THIRST PERCEPTION IN DEHYDRATED SICKLE CELL DISEASE PATIENTS IN STEADY STATE

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Summary: Liberal fluid intake is one of the key management strategies in sickle cell anaemia (SCA) patients in steady state, but less work has been done on the desire of patients to drink water. Using the Visual Analogue Scale we studied thirst perception (TP) in 20 euhydrated SCA patients and 28 control (HbA) subjects, as well as during dehydration in 13 SCA patients and 9 HbA subjects. Serum and urine samples were collected and analyzed for Na, K ions, creatinine concentrations and haematocrit and specific gravity of urine were determined. During euhydration, TP was significantly [$P<0.05$] higher in male SCA patients compared to the HbA subjects. In females, TP in SCA patient was not statistically significant compared with HbA subjects. After 13 hours of dehydration, TP was significantly [$P<0.05$] reduced in female. While dehydration increased TP in HbA subjects, it reduced TP in SCA patients. Fluid intakes after dehydration in SCA patients were not significantly different from the control HbA subjects in both male and female. It can be concluded that female SCA patients do not have normal response to dehydration with regards to TP after a period of dehydration. Since dehydration stimulates the release of vasoactive hormones like vasopressin, this may explain why female patients are less prone to crisis than their male counterparts.

Key words: Thirst Perception, Dehydration, Drinking, Sickle Cell Disease, Anaemia.

Introduction

Thirst is a conscious sensation of a need for water and a desire to drink (Robertson, 1991). Thus the factors recognized as components of thirst include: body water deficit, brain integration of central and peripheral nerve messages relating to the need for water and an urge to drink. The osmotic threshold for the onset of thirst was determined to be about 294mOsm/kgH$_2$0 in healthy humans (Robertson, 1991). This approximates to arginine vasopressin (antidiuretic hormone, ADH) release threshold as being 10mOsm/kgH$_2$0 below that of thirst (McKenna and Thompson, 1998). This analysis suggests that thirst rarely occurs in situations where plasma osmolality lies within the normal physiological range of 281-297 mOsm/kgH$_2$O (O'Neill et. al., 1990). The release of arginine vasopressin due to changes in plasma osmolality has been well documented (Baylis and Robertson, 1980; Robertson and Athar, 1976; Zerbe and Robertson, 1983). The extensive series of experiments in which thirst has been investigated in animals has also been documented (Fitzsimons, 1972). In humans, thirst and ADH are controlled by similar sensitive osmoregulatory mechanisms such that above a certain osmotic threshold (280-288 mOsm/kgH$_2$O), there is a linear relationship between the increase in plasma osmolality and the increase in ADH and thirst (Baylis and Robertson, 1980). Thus both ADH levels and thirst show a very good correlation with serum osmolality (Wazna-Wesly et. al., 1995). Sickle cell disease (SCD) is an autosomal recessive, haemolytic disorder which results from the substitution of a valine residue for glutamic acid at position six (6) in the beta-subunit of haemoglobin molecule (Ingram, 1956). It is prevalent especially among people with ancestry in malaria stricken areas such as Africa, the Mediterranean, India and the Middle East (Kwiatkowski, 2006). Although the molecular nature of the Hb defect underlying SCD is well established (Ingram, 1957; Pauling et al., 1949) details of the pathophysiology are uncertain and treatment remains largely supportive (Serjeant, 2001). Liberal fluid Intake is one of the key management strategies in SCD patients in steady state, but less work has been done on the patients desire to drink water. In this study we therefore examined thirst perception in SCD patients in steady state and during thirteen hours of fluid deprivation.

Materials and method
Subjects:

A total of 20 SCD patients comprising of 11 males and 9 females at the haematology outpatient clinic, University of Benin Teaching Hospital and sickle cell Center, Benin City, who gave their consent were studied following approval from the Ethic Committee of the University of Benin Teaching Hospital, Benin City, Nigeria. Patients with sickle cell trait were excluded because

hypostenuria is also a common abnormality (Gupta *et al*, 1991).

Control subjects:

Sixteen (16) male and twelve (12) female subjects with genotype AA (HbA) who were normotensive (systolic blood pressure, SBP < 140mmHg and diastolic blood pressure, DBP < 90mmHg) and had no diabetes served as control. Both patients and controls were aged between 17 and 38 years. Two groups of studies were carried out. In group A study, the SCD patients and control subjects were in a state of euhydration while in group B study, they were dehydrated for 13hours.

Group A study:

Volunteers arrived at the laboratory on the day of experiment when their sex and age were recorded.

Thirst ratings (the level of perception of thirst):
These were assessed using the visual analogue scale, VAS (Thompson *et al*, 1986). The VAS is a marked but uncalibrated 10cm vertical line with the top and base representing "very thirsty" and "not thirsty" respectively. All the patients and control subjects were educated on how to use the VAS to estimate their level of thirst. They were then asked to mark on the line rating scale in response to the question "**How thirsty are you now?**" The readings obtained in centimeter were recorded as their thirst perception (TP). Anthropometric data such as height, ht (m) and weight, wt (kg) were measured using weighing scale and measuring rule respectively. Body mass index (BMI) was thereafter calculated from the formula, BMI =Wt (kg)/Ht^2 (m^2). Baseline (resting) blood pressures, BP (mmHg) were measured with subjects in the sitting position and after 20 minutes of rest in the laboratory at room temperature. Three basal readings were obtained by indirect auscultatory method using sphygmomanometer and stethoscope on each subject at 3-minutes interval. The mean of these readings were recorded as normal BP. Mean arterial blood pressure (MABP) was calculated from the formula. MABP = pulse pressure / 3 ± DBP where DBP is the diastolic blood pressure and pulse pressure is the difference between the systolic and diastolic blood pressures.

Group B study

A subset of the sample population comprising 5 male and 8 female SCD patients, and control subjects comprising of five (5) males and four (4) females who participated in group A study but voluntarily chose to go on dehydration were enrolled in this study.

Procedure for dehydration:

The day before the experiment, the patients and control subjects were instructed not to drink water or any other form of fluid after 12.00noon. Food was allowed, but watery food was restricted. They however continued to void and discard urine until 9.00pm. Thereafter and up until 9.00am on the next day (day of the experiment) all urine was voided into the provided container. On entering the laboratory at 9.00am, they were requested to empty the content of the bladder for the last time into the container. Thus a 12 hour urine sample was collected.

Blood samples (5ml) were collected and gently transferred into the Lithium Heparin sample bottle to avoid lysis.

TP was assessed; wt and BP were also measured as in group A study. BMI and MABP were subsequently calculated. A known volume of water which is unknown to the subjects was provided in a container for them to drink *ad libitum*. The amount of water intake (W_D) was calculated as the difference between the initial volume of water in the container before drinking (W_i) and the final volume left after drinking (W_f) i.e. $W_D = W_i – W_f$

Serum and urine analyses

All serum and urine samples were analysed for sodium (Na$^+$) potassium (K$^+$) and creatinine (Cr) concentrations at the Chemical Pathology Laboratory of the University of Benin Teaching Hospital using standard procedures. Packed cell volume (PCV), urine volume (V), and specific gravity (SG), were also determined in Physiology Laboratory, University of Benin. PCV was determined using heparinised capillary tube, centrifuge, and haematocrit reader, while V and SG were determined using measuring cylinder and reagent strip respectively.

Urine concentration index (UCI)

Direct urine osmolality was not measured. Urine osmolality was estimated by calculating the urine concentration index. Because water but not creatinine is reabsorbed progressively along the successive nephron segments, creatinine concentration rises proportionally in the tubular and collecting duct fluid above its plasma value. Thus, UCI = Ucr/Scr.

Where Ucr = urine creatinine concentration and Scr = serum creatinine concentration. This ratio of urine to serum creatinine concentration provides an index of urine concentration UCI, which has been shown to be correlated linearly and positively with urinary osmolality (Bankir *et al*, 2004; Perucca *et al*, 2006).

Statistical analyses

Data were presented as mean ± SEM. The significant difference between the means was determined by student *t*-test. P values less than 0.05 were considered statistically significant.

Results

This study compares thirst perception in euhydrate SCD patients and the control subjects. It also compares the effect of dehydration on thirst perception, fluid intake and urine output in SCD patients and the control subjects.

Euhydrate group

The results in table 1 show that the parameters of both male and female SCD patients and control subjects were comparable to each other except for wt, and MABP which were significantly lower in male and female SCD patients. SBP and DBP were significantly lower in only male SCD patients.

Dehydrated group

Results in table 2 show that the anthropometric data of both SCD patients and control subjects were not significantly different. Although, blood pressures were higher while HR was lower in both male and female SCD patients than in the control subjects, these showed no significant difference. While dehydration increased TP in HbA control subjects, the SCD patients had little or no change in TP after dehydration. Figure 2 shows that in male SCD, TP was lower compared to the normal control subjects but this was not significant. In females, TP was significantly lower in SCD patients than in control subjects.

The results in table 3 show that in both male and female SCD patients, serum K^+ and Cr were higher than in control subjects, however, serum Na^+ concentration was significantly lower only in the female SCD patients although the males had a lower serum Na^+ concentration.

Results in table 4 also show that urine creatinine concentration was lower in SCD patients, but only significantly so in the male, while urinary K^+ concentration was also lower in SCD patients, but significant only in the female group. The Sodium/Potassium ratio (an index of aldosterone activity) was higher in both male and

female SCD patients when compared with the control.

Fig 1 shows that TP was significantly higher only in male SCD patients compared to the male control subject but comparable in females SCD and control subjects. The results in table 5 show that, SG and UCI were lower in SCD patients of both sexes than in control subjects, but only in UCI was there a statistically significantly difference. Following dehydration, water intake in both male and female SCD patients was not significantly different from that of the control subjects. This was also applicable to the urine output (figs. 3 and 4).

Euhydrated versus dehydrated

TP was significantly increased in dehydrated normal control subjects after thirteen hours of dehydration while in SCD patients there was no significant difference in TP (figs. 5 and 6).
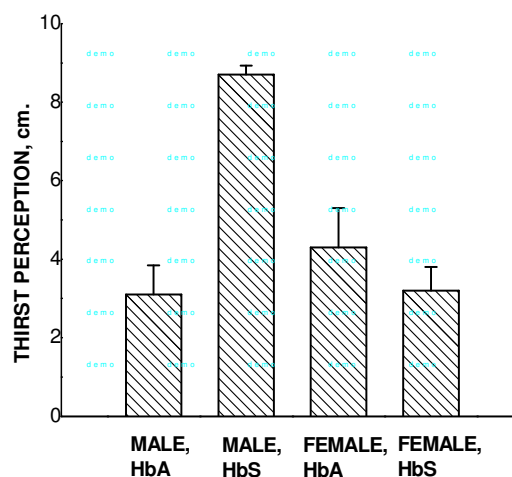

Fig. 1: Thirst perception in euhydrate subjects

Table 1: Anthropometric data in euhydrate subjects

	N	Age, yrs	Weight, kg	Height, M	BMI, kg/m²	SBP, mmHg	DBP, mmHg	MABP, mmHg
Male	16	23.9	67.5	1.78	21.1	118.3	78.8	91.9
control		± 1.1	± 2.2	± 0.01	± 0.6	± 1.4	± 1.3	± 1.2
Male	11	26.2	56.2	1.67	20.1	112.0	66.6	81.7
SCA		± 2.2	± 3.5*	± 0.02	± 1.2	± 2.2*	± 1.8*	± 1.8*
Female	12	23.8	60.7	1.64	22.4	114.6	73.8	87.5
control		± 1.2	± 2.2	± 0.02	± 0.7	± 1.4	± 1.4	± 1.1
Female	9	24.9	53.3	1.6	20.6	109.6	68.4	82.2
SCA		± 2.3	± 2.5*	± 0.03	± 0.6	± 3.0	± 2.9	± 2.6*

* = P < 0.05

Table 2: Anthropometric data in dehydrated subjects

	N	Age, yrs	Weight, kg	Height, m	BMI, kg/m²	SBP, mmHg	DBP, mmHg	MABP, mmHg
Male, Control	5	24.4 ± 1.8	67.8 ± 3.3	1.80 ± 0.001	20.9 ± 1.0	108.4 ± 3.5	73.6 ± 1.6	85.2 ± 1.6
Male, SCA	5	25.6 ± 1.4	58.6 ± 6.9	1.70 ± 0.02	20.7 ± 2.0	109.8 ± 1.8	69.2 ± 2.0	82.7 ± 1.0
Female, control	4	27.0 ± 1.8	61.8 ± 1.9	1.65 ±0.02	22.9 ± 1.5	108.0 ± 0.8	66.0 ± 1.0	80.5 ± 0.7
Female, SCA	8	28.3 ± 2.6	55.5 ± 4.0	1.65 ± 0.03	20.5 ± 0.9	109.5 ± 3.7	76.0 ± 1.3	88.0 ± 4.9

Table 3: Serum parameters in dehydrated subjects expressed as mean ± sem

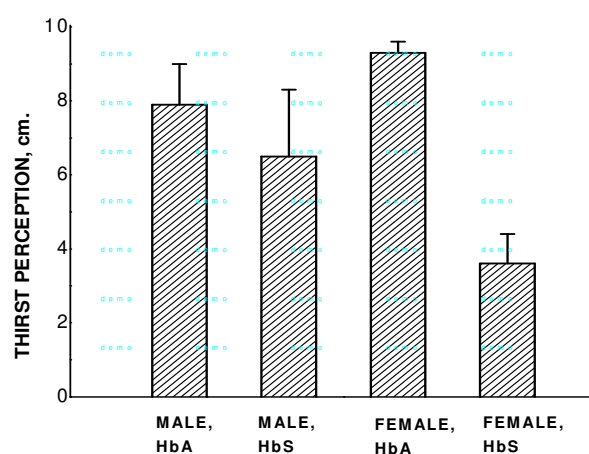|	N	Na⁺ (mmol/l)	K⁺ (mmol/l)	Cr mg/dl	PCV, %
Male, Control	5	136.4 ±2.69	3.3 ±0.28	1.40 ±0.14	42.7 ±2.17
Male, SCA	5	129.4 ±2.25	4.0 ±0.7	1.6 ±0.10	24.4 ±1.9*
Female, control	4	141.3 ±0.6	3.2 ±0.1	1.35 ±0.13	43.98 ±0.4
Female, SCA	8	132.0 ±1.7*	3.6 ±0.2	1.50 ±0.10	23.6 ±1.0*

* = P < 0.05

Fig 2: Mean TP in dehydrated subjects

Table 4: Urine sodium and potassium concentrations and sodium/potassium ratio in dehydrated subjects (mean ±sem)

	N	Na⁺ (mmol/l)	K⁺ (mmol/l)	Urinary Na⁺/K⁺	Cr (mg/dl)
Male, control	5	104.4 ±4.9	115.6 ±43.52	0.90	93.5 ±14.4
Male, SCA	5	120.0 ±16.7	19.5 ±5.0	6.15	16.3 ±1.8*
Female, control	4	124.0 ±14.7	170 ±7.1	0.73	99.8 ±4.3
Female, SCA	8	117.3 ±13.9	13.8 ±3.7*	8.50	49.3 ±16.9

* = P < 0.05

Table 5: Specific gravity, serum creatinine concentrations and urine concentration index in subjects (Mean ± sem)

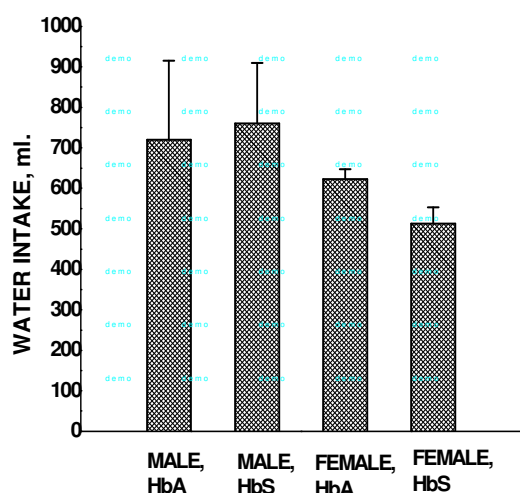|	N	Specific Gravity of urine	Serum Cr, mg/dl	Urine Cr, mg/dl	Urinary Conc. Index, UCI
Male, control	5	1.018 ±0.02	1.40 ±0.14	93.5 ±14.4	70.3 ±11.4
Male, SCA	5	1.016 ±0.02	1.6 ±0.10	16.3 ±1.8	10.5 ±0.9*
Female, control	4	1.02 ±0.01	1.35 ±0.13	99.8 ±4.3	74.9 ±4.1
Female, SCA	8	1.019 ±0.02	1.50 ±0.10	49.3 ±16.9	45.0 ±2.0

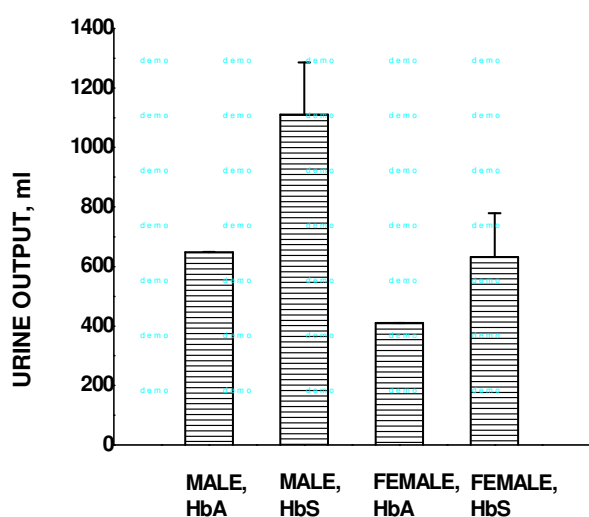*Fig 3: Mean ad libitum water intake immediately after water deprivation*

Fig 4: Urine output immediately after water deprivation

Discussion

These experiments were designed to determine the thirst perception (TP) in SCD patients in steady state and also during a period of dehydration in view of the fact that generally, these patients are in a state of fluid deficit. The results show clearly that in euhydrate state, male SCD patients had significantly higher TP than normal, while female SCD patients had similar TP as normal subjects (fig. 1). After dehydration, the normal male and female subjects showed an increase in TP; in marked contrast, the responses in the male and female SCD patients were not different from the TP values in the euhydrate state (fig. 2). These observations suggest that the SCD patient have a reduced sensitivity to water deficit, and explains the key management strategy of liberal fluid intake in these patients.

The baseline TP reported in these studies agrees with earlier reports of Obika and Mowoe, (1997), of 4.1 ± 0.05 cm and Obika *et al*, (1996) of 2.5 ± 0.5 cm. in young healthy non dehydrated subjects. However, it can be noted that these values are slightly higher than the reports of Burrell *et al*, (1991) and Figaro and Mack (1997) who reported a value of 1.3 ± 0.4 cm and 1.5 ± 0.4cm in experimental and control male subjects respectively as not thirsty. The reason for these variations may be related to the dry and temperate weather in these studies. Furthermore, Obika *et al* (2009), more recently, showed that when their control subjects were given a preload of distilled water, the TP was as low as 1.6 ± 0.4 cm, suggesting that in our environment; we have a higher baseline threshold for TP. In that report the baseline TP varied between 3.0 and 4.5 cm. Although gender seems to have different results in SCD patients, other reports have suggested that in normal subjects, gender may not influence baseline TP. Thus, Igbokwe and Obika (2008) reported that thirst perception and dryness of mouth in healthy young males and females are similar From our results, TP observed in the male group 3.12 ± 0.74 cm did not show any significant difference from that of the female group 4.3 3 ±1.0 cm.

It is clear from this study that SCD patients generally have a reduced response to TP after dehydration; the female patients much more so. The mean water intake immediately after dehydration, although slightly lower in females, was similar in male HbA and HbS and in female HbA and HbS. In addition, the male and female SCD patients had higher urine output after dehydration. Thus, although they had similar water intakes after dehydration, the SCD patients lost more fluid as urine than the normal subjects. These suggest that the SCD patients tend to remain in a state of water deficit, and may explain the most common defect in patients with SCD which is impaired urine concentrating ability or hyposthenuria (Kontessis *et al*., 1992) which is suggested in this study by the lower urine concentration index in these patients.

It is not clear from our study the possible reason for this apparent gender difference in TP in SCD patients. One possible explanation is highlighted in the work of Stachenfield *et al* (1999). Stachenfeld *et al*, (1999) in their work on the effect of oral contraceptives on body fluid regulation, showed that when plasma concentration of the hormone, estradiol was high, plasma osmolality was low throughout rest, exercise and rehydration but plasma arginine vasopressin concentration, thirst and body fluid retention were unchanged indicating a lowering of the operating point for body fluid,
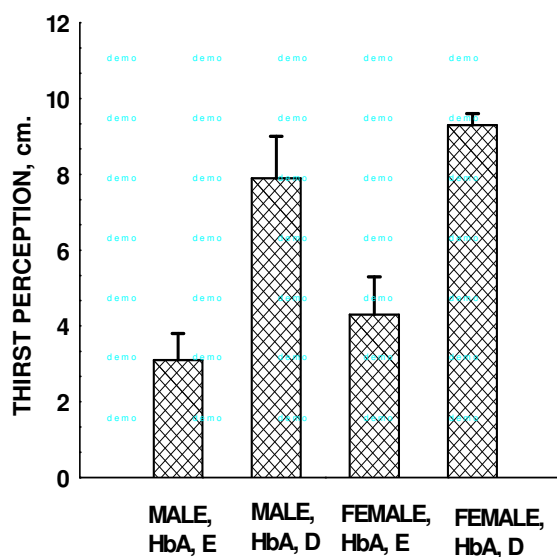
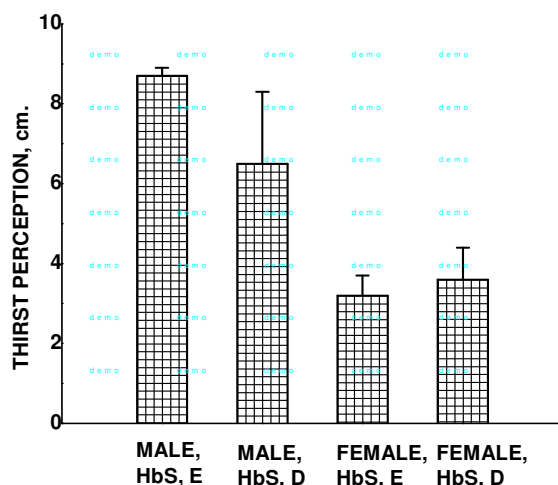Fig 5: Mean TP in euhydrate (E) and dehydrated (D) normal subjects

Fig 6: Mean TP in euhydrate (E) and dehydrated (D) SCD patients

thus the higher TP in male SCD patients compared to the female SCD patients in euhydrated group (8.82 ± 0.76 cm vs 2.94 ± 1.0) and in dehydrated group (4.96 ± 2.7 cm vs 1.95 ± 0.76 cm) suggests that the lower TP in female SCD patients could be due to the influence of the hormone estradiol. We do not have an explanation for a lower urinary potassium concentration compared to the controls, which resulted in a significantly higher sodium/potassium ratio. The high sodium/potassium ratio suggests an enhanced mineralocorticoid activity in these patients.

The reliability and validity of measurements of the subjective ratings of thirst have been previously reported. Thirst correlates positively with plasma osmolality (Baylis and Robertson, 1980). Subjective ratings of thirst using VAS was also found to correlate positively with plasma osmolality (Thompson *et. al.,* 1986; Takamata *et al*, 1994).

It can be concluded that female SCA patients do not have normal response to dehydration with regards to TP after a period of dehydration. Since dehydration stimulates the release of vasoactive hormones like vasopressin, this may explain why female patients are less prone to crisis (Stringer *et al*, 2005) than their male counterparts.

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