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Research Article

Future Rare Diseases

Dercum's disease: estimating the prevalence of a rare painful loose connective tissue disease

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Background: In the USA, the Orphan Drug Act of 1983 defines a rare disease as affecting under 200,000 individuals. Dercum's disease (DD) is a loose connective (adipose) tissue disease characterized by painful lipomas. While considered a rare disease, the prevalence of DD has not been systematically assessed previously. The objective of this paper is to estimate the prevalence of DD to determine if it is rare or not. **Results:** Estimates of prevalence of DD using PubMed, the UK Biobank, the US Agency for Health Research and Quality Healthcare Cost and Utilization, physician practices, social media forums and internet searches found the prevalence of DD to be less than 200,000 individuals in the US. These prevalence likely overestimate the disease; however, underestimation may also occur because DD is not well known and may be misdiagnosed. **Conclusion:** DD meets requirements of the Orphan Drug Act to be classified as a rare disease. Further research should focus on representative population samples in the USA to better estimate the prevalence of DD. Estimating the prevalence is an important first step to increase recognition, research efforts and patient care for people living with DD.

Lay abstract: People with Dercum's disease (DD) have painful lipomas in the fat on their bodies. DD is thought to be rare. A rare disease as defined by the Orphan Drug Act of 1983 means that less than 200,000 people have the disease. The authors of this paper tried to determine whether DD was truly a rare disease or not. They searched published scientific papers, a database from the UK, the US Agency for Health Research and Quality Healthcare Cost and Utilization, questioned physicians, searched social media forums, performed internet searches and made estimates at how many people are affected with DD. The authors determined that DD affects less than 200,000 people in the USA and is therefore a rare disease.

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Keywords: adipofascia • adiposis dolorosa • angiolipomas • angiolipomatosis • Dercum's disease • fatty tissue • lipomas • morbus Dercum • painful fat • painful growth • rare diseases • rare fat disorder

Background

Dercum's disease (DD) also known as adiposis dolorosa or morbus dercum is a rare loose connective (adipose) tissue disorder that is characterized by painful lipomas (fatty masses) or angiolipomas [1]. Pain in skin and adipose tissue is one of the key characteristics of DD. Despite pain in tissues such as muscle, bone or tendon being accepted by healthcare providers as valid, pain in fat tissue is less accepted or understood, although increased fat mass is known to contribute to multi-site pain [2].

DD can be confused with other loose connective tissue diseases such as lipedema, a painful but common disorder affecting the limbs of women [3], or multiple symmetric lipomatosis, a painful disorder usually affecting upper body tissue [4]. DD is also commonly misdiagnosed as obesity [5] or fibromyalgia [6]. Painful lipomas in DD can occur in any part of the body; the most common locations affected are legs, chest, abdomen, pelvis, lower back, arms and buttocks; the painful fat occurs less commonly on the head, hands and feet [7]. Painful lipomas in DD vary in

Table 1. Proposed subtypes of Dercum's disease.

Hansson		Herbst		Herbst revised	Ref.
Subtype	Description	Subtype	Description	Subtype	[1,2,11]
I	Generalized diffuse	I	Juxta-articular	Angiolipoma	
II	Generalized nodular	II	Diffuse generalized	FML	
III	Localized nodular	III	Larger lipomas on the trunk and limbs	Healing disorder	
IV	Juxta-articular			Lipedema	
				Obesity	
				Trauma	

FML: Familial multiple lipomatosis.

size from pea-sized to the size of a fist or larger. Smaller lipomas may be difficult to palpate, and therefore, the fat tissue, rather than lipomas, may be considered painful; hyperalgesia may also be present [8]. Another unique feature of DD is the lipomas are reported to have the ability to "*appear overnight or morph in shape in real time*" [9]. An individual can develop DD at any time in life, but it is reported to begin on average more often in women by the third decade of life [7].

There are different types of DD (Table 1) including obesity-associated, lipedema-associated, familial multiple lipomatosis (FML)-type, angiolipoma-type, trauma-induced and healing disorder type [4]. In one case of a woman with FML-type of DD and cystic lesions of the basal ganglia, neurological and neuropsychiatric manifestations were prominent and are thought to be a relevant and probably underestimated component of DD [10]. Neurological and neuropsychiatric problems may dominate in people with DD leading to an underestimation of the prevalence of this disease especially if physicians think lipomas are not painful.

The healing disorder type of DD (Table 1) may be due to sequelae from infections such as Lyme's disease [12]. Older descriptions of DD types refer to the size or locations of the nodules [13–15] without any further insight into the disease such as family history, past history or whether angiolipomas are present or not (Table 1).

The signs and symptoms of DD include "*chronic pain, fatigue, brain fog, insomnia, cardiac arrhythmia most often tachycardia (palpitations), gastrointestinal distress, often irritable bowel syndrome, muscle weakness, tremor or jerking of muscles (myoclonus), joint pains, insulin resistance and diabetes, hypothyroidism and other autoimmune disorders*" [5]. There are also syndromes associated with DD including a family with dysarthria, visual pursuit defect and progressive dystonia associated with cystic lesions in the basal parts of the putamen [10]. Painful lipomas in people with syndromes may go unnoticed if neurological and neuropsychiatric manifestations dominate leading to underdiagnosis of DD [16].

The pathophysiology of DD is unknown. Mast cell activation syndrome (MCAS) is important in the angiolipoma-type of DD [4] but also in other types. The diagnostic criteria for DD recommended by Hansson requires obesity and chronic pain greater than 3 months in fat tissue, although in one study, about 25% of people with DD did not have obesity [7]. Additional criteria state that upon examination, the fatty lipomas in the fat tissue must be palpable [5].

Orphanet, NORD and the NIH [17] recognize DD to be a rare disease, yet prevalence data are clearly missing from the literature. Misdiagnosis could overestimate and underdiagnosis could underestimate actual prevalence rates of DD. This paper is the first to systematically utilize multiple resources to determine the prevalence of DD.

Materials & methods

Methods used to formulate an estimation for the prevalence of DD included: an in-depth literature review conducted on PubMed from inception through January 2020 using the search words: DD, adiposis dolorosa and angiolipoma, that provided two papers for assessing estimates of DD; a search for individuals with the diagnosis of DD in the UK Biobank; use of the US Department for Health Research and Quality Healthcare Cost and Utilization (AHRQ's HCUP) assessment of incidence of disease in medical practice; use of social media forums; questionnaires to physicians who know DD; and estimates from individual physician practices.

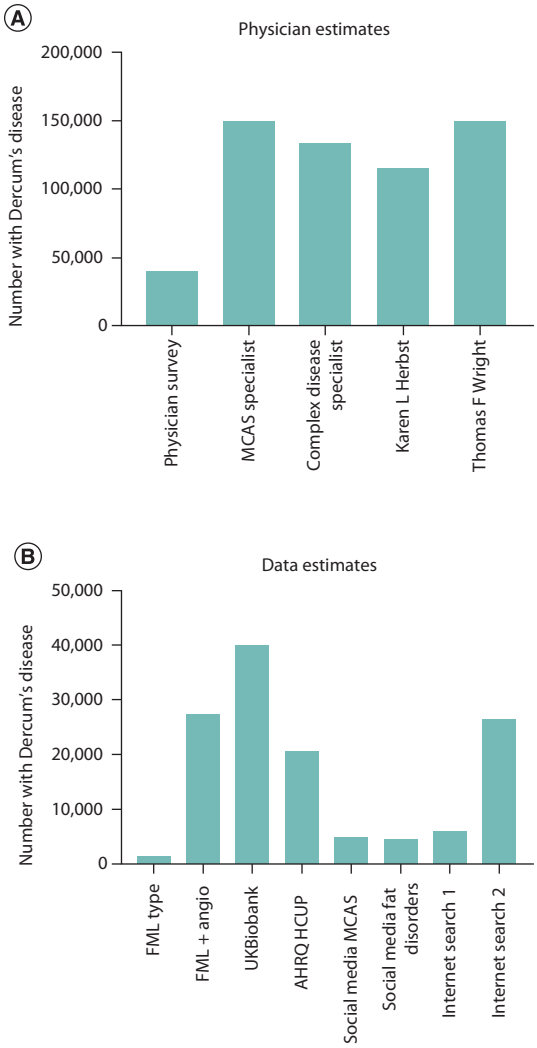

Figure 1. Prevalence estimates of Dercum's disease by different methods. (A) A physician survey was conducted, or physicians provided estimates of the prevalence of DD based on their practice. **(B)** Data from published studies, the UK Biobank, AHRQ HCUP, social media and internet searches. See text for details.
Angio: Angiolipoma; AHRQ HCUP: Agency for Health Research and Quality Healthcare Cost and Utilization; CFS: Chronic fatigue syndrome; DD: Dercum's Disease; FML: Familial multiple lipomatosis; MCAS: Mast cell activation syndrome.

Results

FML-type DD

People with FML have multiple lipomas that are nonpainful. In some families with FML, one or more people can develop painful lipomas consistent with DD [18]. The prevalence of FML is reported as 1/50,000 [11]. Using this estimate of 1/50,000 people having FML in the USA, and 327 M people in the USA (2018 estimate), then 6540 people potentially have FML in the USA. In families of people with FML, about 20% will develop pain and signs and symptoms of DD [18]. Twenty percent of 6540 people with FML is 1308 people in the USA potentially with FML-type DD (Figure 1).

FML-type & angiolipoma-type DD

A population-based study of 743,000 inhabitants in Sweden [19] evaluated nonvisceral lipomas histopathologically from 428 patients during a 1-year period and retrospectively analyzed patient age, duration of symptoms, lipoma size, site (location and depth) and multiplicity of lipomas. 61 people were found to have multiple lipomas or angiolipomas. Assuming all 61 had DD, this represents a prevalence of 61/743,000 = 1/12,000. While this subpopulation was not defined in the article as having DD, it is likely that some may be patients with DD since having multiple lipomas is a significant hallmark of DD. Although Sweden and the USA are different countries, a gross assumption toward the US population can be made. Using 1/12,000 prevalence and a US population of 327 M (US estimate in 2018) results in an estimated prevalence of 27,250 patients with DD.

UK Biobank estimate

The UK Biobank is an international health resource and registered charity with the aim of improving the prevention, diagnosis and treatment of a wide range disorders (UK Biobank, n.d.) [20]. In 2006–2010, 500,000 people between 40 and 69 years of age were recruited from across the UK to take part in this project. They underwent several measures, provided blood, urine and saliva samples for future analyses and detailed information about themselves, and agreed to have their health followed. International Classification of Disease (ICD)-10 codes are available for 410,293 participants. The ICD-10 code for DD is E88.2, for Lipomatosis, Not Elsewhere Classified (NEC). This code includes other rare lipomatous disorders as well. 50 people in the UK Biobank had the ICD-10 code E88.2. Assuming all fifty people had DD of 410,293 people sampled, the prevalence rate in this population is 0.012%, confirming DD is rare in the UK. If we use these data to make a gross assumption for the US population of 327 M people (2018), then 327 M*0.012% = 39,849 people in the USA could have DD.

AHRQ H-CUP database

The HCUP database is maintained by AHRQ [21]. A search was conducted on data from 2007 to 2014 for all emergency department (ED) visits by ICD-9 diagnosis, lipoid metabolic disorder (NEC) 272.8, which includes people with DD. AHRQ maintains a free version of this database with ICD-9 codes from 2006 to 2014. The data after 2014 must be purchased and only from 2016 onward, are ICD-10 codes used.

In 2014, 207 +/-32 (SE) ED visits by patients with lipoid disorder NEC (ICD-9 272.8) were recorded across the USA. Assuming all patients visiting the ED who were classified with ICD-9 code 272.8 were patients with DD, and assuming that for each patient with DD who had pain sufficiently serious to visit the ED, there were 100 who did not, the total prevalence of DD for 2014 would be 207*100 = 20,700 cases. This methodology contains errors that grossly overestimate the prevalence of DD because of the assumptions that: all ED visits falling under this diagnostic code were assumed to be for patients with DD; and assuming people with DD visiting the ED are 1/100 of the population of people with DD.

MCAS Forums

In MCAS patient forums, a group enriched for patients with DD, there are typically 6000–12,000 patients per site. With an estimated 50,000 diagnosed MCAS patients in the USA, this represents a 24–48% forum participation. An assumption can be made that there is a comparable percentage participation among patients with DD, as many patients with DD have MCAS [4]. There are four forums for people with DD on the internet, with participation numbers of 379, 391, 211 and 1427 totaling 2408. Assuming no redundancy for individuals participating in more than one site (thus systematically over-estimating the numbers) and assuming 24% participation (similar to MCAS forums), extrapolating to a rate of 100% participation results in 10,033 total patients with DD; if a 50% participation rate, then the prevalence of DD would be 4816. If assuming only 10% participation, then the prevalence of DD would be 48,160 (Figure 1).

Prevalence of DD from specialists whose practices focus on the diagnosis & treatment of loose connective (adipose) tissue disease

A survey about the prevalence of patients with DD in a practice was requested from physicians who attended the Fat Disorder Resource Society (fatdisorders.org) Annual Congress in 2017, 2018 and 2019. These physicians have focused part of their practice on diagnosis and treatment of Madelung's disease, DD and lipedema. The survey respondents represent University based medical referral practices as well as private practices across the USA. The average number of patients per physician with DD was four (authors were not included or surveyed). While it is logical that individuals diagnosed with or suspected to have DD or a related loose connective tissue disease would either self-refer or be referred to physicians who specializes in the diagnosis and treatment of DD, it is quite possible that only a fraction of such individuals are either self-referred or referred by their primary medical providers. If only a small percentage of individuals with DD, 1/100 or 1/1000, are referred, then one would predict the prevalence of DD to be at an upper limit, four (patients per physician)*10 physicians*1000 = 40,000 (Figure 1).

Social media loose connective (adipose) tissue forum participation rates

In patient forums with a focus on loose connective (adipose) tissue diseases, a group significantly enriched for patients with DD, there are typically 2–3 K patients (on two forums). Of these patients, there are 44 patients who report being diagnosed with DD. These individuals could be duplicated within support forums and may also be

on other support forums. Most rare diseases have social media support group participation in the 20 to 50% range. However, assuming participation at the very lowest rates of 1/100–1/1000, the total prevalence would be for a lower limit, 44*100 = 440, and for an upper limit, 44*1000 = 4440 (Figure 1).

Internet searches for DD (Google AdWords Research)

Digital data collected for nonepidemiological purposes are being used to study health phenomena in a variety of topic domains [22]. Digital epidemiology requires access to large datasets and advanced analytics such as Google search analytics which we used in this paper [23]. In 2013, the Pew Research Center conducted an Internet and American Life Project. They found that 35% of US adults search for information on medical conditions they or someone they know might have [24]. A significant portion of Google search volume represents individuals, their family or close friends searching for information on new symptoms or information on a new medical diagnosis. Physicians increasingly use internet search to help with diagnosis of diseases, especially with uncommon diseases [25]. Physicians use Google searches to access sites such as Medline, Medscape, Up-to-Date, MD Consult, Ovid and many others to aid in diagnosis of their patients [25,26].

Using leukemias as reference diseases, monthly search volume for a disease on Google in the USA was as follows: acute myeloid leukemia (AML) – 27,100 Searches; leukemia —368,000 Searches (all types). In comparison, there were 5400 searches for DD. The search volume for DD is 0.0146 or 1.46% of that of all leukemia searches. The search volume for DD is 0.199 or 19.9% of AML searches. According to the National Cancer Institute [27], it is estimated that there were 414,773 people living with all kinds of leukemia in the USA in 2016. Based on these data, the prevalence of all types of leukemia and the relative percentage of internet searches of 1.46%, the estimated prevalence of people with DD is 6055 individuals in the USA (Internet Search 1, Figure 1).

About 21,450 new cases of AML are diagnosed each year. Most will be in adults, according to the American Cancer Society. AML makes up 32% of all leukemia cases with a prevalence of 132,727 individuals in the US population. Based on the diagnosis and the relative percentage of internet searches of the diagnosis of DD to AML of 19.9%, then 26,412 individuals in the USA would have DD (Internet Search 2, Figure 1).

Physician practices

Karen L Herbst

Approximately 2500 people per year with loose connective (adipose) tissue disease were seen, mostly patients with lipedema, six patients with FML-Type DD and 10 patients with angiolipoma-type DD. The prevalence of DD is 0.64% in this population. The prevalence of lipedema in the USA is thought to be 11% in women though the range is 5 to 39% [4]. A majority of people with DD are women [7,8]. Assuming a US population of 327 M (2018) of which 50% are women, results in total US lipedema prevalence of about 18 M. If we apply the prevalence rate of 0.64%, we obtain an estimated number of 115,000 patients with DD (0.64%*18 M).

MCAS specialty practice

A physician specializing in MCAS – a condition associated with DD – has a patient mix that is 'enriched' for a higher prevalence of DD than in many other practices. This physician has a direct total case experience of 3000 patients over 10 years and another few thousand indirect case experience recalls with only about ten patients in total with DD, an incidence of at most, about 0.3%. This physician estimates 50,000 diagnosed cases MCAS cases in the USA, with a prevalence rate that may be up to 50 M in the US population. An upper limit prevalence of DD would be 0.3%*50 M = 150,000 cases, and a lower limit of 0.3%*50 K = 150 cases.

Complex disease specialty practice

A physician specialist with expertise in chronic fatigue syndrome and other complex chronic diseases reports two cases of DD in a case experience of 1500 patients over 5 years, an upper limit, as this practice is enriched with complex cases. If one assumes that there are 133 M people in the USA with a chronic illness (nationalhealthcouncil.org), 0.1%*133 M = 133,000 people with DD in the USA.

B Robert Mozayeni

In 27+ years of medical practice, three patients with DD were actively managed. Two other suspected cases over the past 2 years have been seen (co-managed by KL Herbst), therefore a total of four unique patients with DD in 3000 patients over 10 years for a prevalence rate of 0.13%.

Survey of physicians who specialize in loose connective tissue disease

Most of TF Wright's practice is focused on treating loose connective (adipose) tissue diseases for the past decade. In the past decade about 30 patients with DD have been seen. Practice referrals come from throughout the USA for loose connective (adipose) tissue disease such as lipedema, DD and Madelung's Disease. Currently, there are 20 patients with DD of all subtypes. Several of the patients are co-managed with KL Herbst. As a conservative estimate, there are at most ten physicians in the USA who focus on the diagnosis and treatment of loose connective (adipose) tissue diseases; the most liberal estimate would be 100 physicians. If 10 to 100 physicians have 10–50-times as many DD patients as similarly focused medical practices, the largest estimate of prevalence of individuals with DD based on those who are seeking treatment from physicians who specialize in the treatment of loose connective (adipose) tissue disease would be 20 patients*50*100 physicians = 150,000 individuals with DD.

Discussion

DD is considered a rare disease by the NIH, Orphanet and NORD, but there are few publications in support of this designation. The methods utilized in this paper favor data gathered in the USA, but data from the UK and Sweden, as well as online forums and Google searches were also used, therefore the estimates of prevalence in this paper can be considered useful for both the USA and parts of Europe.

The requirement for data to support a determination of low prevalence or rarity presents a paradox. If the condition is rare, how will it be proven with data that is scarce to prove that it is rare? Rather, the proof, for now, must be made by inference. The methodology presented herein is such an approach. Our methods provide an upper limit estimate of the prevalence of this rare disorder of 150,000. According to Auvin, such an incidence-based approach to prevalence estimation yields an estimate that should be adjusted downward because 'methodological challenges in counting small populations, coupled with advances in rare disease discovery, may cause discrepancies' [28]. According to Auvin, incidence-derived prevalence estimation should be reduced by 17%. Our estimations, however computed, are likely to be OVER-estimating the prevalence by 17%. Other methods in this paper support the prevalence is much lower than 150,000, which is less than 200,000 required to be considered as a rare disease. One can, with assurance, reasonably assume that the rarity of DD qualifies it to meet the important central criterion of less than 200,000 affected.

While there are different subtypes of DD, there is only one paper that estimates the prevalence of the angiolipoma-type DD; there are no data to estimate the prevalence of other subtypes. Hansson *et al.* [8] and Herbst [5] described subtypes of DD based on size and location of lipomas (Table 1). More recently, Herbst revised the subtypes referencing medical history, family history and type of lipoma (Table 1) [4]. Providing a subtype for people with DD may be important for assessing the therapeutic index of a drug during a proposed study but is not helpful in assessing prevalence or rarity of DD. If the subtypes were different with respect to a pain measure, a subtype classification may have been helpful. However, the fact that DD is often not known by providers, misdiagnosis of DD may be high especially when DD is part of a syndrome [16,29]. Accessibility to information on a rare disease is the most critical factor influencing a patient's chances of being misdiagnosed [30]. Misdiagnosis may add to an underestimate of prevalence of DD especially in large currently available databases. Future estimates of prevalence of DD will be improved by finding a causative gene or pathway that can be targeted for treatment, improved education about the disease and greater awareness of subtypes of DD. Healthcare providers need to be alerted to publications that address different types of DD [4]. In the future, better data may be available when Medicare releases searchable diagnostic code inventories.

In addition to social advocacy groups that are available for people with DD, they need clinicians and scientists within the medical community to champion their cause. These clinicians and/or scientists should be familiar with the diagnosis of DD available in publications [4,5] and with subtype descriptions in this paper (Table 1). We hope this paper brings awareness to DD, including the ICD-10 code E88.2, to increase knowledge in communities around the globe.

A questionnaire including 110 patients with DD disclosed common symptoms; these included pain, fatty deposits unaffected by weight loss, easy bruisability, sleep disturbances, impaired memory, depression, difficulty concentration, anxiety, rapid heartbeat, shortness of breath, diabetes, bloating, constipation, fatigue, weakness, joint aches and muscle aches [7]. It cannot be assumed that a patient with DD will have a given number or specifically any one of these associated symptoms. The association of these other symptoms suggest a systemic illness with local or focal manifestation in a painful fat compartment.

Study limitations

This study was limited primarily by the dearth of papers in the literature on the prevalence of DD. The restricted data required assumptions to be made, which are by definition, limitations. These limitations led to a likely overestimation of the prevalence of DD.

Conclusion

In summary, no matter the source or what method is applied, the maximum number for the prevalence of DD is estimated to be less than 200,000. These data meet the requirements of the Orphan Drug Act, which requires 200,000 individuals or less to be affected by a disorder for it to be classified as rare. These conclusions may apply to Europe as supporting data was utilized from Sweden, the UK, online forums and Google. Further research must be conducted to better understand subtypes of this rare disorder.

Summary points

- People with Dercum's disease (DD) have painful lipomas in subcutaneous adipose (loose connective) tissue.
- DD is considered to be a rare disease.
- There are limited data available to support this assumption.
- This paper demonstrates by a search of the literature, databases, physician questionnaires and social media that DD meets the criteria for a rare disease.
- Confirming that DD is a rare disease opens up the possibility for development of medications and devices to improve the health of people with this disease.

Author contributions

N Munguia, KL Herbst, TF Wright and BR Mozayeni contributed to writing and modifying the manuscript. All have accepted the final manuscript for publication.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Data sharing statement

All data is referenced or listed; there is no additional repository of data or materials.

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