Desmopressin Dose Requirements in Adults with Congenital and Acquired Central Diabetes Insipidus

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ABSTRACT

Central diabetes insipidus is a rare disorder characterized by a deficiency of vasopressin. The first line drug to treat this disorder is a synthetic analogue of vasopressin, desmopressin.The primary aim of this retrospective register study was to compare desmopressin dose requirements in patients with acquired and congenital DI, and secondly to assess the influence of BMI on dose requirement and risk of hyponatremia with different drug administrations. We included all patients with suspected DI attending the endocrine department at Rigshospitalet, Copenhagen, Denmark in 2022. We identified 222 patients who were included whereof 130/222 (58.6 %) were females and median age was 53 years (IQR 35 to 63). The etiology included 7/222 (3.2 %) congenital and 215/222 (96.8 %) acquired. After converting nasal and sublingual doses to equivalent oral doses, the median daily dose requirement was 600 µg in patients with congenital etiology compared to 200 µg in patients with acquired etiology (p = 0.005). We found no association between BMI and desmopressin dose requirements (p = 0.6). During the past 12 months, 66/215 (30.7 %) had sodium levels < 136 mmol/l including 20/215 (9.3 %) with sodium levels < 131 mmol/l. No increased risk of hyponatremia was found, when nasal and oral were compared (p = 0.9). Daily desmopressin dose requirements were higher in patients with congenital DI compared to patients with acquired DI. However, this result was associated with uncertainty due to the small congenital group. BMI did not influence daily dose requirements and nor did type of administration influence the risk of hyponatremia.

Introduction

Central diabetes insipidus (cDI) is a rare disorder characterized by hypotonic polyuria due to a deficiency in the secretion of antidiuretic hormone from the pituitary gland. The various etiologies of DI include congenital and acquired causes [1, 2]. Most cases of cDI are acquired and may be due to neoplasm, infection, head trauma, hypophysitis, or surgery affecting the pituitary gland with the majority being due to neurosurgery, which may lead to both partial cDI and complete cDI [3, 4].

The congenital etiologies include genetic etiologies, which are characterized by a deficiency in the secretion of the antidiuretic hormone due to pathogenic variants in the arginine vasopressin (AVP) gene, with at least 83 known variants [3]. There are at least five different forms of hereditary cDI. The most common is inherited in an autosomal dominant mode, caused by the mutant precursor to misfold, accumulate and in the end destroy the magnocellular neurons, which later leads to inhibited expression of the normal allele. At the beginning of this form of DI, the deficiency of AVP is partial and the symptoms typically begin to appear from the age of 6 months to 6 years and usually progress to a severe if not complete lack of AVP [5].

The diagnosis of DI is based on a water deprivation test and once the patient has been diagnosed with DI, they should be treated with a vasopressin analogue – desmopressin [6]. Desmopressin can be administered in oral, sublingual, and intranasal forms. Bioavailability and onset of action are higher and faster for the intranasal form compared to the oral administration, though the effectiveness of the intranasal administration may be reduced if there is nasal mucosa inflammation [5]. An earlier study found that children with a higher body mass index (BMI) needed higher doses of desmopressin [1]. In addition, associations between dose, age, and weight have previously been reported [7]. Hyponatremia is the major complication when treated with desmopressin [6] and earlier studies have found a higher risk of hyponatremia in patients using intranasal administration compared to oral administration [8, 9]. Hence, treatment with vasopressin analogues often requires close monitoring to ensure the most optimal desmopressin dose in order to obtain the best effect and no or little side effects [8]. Chronic hyponatremia affects the ability to walk and increases the risk of falls, fractures, seizures, and mortality [10, 11] emphasizing the need for careful monitoring of sodium levels in patients with DI.

The main objective of this study was to compare the desmopressin dose requirements in DI patients with a congenital etiology with patients having acquired DI. The second objective was to assess the association between BMI and desmopressin dose requirements and the risk of hyponatremia in patients using different modes of desmopressin administration.

Hypothesis

We hypothesized that patients with congenital DI have higher daily dose requirements of desmopressin compared with patients having acquired DI. Also, that the daily desmopressin dose requirement was positively associated with BMI, and that patients treated with intranasal desmopressin would have lower sodium levels compared to patients receiving oral desmopressin.

Patients and Methods

Study design

This study was a retrospective study including all patients with cDI and treated with desmopressin attending Department of Medical Endocrinology and Metabolism at Rigshospitalet, Copenhagen, Denmark during 2022. Diagnosis was based on clinical assessment or by water deprivation test. Patients with nephrogenic DI or gestational DI were excluded. Patient files were retrospectively assessed, and the following data were registered: sex, current age, disease duration, weight (kg), BMI, etiology of DI, desmopressin doses (µg), desmopressin administration, adjusted dose at last consultation, concurrent pituitary deficiencies, the lowest Na-concentration measured in the past 12 months (mmol/l) and hospitalizations due to hyponatremia within the last two years. In Denmark, a sodium concentration lower than 136 mmol/l is used as the threshold value for hyponatremia. Regarding controls of sodium concentration, there is no specific test interval, while our Danish guidelines suggest every 6–12 months in patients with DI who are in stable treatment.

Primary outcome

The etiology of DI was classified as either congenital or acquired. Congenital etiologies included genetic mutations and structural brain abnormalities [1]. Acquired etiologies included pituitary tumors, craniopharyngioma, other CNS tumors, idiopathic etiologies, and hypophysitis [12]. Hypophysitis included primary and secondary hypophysitis (Langerhans cell histiocytosis, sarcoidosis, and Wegener's granulomatosis) [13]. Daily desmopressin doses between the different etiologies and patient characteristics were compared.

For calculation of the daily dose requirements, we converted the nasal and sublingual doses to the equivalent oral doses. Previous studies have found a bioavailability of 10–20 times higher with the nasal administration than with the oral form [5, 9, 14–16]. Based on previous practice, we decided to multiply the dose with 20 when converting nasal dose to oral dose, and multiply with 1.67 when converting sublingual dose to oral dose [3, 7]. The "desmopressin dose requirement" was calculated as the sum of all desmopressin taken during one day after converting it to the equivalent oral doses.

Secondary outcomes

The association between BMI and daily dose requirements of desmopressin were assessed by linear regression with desmopressin dose requirement as the dependent variable and BMI as the independent variable. The association between type of medication, that is, intranasal versus oral tablets, and risk of hyponatremia was conducted by comparing the number of patients who had experienced hyponatremia at least once in the past 12 months. Mild hyponatremia was defined as a sodium concentration < 136 mmol/l, and moderate hyponatremia was defined as a sodium concentration < 131 mmol/l as in an earlier study by Garrahy et al. (2019) [10].

Post-hoc analysis

In addition to the pre-planned analysis, the association between desmopressin dose and patient characteristics were assessed by comparing daily desmopressin dose requirement and sex, current age, years with diagnosis, weight (kg), other pituitary deficiencies, adjusted dose at last consultation, and concurrent pituitary deficiencies. Moreover, daily desmopressin doses between patients with DI due to pituitary tumors and craniopharyngiomas were compared.

Statistics

All continuous variables were reported in median (Mdn) and interquartile range (IQR) as the 25th and 75th percentile while categorical variables were reported in percentages. Continuous variables were compared using Mann–Whitney U non-parametric test whereas categorical variables were compared using the χ^2-test. When testing for associations between daily dose requirement and patient characteristics we used linear regression. A p-value ≤ 0.05 was considered statistically significant, and for inclusion in the multivariate analysis, we included all variables with univariate association of $p < 0.2$ in order to avoid overfitting of the final model. In case of a strong correlation between independent variables, for example, weight and BMI, the variable with the strongest association assessed by the standardized beta value was included in the multi-

▶ **Table 1** Patient characteristics.

Characteristics	Total (n = 222)
Female, n (%)	130/222 (58.6)
Age, median (IQR)	53 (35 to 63)
Disease duration, median (IQR)	11 (5 to 19)
BMI, median (IQR)	27.5 (24.4 to 32.0)
DI confirmed with water deprivation test, n (%)	23 (10.4)
Etiologies, n (%)	
▪ Pituitary tumors	84 (37.8)
▪ Craniopharyngioma	57 (25.7)
▪ Other CNS tumors	21 (9.5)
▪ Hypophysitis	19 (8.6)
▪ Congenital	7 (3.2)
▪ Idiopathic	10 (4.5)
▪ Other	24 (10.8)
Form of desmopressin administration, n (%)	
▪ Oral	134 (60.4)
▪ Intranasal	41 (18.5)
▪ Sublingual	32 (14.4)
▪ More than one form of administration	15 (6.8)
Daily desmopressin dose (microgram/Day)	
▪ Daily desmopressin dose, median (IQR)	200 (100 to 400)
▪ Oral tablets, median (IQR)	200 (100 to 300)
▪ Nasal spray, median (IQR)	20 (10 to 30)
▪ Sublingual melt tablets, median (IQR)	135 (75 to 240)
Experiencing hyponatremia in the past 12 months	
▪ All cases with sodium level < 136 mmol/l, n (%)	66/215 (30.7)
▪ Severe hyponatremia, n (%)	20/215 (9.3)
Other pituitary hormone deficiencies, n (%)	198 (89.2)
▪ Thyroid deficiency	194 (87.4)
▪ Adrenal insufficiency	157 (70.7)
▪ Gonadotropin deficiency	148 (66.7)
▪ Growth hormone deficiency	134 (60.4)
Time of day when desmopressin is taken, n (%)	
▪ Morning	155/213 (72.8)
▪ Noon	83/213 (39.0)
▪ Evening	112/213 (52.6)
▪ Night	115/213 (54.0)

variate analysis. Data were analyzed using the statistical software SPSS, version 28.0 (IBM Corp).

Results

Patient characteristics

A total of 225 patients with suspected DI were identified and three patients were excluded due to either gestational DI or because DI was no longer suspected, thus 222 patients were included in the current study. The majority of patients were female 130/222 (58.6 %) with a median age of 53 (IQR: 35 to 63) years and a median disease duration with DI of 11 (IQR: 5 to 19) years. The different etiologies included patients with acquired etiologies (n = 215/222; 96.8 %) and congenital etiologies (n = 7/222; 3.2 %), of which five were genetic and two were structural brain abnormalities. The most common acquired causes were pituitary tumors (n = 84/222; 37.8 %), craniopharyngioma (n = 57/222; 25.7 %), other CNS-tumors (n = 21/222; 9.5 %), and hypophysitis (n = 19/222; 8.7 %). Diabetes insipidus were confirmed with a water deprivation test in 23/222 (10.4 %). The patients were treated with different forms of administration; 134/222 (60.4 %) received oral tablets, 41/222 (18.5 %) nasal spray and 32/222 (14.1 %) sublingual melt tablets. The remaining 15/222 (6.8 %) were treated with a combination of at least two forms of administration. The patient characteristics are summarized in ▶ **Table 1**.

Desmopressin dose in congenital versus acquired DI

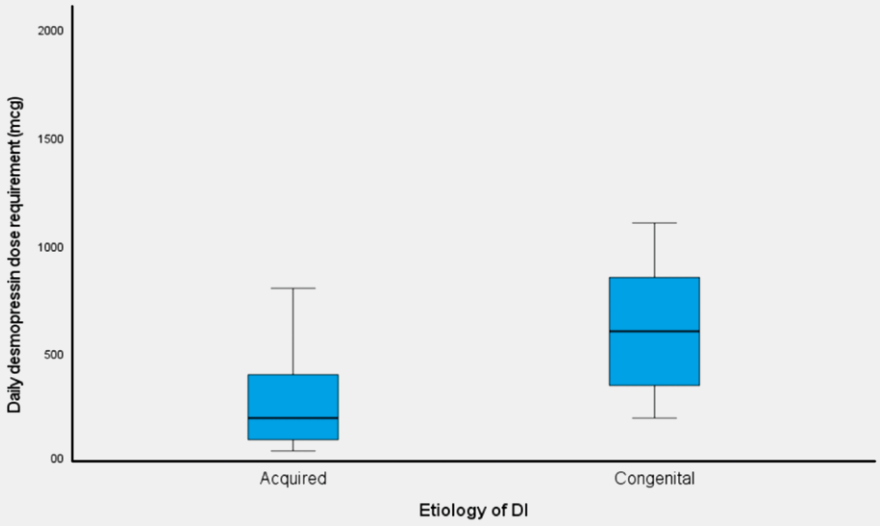
The median daily dose requirement in the acquired group was 200 mcg (IQR 100 to 400) versus 600 µg (IQR 200 to 900) in patients with congenital DI (p = 0.005), as illustrated in ▶ **Fig. 1**. Patients with acquired DI were older (p = 0.0005), had shorter disease duration (p = 0.04), and were more likely to have other pituitary deficiencies (n = 196/215; 91.2 %) compared to patients with congenital DI (n = 2/7; 28.6 %), (p = 0.0005). Patients with acquired DI were more likely to use oral administration (p = 0.0005) while patients with congenital DI were more likely to use sublingual (p = 0.03) or more than one type of administration (p = 0.02), as shown in ▶ **Table 2**.

Desmopressin dose and BMI

There was no association between BMI and desmopressin dose requirement (p = 0.6) when assessing the whole population. However, as shown in ▶ **Table 3**, body weight was positively associated with dose requirements in multivariate analysis (p = 0.048). Post-hoc analysis restricted to patients who used oral desmopressin supported the finding of a positive association between dose and weight (p = 0.003), while this was not confirmed in patients using nasal spray or sublingual melt tablets (all p-values > 0.5). As shown in ▶ **Table 4**, the association between weight and oral desmopressin was further explored in a multivariate analysis finding a borderline significant association between BMI and oral dose requirement (p = 0.05) and a stronger association between weight and oral dose requirement of desmopressin.

Administration form and risk of hyponatremia

During the last two years 5/222 (3.7 %) patients were hospitalized due to hyponatremia, all of whom received desmopressin as oral tablets. During the last 12 months, 66/215 (30.7 %) had sodium levels 136 mmol/l including 20/215 (9.3 %) with severe hyponatremia. Sodium levels < 136 mmol/l occurred in 38/131 (29 %) of patients using oral tablets compared to 12/40 (30 %) inpatients using nasal spray (p = 0.9), as shown in ▶ **Table 5**. Nor was there any difference between the proportion of patients with severe hyponatremia (Na < 131 mmol/L) in patients using oral tablets n = 12/131 (9.2 %) compared to patients using nasal spray n = 4/40 (10 %) (p = 0.9). Among the group treated with sublingual melt tablets



▶ **Fig. 1** Daily desmopressin dose requirements in patients with acquired (n = 215) or congenital (n = 7) diabetes insipidus (DI) (p = 0.005).

▶ **Table 2** Comparison of characteristics of acquired and congenital DI.

	Acquired	Congenital	p-Value
n	215	7	
Female (%)	125 (58.1)	5 (71.4)	0.5
Age, median (IQR)	54 (36 to 63)	27 (24 to 34)	0.0005
Disease duration, median (IQR)	11 (5 to 18)	20 (16 to 25)	0.04
BMI, median (IQR)	27.5 (25 to 32)	26.6 (20 to 37)	0.6
Weight, median (IQR)	85 (73 to 97)	79 (58 to 112)	0.6
Daily dose requirement (µg), median (IQR)	200 (100 to 400)	600 (200 to 900)	0.005
Na-concentration, median (IQR)	138 (135 to 139)	136 (132 to 137)	0.3
Hyponatremia, < 136 mmol/l, n (%)	20/211 (9.5)	2/4 (50)	0.4
Severe hyponatremia, < 131 n (%)	64/211 (30.3)	0 (0)	0.5
Adjusted dose at last consultation, n (%)	14 (6.5)	0 (0)	0.5
Other pituitary deficiencies, n (%)	196 (91.2)	2 (28.6)	0.0005
Thyroid deficiency, n (%)	192 (89.3)	2 (28.6)	0.0005
Gonadotropin deficiency, n (%)	146 (67.9)	2 (28.6)	0.03
Adrenal insufficiency, n (%)	155 (72.1)	2 (28.6)	0.01
Growth hormone deficiency, n (%)	132 (61.4)	2 (28.6)	0.08
Oral administration, n (%)	134 (62.3)	0 (0)	0.0005
Nasal administration, n (%)	39 (18.1)	2 (28.6)	0.5
Sublingual administration, n (%)	29 (13.5)	3 (42.9)	0.03
More than one form of administration, n (%)	13 (6.0)	2 (28.6)	0.02

The “Daily dose requirement” was calculated as the sum of all desmopressin taken during 24 hours after converting it to the equivalent oral doses. Na-concentration denotes the lowest sodium level measured in the past 12 months.

▶ **Table 3** The association between daily desmopressin dose and patient characteristics in linear regression analysis.

Independent variable	B-value (CI)	p-Value	Multivariate	p-Value
Female	−47.1 (−111.2 to 17.1)	0.15	−49.1 (−114.0 to 15.8)	0.1
Age	−2.6 (−4.3 to −0.9)	0.003	−3.0 (−4.7 to −1.3)	0.0005
Disease duration	6.4 (4.1 to 8.7)	0.0005	6.9 (4.6 to 9.2)	0.0005
Age at the diagnosis	−4.4 (−5.8 to −3.0)	0.0005		
BMI	2.0 (CI: −3.1 to 7.0)	0.6		
Weight (kg)	1.3 (0.0 to 2.5)	0.048	1.7 (0.2 to 3.3)	0.03
Na-concentration (mmol/l)	−3.0 (−10.1 to 4.1)	0.4		
Adrenal deficiency	−65.9 (−135.1 to 3.3)	0.06	−33.8 (−111.7 to 44.2)	0.4
Thyroid deficiency	−99.3 (−194.0 to −4.6)	0.04	−68.6 (−177.8 to 40.5)	0.2
Gonad-axis replacement	−9.0 (−76.3 to 58.3)	0.8		
Growth hormone deficiency	18.2 (−46.6 to 83.1)	0.6		

A multivariate model including age at diagnosis rather than years living with DI produced similar results.

▶ **Table 4** The association between patient characteristics and dose requirements using linear regression model in patients treated with oral tablets (n = 134).

Independent variable	B-value (CI)	p-Value	Multivariate	p-Value
Female	−39.5 (−104.1 to 25.0)	0.2		
Age	−1.9 (−3.8 to −0.1)	0.04	−2.3 (−4.1 to −0.6)	0.01
Disease duration	5.1 (2.7 to 7.4)	0.0005	5.8 (3.4 to 8.1)	0.0005
Age at the diagnosis	−3.8 (−5.4 to −2.2)	0.0005		
BMI	5.1 (−0.0 to 10.3)	0.05		
Weight (kg)	2.4 (0.8 to 4.0)	0.003	2.5 (1.1 to 4.0)	0.0005
Na-concentration (mmol/l)	3.8 (−3.1 to 10.6)	0.3		
Adrenal deficiency	18.5 (−53.7 to 90.8)	0.6		
Thyroid deficiency	−50.8 (−171.3 to 69.7)	0.4		
Gonad-axis replacement	39.0 (−29.1 to 107.1)	0.3		
Growth hormone deficiency	87.6 (24.8 to 150.3)	0.007	57.5 (−2.5 to 117.6)	0.06

The dependent variable is oral desmopressin dose (µg/day); Na-concentration denotes the lowest sodium level measured in the past 12 months; Including 'BMI' rather than 'Weight' did not markedly change the multivariate analysis.

11/32 (22.4 %) patients experienced sodium levels < 136 mmol/l, which was no different from either oral tablets (p = 0.5) or nasal spray (p = 0.6). Severe hyponatremia was experienced in 2/32 (6.5 %) patients treated with sublingual tablets, which did not defer from oral tablets (p = 0.6) or nasal spray (p = 0.6), as shown in **Supplementary Table 4 S** and **Supplementary Table 5 S**.

Clinical characteristics and dose requirements

As shown in ▶ **Table 3**, assessment of clinical characteristics and daily desmopressin dose requirement suggested that short duration of disease and older age were associated with lower daily dose requirements. Patients with craniopharyngioma were treated with higher doses (Mdn = 300 µg; IQR: 125 to 400) compared to patients with pituitary tumors (Mdn = 200 µg; IQR: 100 to 250; p = 0.0005), as illustrated in **Supplementary Fig. 1S**. The patient characteristics of pituitary tumors and craniopharyngioma are summarized in **Supplementary Table 1S**. The inverse association between duration of disease, age and daily dose requirement were maintained after excluding patients with congenital etiology, and when restricting the analysis to patients receiving only oral desmopressin. This was also the case for the dose comparison of craniopharyngioma versus pituitary tumors. Patients with onset of DI at the age ≤ 21 years (n = 66) had significantly higher daily desmopressin dose requirements 350 (200 to 600) than those with onset age > 21 (n = 156) who required 200 µg (100 to 300) (p = 0.0005). The were more patients with pituitary tumors in the group who had an onset

▶ **Table 5** Characteristics of patients treated with oral tablets and nasal spray.

	Oral tablets	Nasal spray	p-Value
n	134	41	
Female, n (%)	81 (60.4)	23 (56.1)	0.6
Age, median (IQR)	57 (42 to 67)	45 (30 to 55)	0.0001
Disease duration, median (IQR)	8 (4 to 16)	16 (12 to 27)	0.0001
BMI, median (IQR)	28 (25 to 32)	27 (25 to 31)	0.4
Weight, median (IQR)	85 (74 to 97)	85 (67 to 101)	0.7
Na-concentration, median (IQR)	138 (135 to 140)	138 (135 to 140)	0.8
Hyponatremia, < 136, n (%)	38/131 (29.0)	12/40 (30.0)	0.9
Severe hyponatremia, < 131 n (%)	12/131 (9.2)	4/40 (10.0)	0.9
Hospitalizations due to hyponatremia, n (%)	5 (3.7)	0 (0)	0.2
Adjusted dose at last consultation, n (%)	9 (6.7)	2 (4.9)	0.7
Thyroid deficiency, n (%)	124 (92.5)	35 (85.4)	0.2
Gonadotropin deficiency, n (%)	92 (68.7)	28 (68.3)	0.97
Adrenal insufficiency, n (%)	99 (73.9)	29 (70.7)	0.7
Growth hormone deficiency, n (%)	79 (59)	30 (73.2)	0.1
Desmopressin morning, n (%)	90/127 (70.9)	29 (70.7)	0.99
Desmopressin noon, n (%)	45/127 (35.4)	15 (36.6)	0.9
Desmopressin evening, n (%)	61/127 (48.0)	25 (61)	0.2
Desmopressin night, n (%)	74/127 (58.3)	18 (43.9)	0.1

The "Daily dose requirement" was calculated as the sum of all desmopressin taken during 24-hours after converting it to the equivalent oral doses. Na-concentration denotes the lowest sodium level measured in the past 12 months.

age > 21 n = 74/156 (47.4 %) than the group with earlier onset n = 10/66 (15.2 %), (p = 0.0005) as shown in **Supplementary Table 8S**.

Discussion

We found that the daily desmopressin dose requirements of patients with congenital DI were higher compared to patients with acquired DI. There was no association between BMI and dose requirements, though patients with a higher weight received higher doses. Furthermore, type of administration mode of desmopressin did not affect risk of hyponatremia. Other predictors of high desmopressin dose requirements were craniopharyngioma, long duration of disease and young age at the time of diagnosis.

Desmopressin dose in congenital versus acquired DI

According to our knowledge, only one study by Almutlaq and Eugster (2021) [1] has compared desmopressin dose requirements between congenital and acquired cDI finding that children with acquired cDI were more likely to require larger doses of desmopressin, than children with congenital cDI. The deficiency of AVP is typically partial, to begin with in children who have the most common variant of genetic cDI, and the AVP deficiency usually progresses to a severe if not complete lack of AVP later in life [5]. Thus, patient's age can be a factor of great importance when comparing the dose requirement in patients with congenital and acquired etiologies, which may explain the opposite finding in our study. Another discrepancy between the findings of this study and the findings of Almutlaq and Eugster (2021) [1] was that most of the congenital etiologies were structural brain abnormalities, contrary to this study, where genetic etiologies were more represented. In the current study, we identified several factors associated with variation in desmopression dose requirements: current age was inversely associated with dose requirements, while duration of DI and weight in kg was positively associated with daily desmopressin dose requirements. However, patients with congenital disease were younger compared to patients with acquired disease, and the confounding effect of age does not explain the observed findings. The two groups had similar body weight while patients with congenital disease had lived longer with disease, which may in itself explain the observed differences. The difference in form of administration may be due to the fact that the patients with congenital DI had a need for desmopressin since childhood. Children have difficulty swallowing tablets and might be more likely to be treated with nasal or sublingual administration. These forms of administration may have continued into adulthood and could perhaps explain the difference in form of administration. Due to the small number of individuals with congenital disease we were not able to build a satisfactory regression model for multivariate analysis. When comparing the groups based on DI onset before and after the age of 21, We found that patients who had onset of DI before the age of 21 years had greater daily desmopressin dose requirements than those

who had later age of onset. This could indicate that the dose requirement is influenced not only by the onset during childhood but also if onset occurs later during the teenage years. Furthermore, there were more patients with pituitary tumors in the group with late onset of DI than in the group with earlier onset, which also could explain the difference in daily dose requirements. In the included cohort, our hypothesis regarding higher daily desmopressin dose requirements were confirmed, however, this observation may be due to confounding factors and not the disease etiology itself.

Desmopressin dose and BMI

In contrast to the study by Almutlaq and Eugster (2021) [1], we did not find any association between dose and BMI in the full sample, however restricting our analysis to patients receiveing oral treatment did show a positive association between BMI and daily dose requirements. We did observe a much stronger association between higher dose requirement and higher weight, which is in agreement with other studies of children using oral tablets by Ooi et al. (2013) [7] and Boulgourdjian et al. (1997) [17]. Oral desmopressin must be absorbed in the digestive system before entering the bloodstream, while nasal and sublingual formulations are absorbed directly into the bloodstream through the mucosa [18]. This difference in pharmacokinetics may explain why an association is seen for oral administration and not for nasal and sublingual administration forms.

Administration form and risk of hyponatremia

During the last 12 months, 30.7 % had experienced hyponatremia of which 9.3 % had experienced severe. However, this did not differ between patients having nasal administration compared to oral administration. Nor did we find a difference in risk of hyponatremia when sublingual administration was compared to oral tablets and nasal spray. Contrary to the current finding, other studies have found a lower risk of hyponatremia when using oral compared to nasal administration [7, 12, 19, 20]. Almost 10 % had severe hyponatremia during the past 12 months, which may suggest administration of too high desmopressin doses or that patients sometimes regulate dosing themselves. In comparison a similar study by Behan, Sherlock, Moyles et al. (2015) [21] found a prevalence of mild hyponatremia of 27 % and moderate hyponatremia of 15 %, which is in comparison with the current study.

Desmopressin dose in pituitary tumors versus craniopharyngioma

The patients with craniopharyngioma received higher doses than patients with pituitary tumors. In line with the present findings, Woods and Thompson (2008) [22] and Joshi et al. (2022) [11] have previously reported a higher risk of permanent DI after surgery for craniopharyngioma compared with surgery for pituitary tumors. This is most likely because the suprasellar site of craniopharyngiomas often demands more comprehensive surgery and can involve resection of the pituitary stalk and hypothalamic structures [11, 22, 23]. Postoperative DI is believed to arise from damage to the magnocellular neurons, which are connecting the supraoptic and ventricular nuclei in the hypothalamus with the posterior pituitary via the pituitary stalk [23]. The degree of AVP deficiency could probably be affected by the degree of damage to these structures, which may explain why patients with craniopharyngioma required higher doses than patients with pituitary tumors. Moreover, the patients with craniopharyngioma had a higher percentage of GH deficiencies, a lower age median, and a longer disease duration compared to patients with pituitary tumors, which may contribute or explain the observed findings.

Strengths and limitations

The strengths of this study include the size of the study population considering the rarity of DI. Though this study also has limitations primarily caused by the retrospective design and the lack of confirmatory water deprivation test in the majority of patients.

Another possible source of error is the conversion of nasal and sublingual doses to the equivalent oral doses of desmopressin, though this source is inevitable when comparing different forms of administration, and the calculated dose requirements are associated with some uncertainty. Another important confounder is that some patients do not have intact thirst, which other studies have found a higher risk of hyper- and hyponatremia [21]. There may be an underlying confounder that affects whether certain patient groups are treated with either one or the other form of administration, which increases the risk of selection bias. Ideally, it would be necessary to examine the sodium concentrations in the same patients before and after they switch from one to the other form of administration. Also, data about comorbidities associated with hyponatremia such as chronical heart-, liver- and kidney-diseases were not considered. Finally, it is important to mention that the prescribed doses in the patients' files may not represent the optimal dose for each patient. Taking this into account would require a more qualitative study, which could also investigate the patient's perception of the effect.

Conclusion

This study found that the patients in the congenital group required higher desmopressin doses compared to the patients in the group with acquired DI, a finding limited by the low number of patients with congenital DI. There were no association between BMI and desmopressin dose requirement in the full sample, nor between the risk of hyponatremia and the mode of administration. Nonetheless, the current study suggests that higher body weight, younger age, and a larger number of years living with DI were associated with higher dose requirements in patients treated with oral tablets. Also, patients with craniopharyngioma received higher doses of desmopressin compared to patients with pituitary tumors.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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