]). Reasons for low rates may include: (1) lack of information about preemptive transplants in a timely manner; (2) hesitancy to ask donors due to worries for the donor's health; (3) financial concerns [35]. In addition to these concerns, DDD patients must also consider the high rate of recurrent disease and graft loss.

Study limitations

The length of our survey may have been a deterrent to its completion. In some cases, participants also encountered problems entering data and did not request help. In addition, even though we offered the option of a paper survey, it is possible that some individuals felt intimidated by the online method and chose not to participate rather than request a paper copy. The majority of participants were English-speaking Caucasians from the USA. Language may therefore have limited the participation of non-English speaking patients. Accurate recollections of the information by the informant can be a limitation. Biopsies were not reviewed by the research team, allowing for possible misdiagnoses. This is particularly true now that C3 glomerulonephritis (C3GN) has recently been recognized as a disease distinct from DDD [5].

Implications for practice and research

One-fifth of DDD patients had silent symptoms (microscopic proteinuria, hematuria, and hypertension) that were detected on routine physical examinations, stressing the importance of screening for hematuria, proteinuria, and

hypertension even in routine physical checkups for children. The American Academy of Pediatrics recommends yearly blood pressure screening beginning at 3 years of age [39]. Early detection of DDD symptoms and treatment could potentially slow the progression to ESRD[40].

There is a need to increase healthcare provider awareness of DDD to optimize and to provide best practices for the care of DDD patients. Resources include Kidneeds (<http://www.healthcare.uiowa.edu/kidneeds>), the National Organization for Rare Disorders (<https://rarediseases.org>), and Gene Reviews (<http://www.ncbi.nlm.nih.gov/gooks/NBK1425>). An Italian resource related to DDD is PROGETTO DDD (<http://dddonlus.org>). There is also a need to organize all disease-related information and healthcare support in a way that is accessible and understandable by DDD patients and their families. DDD family support groups should be established in different geographical areas to provide both emotional support and the knowledge for coping with different levels of disease progression. There is a private Facebook Group available by invitation only to patients who have completed the survey, and currently, over 55 patients have registered and participate. These patients provide support to each other and exchange information. There are patients from the USA, Italy, UK, and Israel who regularly participate in discussions. Health professionals can provide assistance in identifying resources for these families [41].

There is a need for research to explore the findings of this study, such as the high incidence of T1D in family members and the greater risk for progression to ESRD in young females. Research must be supported by the participation of a sufficient number of DDD patients to establish evidence-based practice guidelines for the management of DDD. Therefore, an international collaborative

research survey of DDD patients should be supported. Non-English versions of this survey will encourage broader access and participation. To that end, an Italian translation of this survey has been completed and is available to DDD patients (<http://dddonlus.org>). Similar expansion of data collection to other countries should be encouraged.

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