SERUM URIC ACID AND RENAL FUNCTION IN ADULT SICKLE CELL DISEASE PATIENTS AT KENYATTA NATIONAL HOSPITAL (KNH)

BY

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DECLARATION

I declare that this dissertation is my original work and has never been presented as a thesis in any other University

Signed .....

Candidate Dr. Ndambuki Kinguyu Mboloi

We certify that this dissertation has been submitted for the examination with our approval.

Signed 17/2/84

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SUMMARY.

56 sicklers attending the adult haematology clinic or admitted to the Medical Wards - KNH were studied during the period from December, 1981 to November, 1982. Patients studied comprised 30 males and 26 females most of them young adults under 25 years old. Hyperuricaemia in sickle cell disease, reported in the past (1,2,3) was a frequent finding in this study with a prevalence of 47.9%. The hyperuricaemia was shown to be related directly to the increased cell turnover due to haemolysis in sickle cell disease (1).

Mean BUN, serum creatinine and electrolytes were normal suggesting very low incidence of renal insufficiency in sickle cell disease, (4,5,6).

Urine concentrating defect described in sickle cell disease was confirmed in this study (6). Haematological parameters were consistent with haemolytic anaemia.

INTRODUCTION

Sickle cell desease is a hereditary disorder of haemoglobin and is due to the presence of sicle cell haemoglobin in the red blood cells (rbc).

The basic defect in the haemoglobin molecule is substitution of valine for glutamic acid in position 6 of the B globin chain. The mode of inheritence is either autosomal recessive or autosomal dominant with variable penetrance and expressivity. The disease is usually manifested in the homozygous state (Hbss) but in some situations disease manifestations may be observed in the heterozygous state if Hbs is 40% or more.

The disease is common in equatorial Africa and among communities with Congoloid ancestry elsewhere in the world.

Anaemia is the main feature of the disease. Sickle cell haemoglobin is known to undergo gellation in condition of hypoxia, low pH, or hypertonicity. This is due to the polymerisation of haemoglobin molecules in this state. Tactoids and fibrils of these polymers are formed within the rbc resulting in changes in the rbc shape to bizzare forms and th characteristic sickle shape. These changes are associated with increased rigidity of the rbc. Repeated gellation of the haemoglobin causes irreversible changes in the rbc membrane which then leads to haemolysis of the cells and their eventual removal from circulation by the reticuloendothelial system.

Gellation of haemoglobin S results in increased blood viscosity and diminished filterability of the red blood cells in microcirculation due to increased rigidity. This causes sludging and small vessel occlusion which is associated with painful crisis.

Patients may present in any of the following crisis:-

(1) Thrombotic (Vasocclusive) crisis is quite common and causes the painful episodes mentioned above. It may result in multiple microinfarcts in various organs.

(2) Sequestration crisis which will occur in association with persisting enlarged spleen and presents as severe anaemia of acute onset.

(3) Haemolytic crisis presents as severe anaemia associated with deepening jaundice. It is associated with infections bacterial or parasitic, usually malaria.

(4) Aplastic crisis occurs where erythopoiesis fails in face of severe anaemia.

(5) Mixed crisis is the situation where the above are combined in varying proportions in the same patient.

M.S. Gold, J. C. Williams, M. Spivack and V. Grann (1) reported hyperuricaemia in sickle cell disease patients and observed that such patients could present with secondary gout. They observed that hyperuricaemia occurs frequently and serum uric acid levels in sicklers studied were above 6 mg/dL. Similar observations were made by other investigators (3, 7). Uric acid is a product of purine metabolism and is derived mainly from endogenou purines.

Renal insufficienty is known to occur in sickle cell disease but is common over 30 years of age. E.L. Friedmann, T. K. S. Rao, C. L. Sprung and T. Manis (5) reported overt renal disease in sickle cell disease patients. It was difficult to determine the precise cause of the renal failure as different histological lessions were demonstrated. It has thus been shown that hyperuricaemia occurs in sickle cell disease (1, 3). Renal insufficiency does occur (1, 4, 5, 6, 7, 8, 9) but the incidence of insufficiency resulting directly from the sickling phenomenon is not known. Histological lessions of the glomeruli suggested post streptococcal glomerunephritis in a proportion of patients above (5). Hyposthemuria has been demonstrated in sickle cell disease patients and in high proportion of sickle cell trait patients (4, 5, 6, 7, 9, 10, 11).

The present study was carried out to determine the pattern of serum uric acid among sickle cell disease patients seen at Kenyatta National Hospital and to correlate this with renal function and haematological parameters.

Parameters studied were:-

(1) Serum Uric acid levels (Normal levels 2-7 mg/dL)

(2) BUN, Serum creatinine and electrolyte levels

(3) Urine specific gravity and pH

(4) Coultergram and Reticulocyte count

(5) Haemoglobin Electrophoresis.

MATERIALS AND METHODS

The study covered 56 sickle cell disease patients attending the adult haematology clinic or admitted to the Medical Wards at KNH. The study included patients in the steady state and in crisis and covered 30 males and 26 females.

The following information was recorded by the author on all patients:-

(1) Name

(2) Age

(3) Sex

(4) Any current treatment (with particular interest to diuretics).

(5) Haemoglobin electrophoresis results

(6) Type of crisis or complication where applicable

(7) Number of hospital admissions in crisis in the preceding one year. This was intended as a measure of severity of the disease

(8) Blood pressure (lying)

Full physical examination was done on all patients (by the author).

Venous blood specimens were then taken for the various determinations as follows:-

(i) 2 millilitres of blood in sequestrene for full blood counts and reticulocyte count and Hb electrophoresis Coultergram was obtained on the coulter counter model S, in the department of haematology. For reticulocyte count, supravital staining was done with with brilliant cresyl blue (12) and the count done in the laboratory department of Medicine.

Haemoglobin electrophoresis was done by Cellulose acetate paper electrophoresis (C.A.P.E.) (13) in the department of haematology. Foetal Haemoglobin (HbF) level was determined by the one minute alkaline denaturation method (14) Normal levels of HbF in sickle cell disease was taken as 4-6% (15). Proportions above this level or a broad HbF band on electrophoresis was taken as high HbF.

(ii) 2 millilitres of venous blood in plain bottle was taken for the determination of serum uric acid. The serum was separated and frozen for the determination of uric acid in the laboratory - department of Medicine. Uric acid was estimated by the phosphotungstic acid reduction method - (Caraway Modification of 1955 and 1963). Normal serum uric acid level was taken as 2-7 mg/dL (1, 2, 16).

(iii) 3-4 mililitres of blood in a plain bottle was taken for BUN, Serum creatinine and electrolyte levels. These were done in the department of Biochemistry using the autoanalyser - Technicon SMA - II.

For admitted patients the first morning specimen of urine following overnight fast, was collected and the following determinations done by the author:-

(1) Specific gravity (SG) using a hydrometer

(2) pH. - was estimated using comburtest strips from freshly opened containers.

These tests were done within two hours of the collection of the specimen.

Urine specific gravity for the first morning specimen following overnight fast was used as a measure of the ability of the kidneys

to concentrate urine. Water deprivation test was not done because it was considered hazardous for sicklers who in most-cases had been admitted in painful crisis. Urine osmolality would have been a better test but there were no facilities for this test at KNH where the study was carried out. The less sensitive test of urine S.G. was thus carried out (7, 17).

RESULTS

The patients studied comprised 30 males and 26 females majority of whom were young adults. The ages of the patients ranged from 11 years to 42 years. The patients were divided into age groups at 5 years intervals and their distribution by age and sex is as shown in Table 1 and Figure A.

Table 1 Age and Sex distribution of 56 Sickle Cell disease patients

Age Group		10-15 yr	16-20 yr	21-25 yr	26-30 yr	31-35 yr	36-40 yr	41-45 yr	Total
M	NO	10	15	2	1	1	0	1	30
	%	17.8	26.8	3.6	1.8	1.8	0	1.8	53.6
F	NO	4	12	7	2	0	1	0	26
	%	7.1	21.4	12.5	3.6	0	1.8	0	46.4
ALL	NO	14	27	9	3	1	1	1	56
	%	25	48.2	16.1	5.4	1.8	1.8	1.8	100%

More than 70% were in the age groups 10-20 years and 89.3% were age less than 25 years.

Only 5.4% of the patients were aged more than 30 years.

All patients studied had normal blood pressure with systolic pressures of 100-120 mm Hg and the diastolic pressures of 60-80 mm Hg (18,19).

None of the patients had had diuretic treatment.

Figure A: Age/sex distribution of 56 sickle cell disease patients

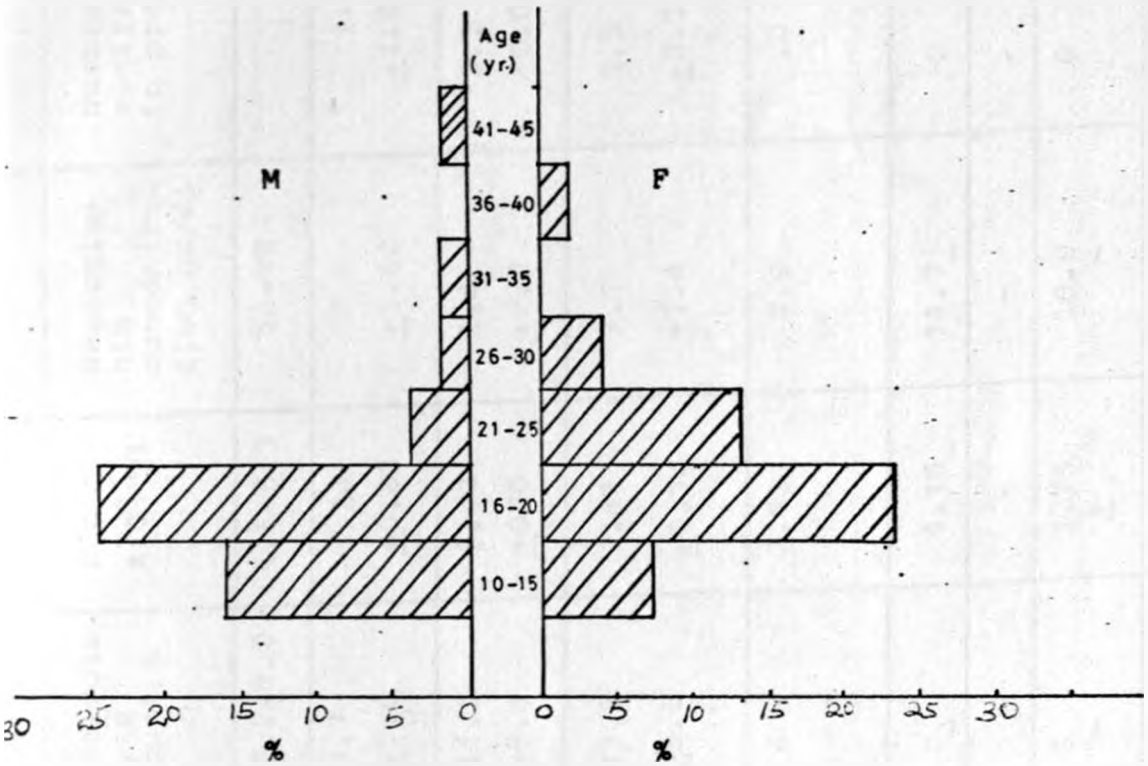


Figure B: Admission rates for the 56 sicklers compared to that of Hyperuricaemic sicklers in 1 year

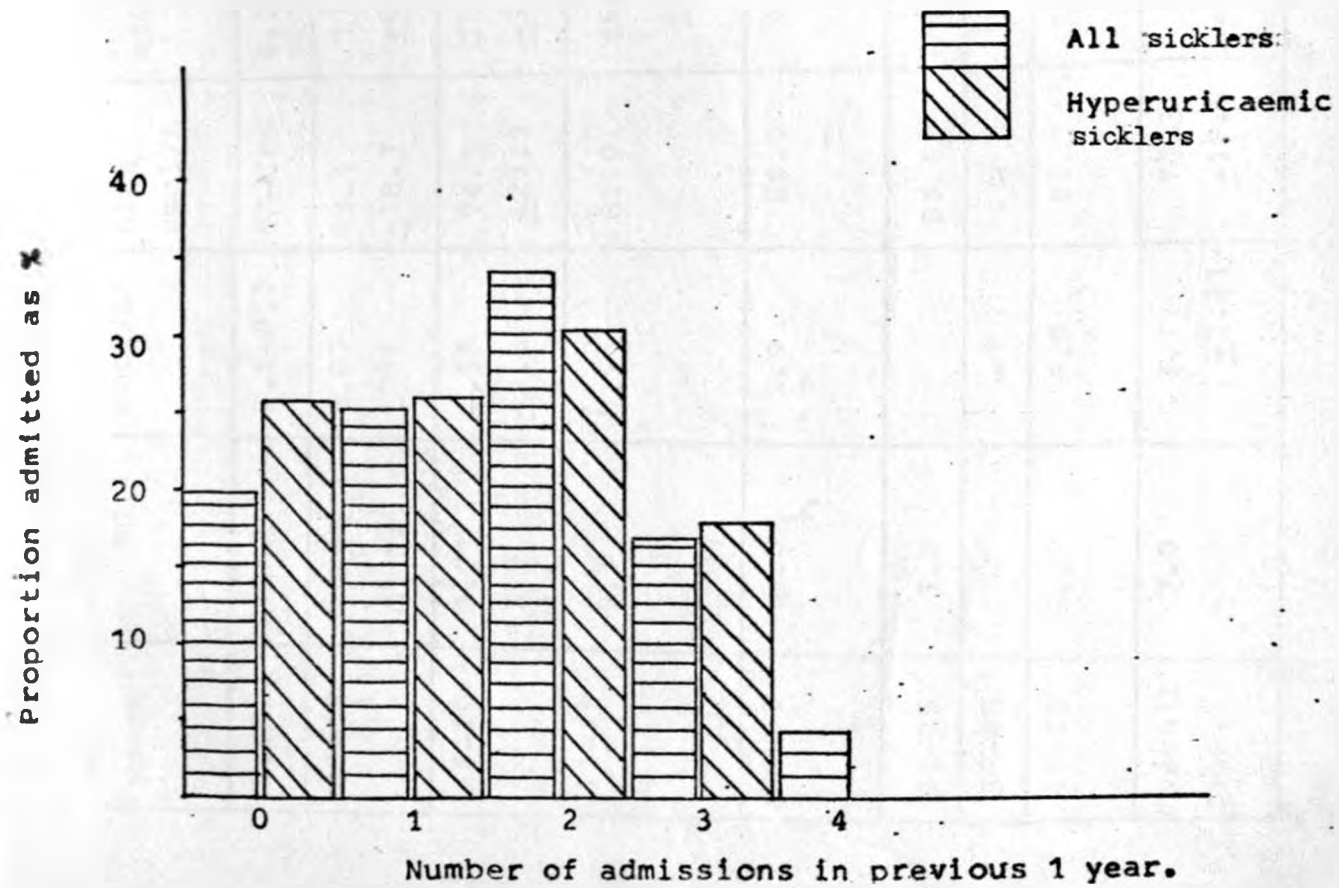


Table 2: Effect of age on Mean serum uric acid and other parameters (Males)

Age - years	Uric acid mg %	B U N mmol/L	Creatinine umol/L	W B C $x10^9$/L	Reticulocyte count %	R B C $x10^{12}$/L	Haemoglobin concentration gm/dL	Number of admissions in prev. 1 yr
Normal	2-7	2.5-6.7	62-106	4.0-10.0	0.2-2.0	4.5-6.3	14-18	
10-15	5.56 ±1.79	2,87 ±083	63.1 ±18.7	17.3 ±6.4	9.7 ±5.6	3.24 ±0.63	8.8 ±1.60	1.7 ±1.0
16-20	7.71 ±3.9	4.57 ±2.8	74.1 ±21.9	15.1 ±3.3	14.2 ±9.4	3.40 ±070	3.4 ±2.2	2.1 ±1.0
21-25	9.7	0.9	62.0	16.25 ±6.4	13.5 ±3.5	2.41 ±0.74	7.7 ±1.4	0.5 ±0.1
26-30	8.5	3.9 -	66.0 -	13.1 -	6 -	2.63 -	7.0	.0
31-35	5.8		83.0	5.4	2.	4.16	14.7	0
36-40	-	-	-	-	-	-	-	.
41-45	5.3	4.0 -	93.0 -	12.3 -	6 -	3.76 ±	10.0 -	0
Overall mean.	7.0 ±3.2	3.71 ±2.21	70.3 ±19.8	15.1 ±5.1	11.8 ±8.1	3.30 ±0.70	8.7 ±2.2	1.7 ±1.1

Table 3: Effect of age on Mean serum uric acid / other Parameters – (Female)

Age-years	Uric acid mg %	B U N mmol/L	Creatinine umol/L	W B C $x10^9$/L	Reticulocyte count %	R B C count $x10^{12}$/L	Haemoglobin concentration gm/dL	No. of admissions 1 year
normal	2-7	2.5-6.7	62-106	4.0-10.0	0.2.2.0	4.2-5.4	12-16	
10-15	5.9 ±1.97	3.1 ±0.3	47.0 ±8.4	18.5 ±3.3	14.0 ±3.4	2.62 ±0.20	7.0 ±1.5	1.2 ±0.9
16-20	7.2 ±3.1	2.7 ±1.2	55.4 ±11.8	13.5 ±4.2	14.0 ±3.0	2.79 ±0.74	8.1 ±1.4	1.8 ±0.9
21-25	8.8 ±6.1	3.5 ±1.6	70.4 ±26.4	14.1 ±8.4	14.1 ±9.1	3.14 ±0.53	9.0 ±1.2	2.1 ±0.9
26-30	7.3 –		–	16.4 ±4.8	10.0 ±2.8	2.58 ±0.14	8.1 ±0.9	1.0 ±1.0
31-35	–	–	–	–	–	–	–	–
36-40	–	–	–	–	–	–	–	–
41-45	–	–	–	–	–	–	–	–
Overall Mean.	7.6 ±4.4	3.0 ±1.3	59.8 ±19.1	14.5 ±5.6	13.62 ±6.5	2.86 ±0.61	8.2 ±1.4	1.7 ±1.0

Serum uric acid was found to be elevated in 11 out of 27 males and in 12 out of 21 females in whom the investigation was carried out. This gave the hyperuricaemia rate as 47.9%

Most of the hyperuricaemic patients had serum uric adid levels between 7.1 mg/dL and 10.0 mg/dL (1). 18.7% had serum uric acid levels above 9.0 mg/dL. 3 patients (6%) - 2 females and 1 male - had serum uric acid levels above 15.0 mg/dL.

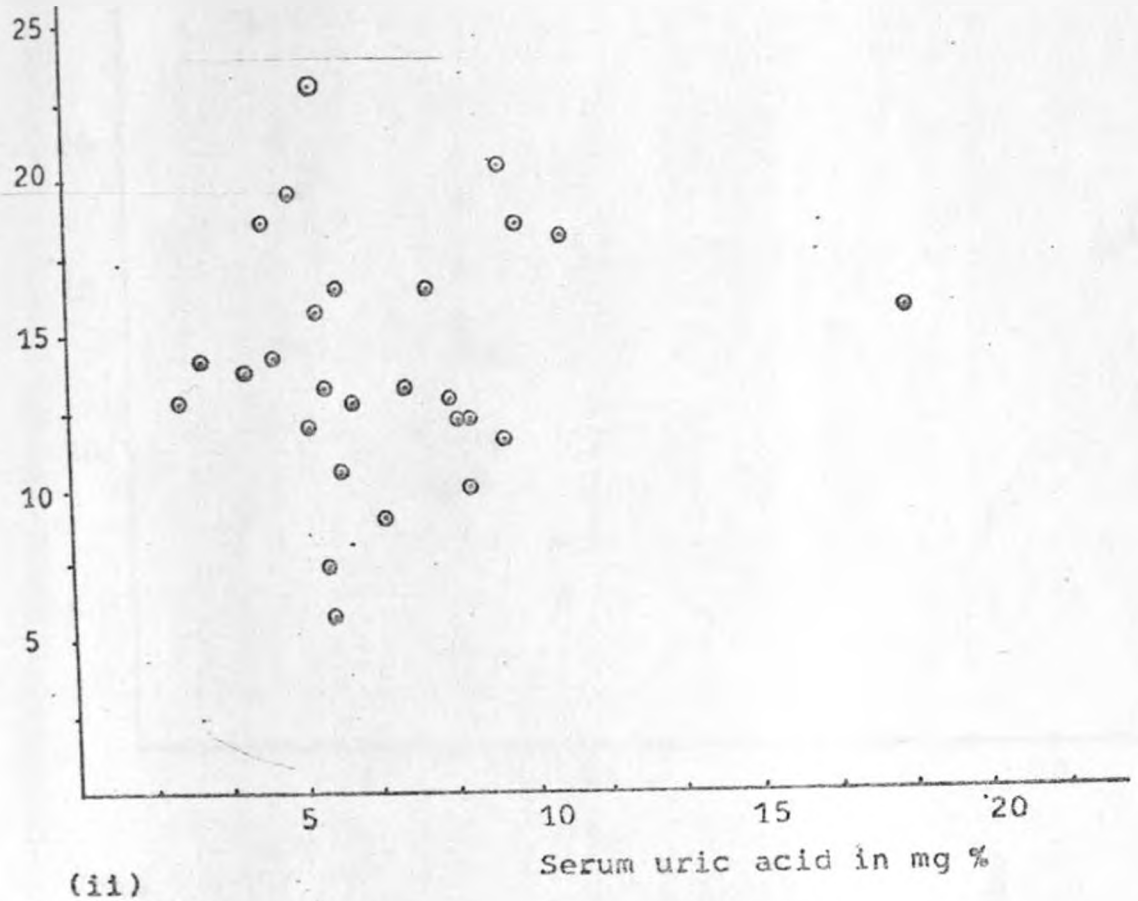
The male patient aged 19 years, but having severe growth retardation had very painful swelling of the distal interphalangeal joint of the right middle finger. This swelling was demonstrated radiologically to be consistent with urate arthropathy. This was not found in the other patients studied (1) and gave the incidence of urate arthropathy in sickle cell disease as 2.1%. Painful episodes in this patient were most likely due to the hyperuricaemia. Hyperuricaemia was found in patients during the steady state as well as during crisis (1).

Mean values of serum uric acid, BUN, serum creatinine, white blood cell count, reticulocyte count, red blood cell count, haemoglobin concentration and number of hospital admissions in the preceding one year were as shown in tables 2 and 3.

The mean serum uric acid rose with age up to age 21-25 years when the maximum mean value was attained then there was progressive decrease as in tables 2 and 3, figure E. Apart from age group 10-15 years, the age groups with elevated mean serum uric acid had elevated mean white cell count as well. The reticulocyte counts were elevated in all age groups with the highest

Figure C : Association between serum uric acid and
(i) W B C count
(ii) Reticulocyte count
} in male sickleers.

(i)



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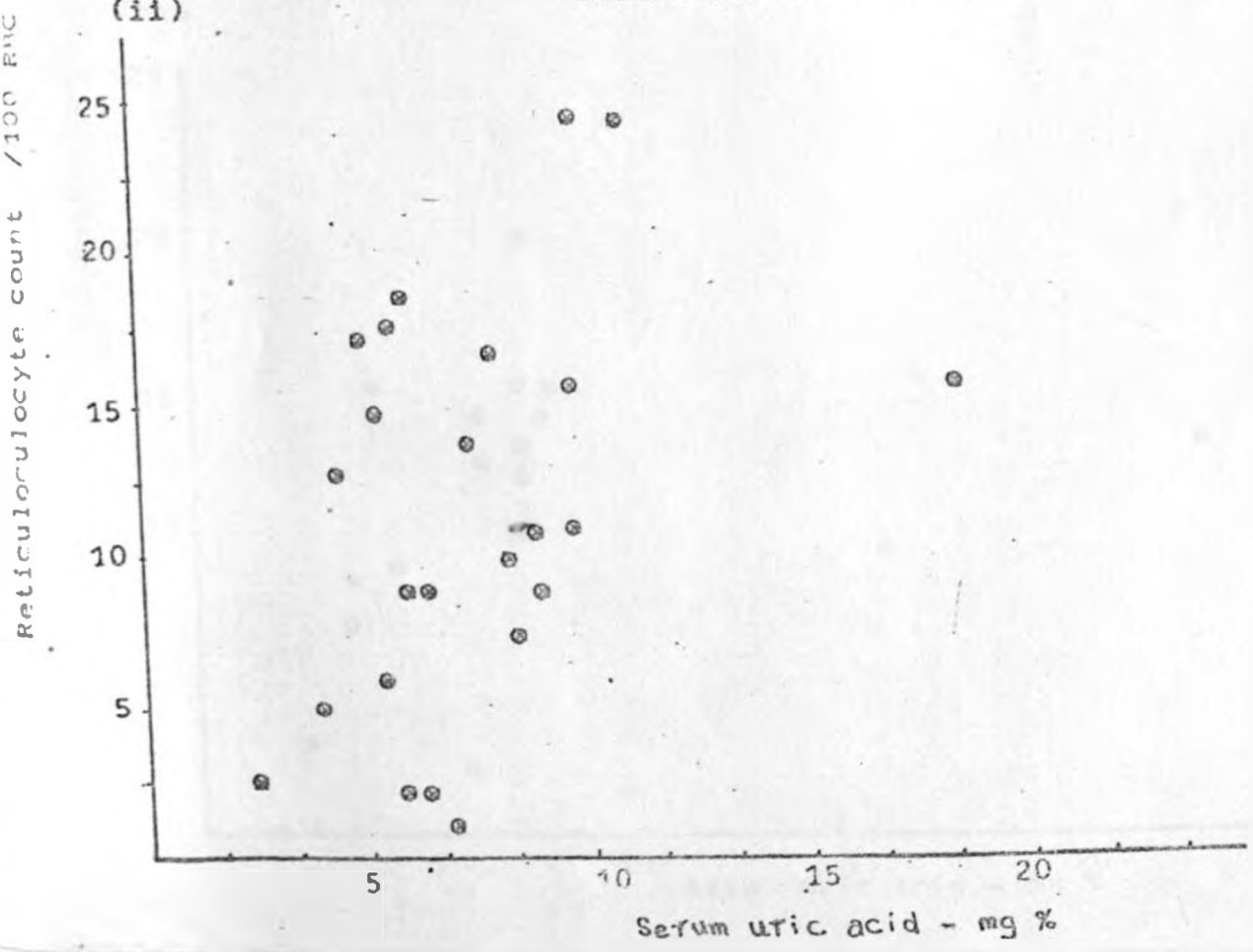


Figure D: Association between serum uric acid and (i) W B C count (ii) Reticulocyte count in female sicklers

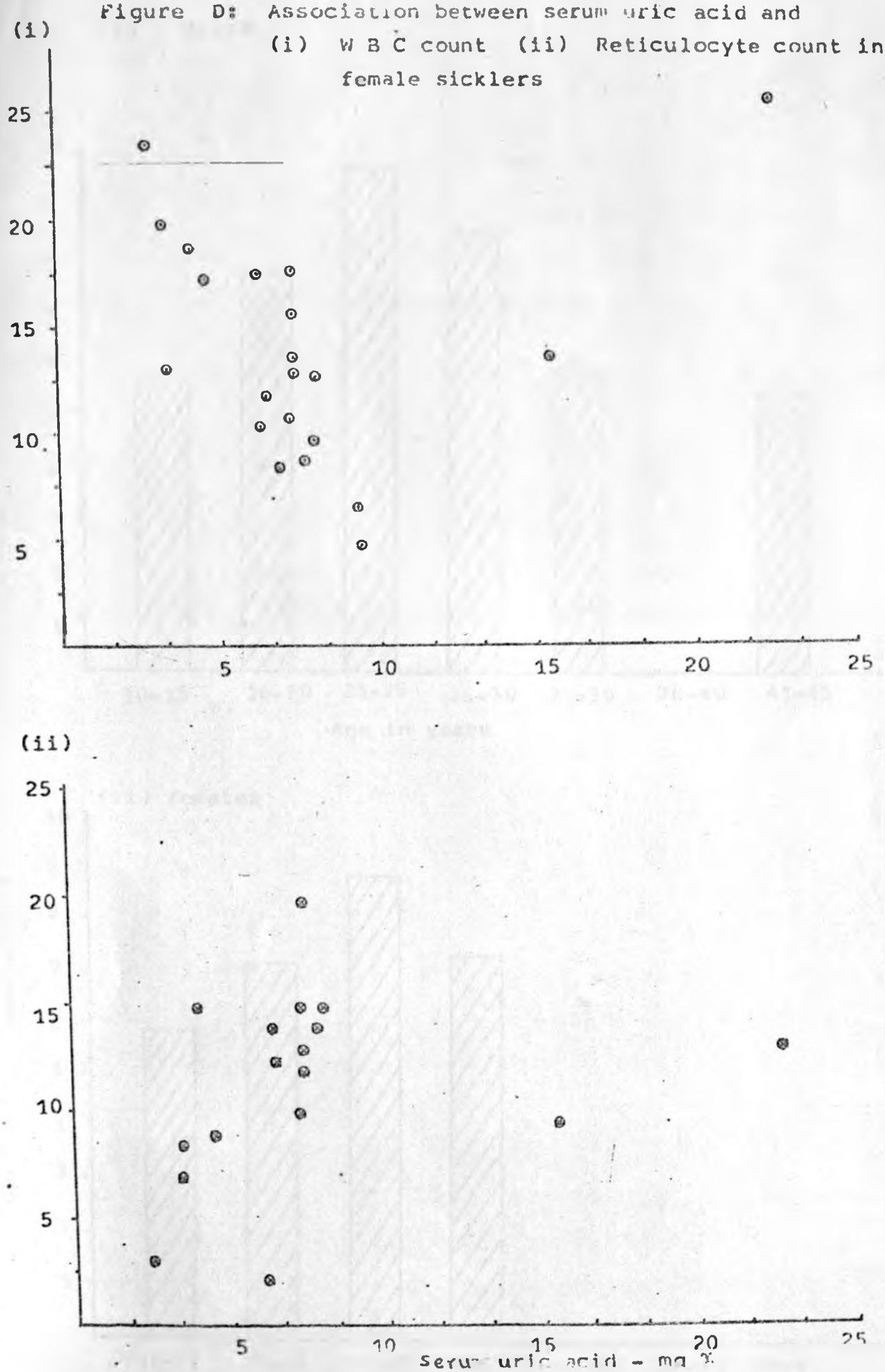
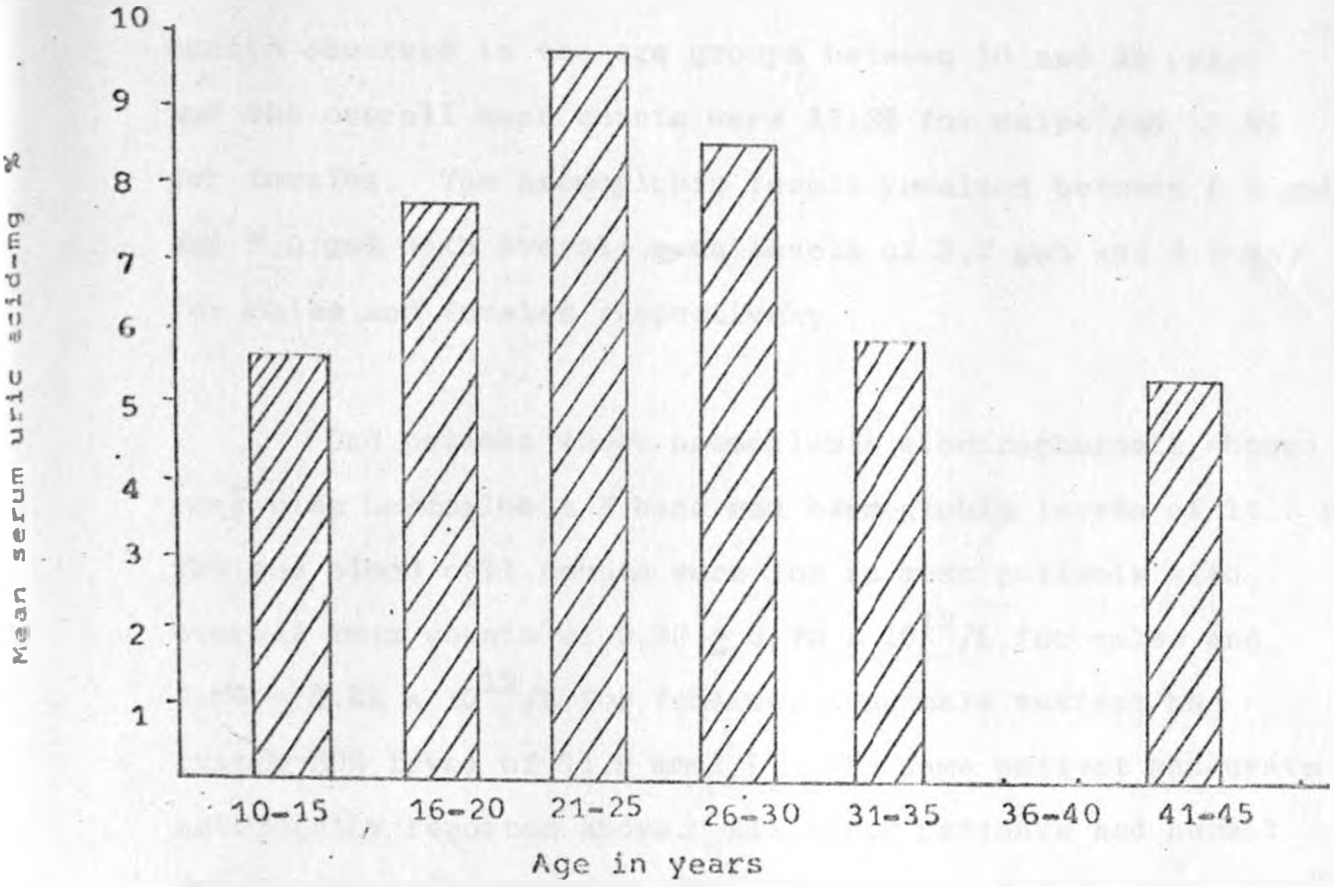
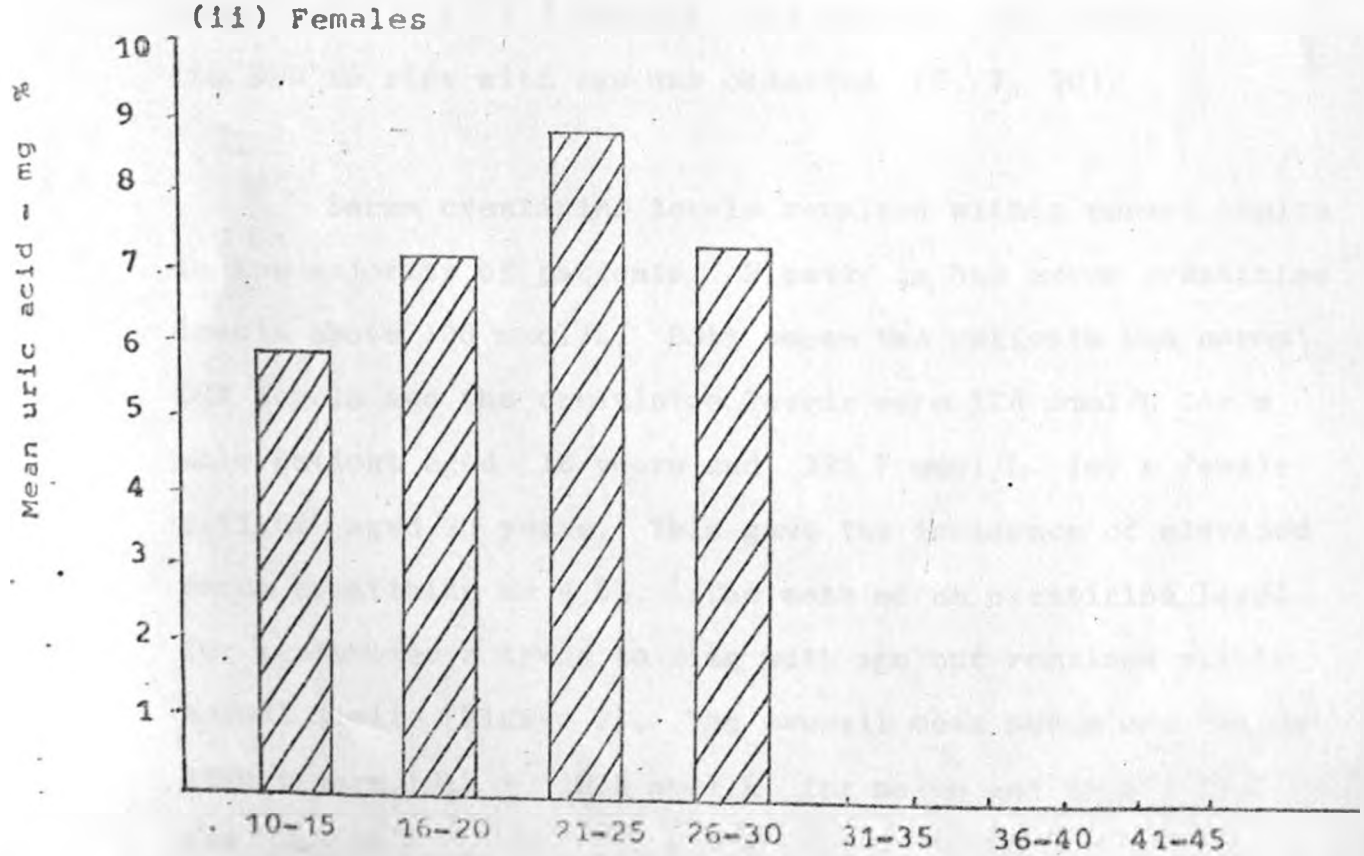


Figure E: Changes in mean serum uric acid with age
S C D

(i) Males



(ii) Females

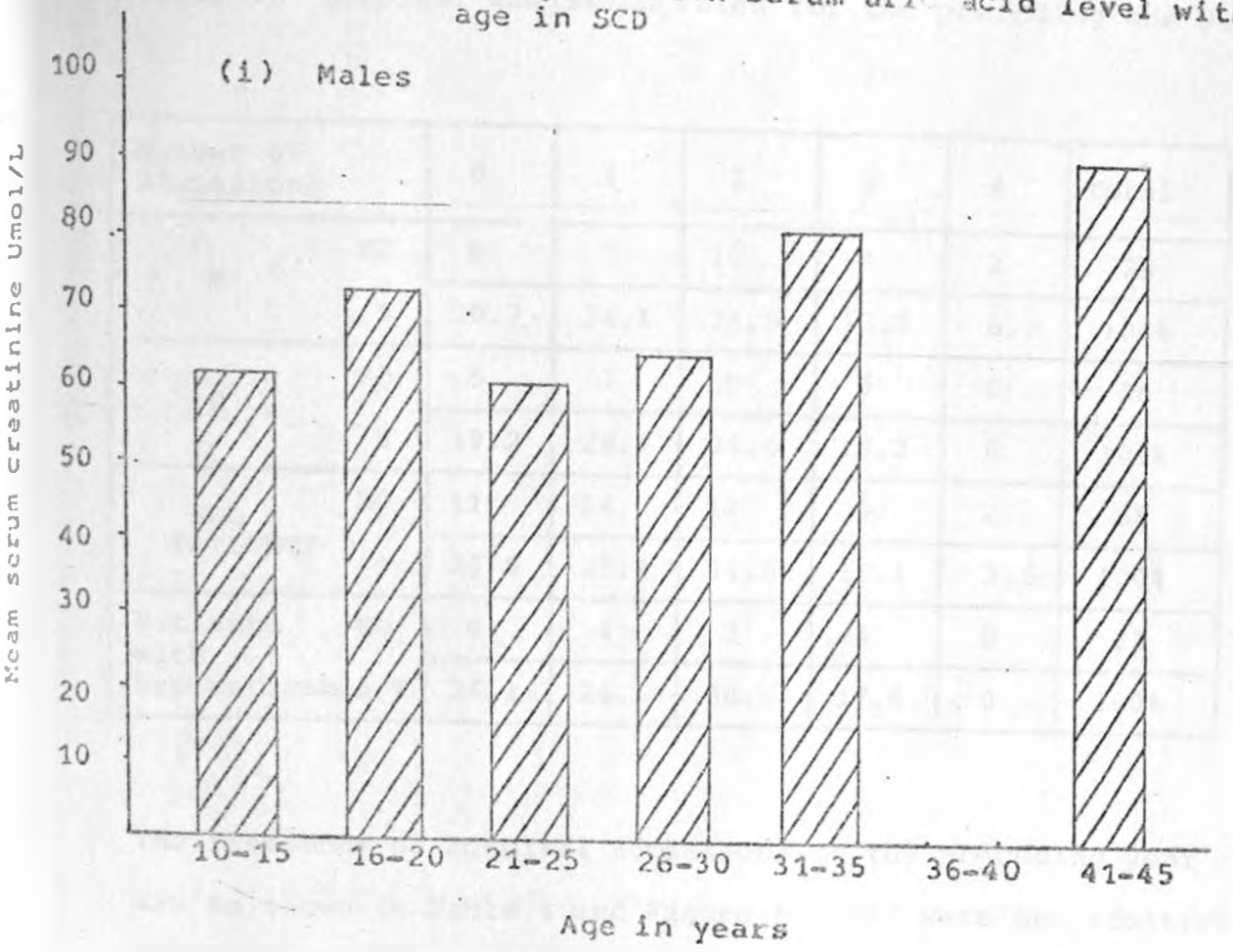


counts observed in the age groups between 10 and 25 years and the overall mean counts were 11.8% for males and 13.6% for females. The haemoglobin levels remained between 5.0 gm% and 9.0 gm% with overall mean levels of 8.7 gm% and 8.2 gm% for males and females respectively.

One patient whose haemoglobin electrophoresis showed a very wide haemoglobin F band had haemoglobin levels of 14.7 gm%. The red blood cell counts were low in most patients with overall mean counts of $3.30 \pm 0.70 \times 10^{12}$/L for males and $2.86 \pm 0.61 \times 10^{12}$/L for females. One male patient had evated BUN level of 11.9 mmol/L. The same patient had urate arthropathy reported above. All other patients had normal BUN levels with overall mean levels of 3.7 ± 2.2 mmol/L for males and 3.0 ± 1.3 mmol/L for females. No tendency for the BUN to rise with age was observed (6, 7, 20).

Serum creatinine levels remained within normal limits in the majority of patients. 2 patients had serum creatinine levels above 106 mmol/L. Both these two patients had normal BUN levels and the creatinine levels were 114 mmol/L for a male patient aged 18 years and 123.7 mmol/L for a female patient aged 23 years. This gave the incidence of elevated serum creatinine as 4.6%. The mean serum creatinine level for age showed a trend to rise with age but remained within normal limits (Figure F). The overall mean serum creatinine levels were 70.3 ± 19.8 mmol/L for males and 59.8 ± 19.7 mol/l for females.

Figure F: Change in mean serum uric acid level with age in SCD



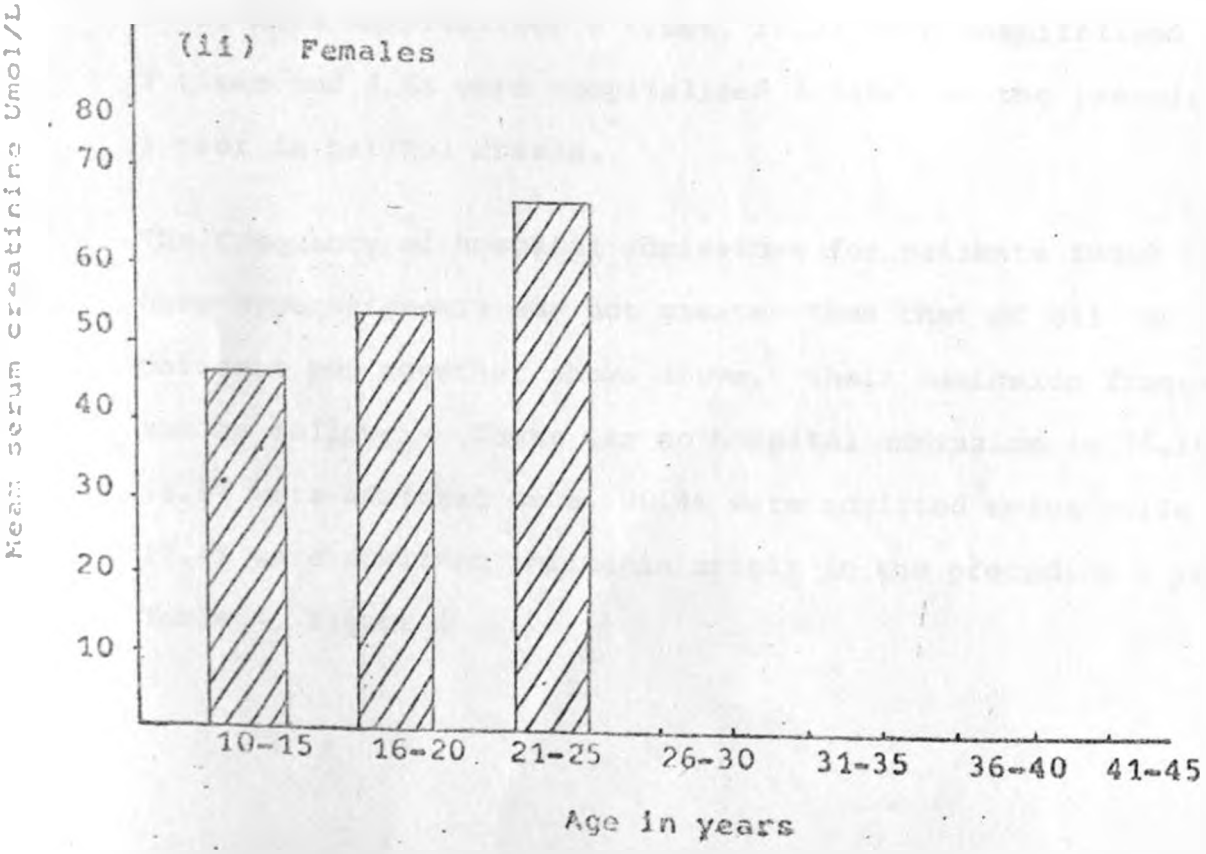


Table 4: Hospital admission rates for the preceding one year (%)

Number of Admissions		0	1	2	3	4	Total
M	NO	6	7	10	4	2	29
	%	20.7	24.1	34.5	13.8	6.9	100%
F	NO	5	7	9	5	0	26
	%	19.2	26.9	34.6	19.2	0	100%
ALL PATIENTS	NO	11	14	19	9	2	55
	%	20.0	25.4	34.5	16.4	3.6	100%
Patients with Hyperuricamia	NO	6	6	7	4	0	23
	%	26.1	26.1	30.4	17.4	0	100%

The frequency of hospital admissions in the preceding year was as shown in Table 4 and Figure B. 20% were not admitted to hospital in the preceding 1 year, 25.4% were admitted once, 34.5% were hospitalised 2 times, 16.3% were hospitalised 3 times and 3.6% were hospitalised 4 times in the preceding 1 year in painful crisis.

The frequency of hospital admissions for patients found to have hyperuricaemia was not greater than that of all the patients put together shown above. Their admission frequency was as follows:- There was no hospital admission in 26.1%. 26.1% were admitted once, 30.4% were admitted twice while 17.4% were admitted thrice in crisis in the preceding 1 year. Table 4, Figure B

Table 5: Comparision between male sickles with Hyperuricaemia and those with normal uric acid levels

Mean	Serum uric acid 7mg %	Serum uric acid 2-7mg %	't' Test
Serum uric acid mg ldL	(7.5-18.6) 10.0±2.9	(2.5-6.9) 5.1±1.1	
Age in year	(15-30) 19.5±4.2	(11-42) 18.3±8.4	
B U N mmol/L	(1-11.9) 4.7±3.2	(1.6-5.2) 2.8±1.6	t = 1.8645 P ≤ 0.05
Serum creatinine Umol/L	(62-114) 80.0±16.1	(38-94) 63.3±17.8	t = 2.1127 P < 0.05
Reticulocyte count /100 R B C	(6-25) 13.5±6.4	(1-22) 9.4±6.9	t = 1.4333 P < 0.20 > 0.10
W B C count - $X10^9/L$	(10.2-20.8) 15.0±3.2	(5.4-23-6) 13.9±4.6	t = 0.652 P > 0.50
R B C $X10^{12}/L$	(1.88-4.12) 3.00±0.6	(2.3-6.2) 3.60±1.6	t = 1.1656 P = 0.20
Haemoglobin gm ldL	(6.6-9.9) 8.5±1.2	(5.5-14.7) 9.0±2.1	t = 0.7396 P < 0.50 > 0.20
M C V fl	(79-106) 90.4±7.4	(60-100) 80.4±9.5	t = 2.7173 P = 0.01

Table 6: Comparison between female sickles with Hyperuricaemia and those with normal serum uric acid

Mean	Serum uric acid 7mg %	Serum uric acid 2-7 mg %	't' Test
Serum uric acid mg/dL	(7.2-23.1) 9.7 ± 4.6	(2.7-7.0) 4.9±1.6	
Age in year	(10-26) 19.0±3.7	(13-22) 18.5±2.8	
B U N mmol/L	(1.3-6.6) 3.3±1.5	(1.1-4.1) 2.7±0.9	t = 0.9771 P < 0.50 > 0.20
Serum creatinine umol/L	(43-123.7) 66.7±20.1	(39-77) 51.4±10.4	t = 1.8892 P < 0.10 > 0.05
Reticulocyte counts /100 R B C	(9-40) 66.7±20.1	(2-20) 51.4±10.4	t = 1.08314 P=0.20
W B C $X10^9/L$	(4.8-26.6) 12.8±5.4	(8.4-24.6) 15.8±4.8	t = 1.2425 P = 0.20
R B C $X10^{12}/L$	(1.7-4.2) 2.6±0.6	(2.4-4.1) 3.2±0.5	t = 2.05294 P = 0.05
Haemoglobin concerysation gm 1dL	(6.0-9.9) 7.8±1.4	(7.8-11-2) 9.1±1.2	t =2.2605 P < 0.05 > 0.02
M C V fL	(75-112) 92.8±10.2	(73-100) 85.6±8.7	t = 1.5483 P = 0.10

In tables 5 and 6, comparison between the group with hyperuricaemia and that with normal serum uric acid is made for the various parameters. The mean ages for both groups do not show significant difference with overall mean of 18.4 years for males and 18.6 years for the females.

The mean BUN level was higher in patients with hyperuricaemia than in those with normal serum uric acid but in both groups the mean BUN levels were within normal limits. The difference between the means was statistically significant for the males as shown by the student 't' Test $t = 1.8645$, $P \leq 0.05$ for the males while $t = 0.9771$, $P < 0.050 > 0.20$ for the females.

The mean serum creatinine level was higher for those with hyperuricaemia than for those with normal serum uric acid. The difference was statistically significant for both males and females - $t = 2.1127$, $P < 0.05$ for males and $t = 1.8892$, $P < 0.10 > 0.05$ for females.

The mean reticulocyte count was higher for those with hyperuricaemia but the difference was not statistically significant- $t = 1.0831$, $P = 0.20$ for females and $t = 1.43325$, $P < 0.20 > 0.10$ for males.

The mean white cell count was higher in males with hyperuricaemia than in those with normal serum uric acid whereas the reverse was observed in the females. The differences were not statistically significant - $t = 0.652$, $P > 0.50$ for males and $t = 1.24249$, $P = 0.20$ for females. All the males with hyperuricaemia had white blood cell count above 10×10^9/L while 19.0% of males with normal serum uric acid levels had WBC counts less than 10×10^9/L. This difference cannot be explained and its existence needs to be confirmed before further search for an explanation.

The mean red blood cell count was lower for those with hyperuricaemia than for those with normal serum uric acid. This difference was statistically significant for the females $t = 2.05295$, $p = 0.05$.

Mean haemoglobin concentration for those with hyperuricaemia was lower than that for those with normal serum uric acid. This difference was statistically significant for the females where $t = 2.2605$, $p < 0.05 > 0.02$.

The mean MCV for those with hyperuricaemia was greater than that for those with normal serum uric acid levels.

The difference was statistically significant for the males where $t = 2.7173$, $p = 0.01$. (21)

Mean urine specific gravity and pH and mean serum bicarbonate levels were as shown in Table 7.

The mean urine specific gravity was 1.014 ± 0.0013.

Table 7: Mean urine SG, Urine pH, Serum HCO_3 in Sickle cell disease

	M	F	Pooled results
Urine Specific gravity	(1.012 - 1.017) 1.014 ± 0.0013	(1.012 - 1.016) 1.014 ± 0.0012	1.014 ± 0.0013
Urine pH (4.6 - 8.0)	(5.5 - 9.0) 6.8 ± 1.3	(5.5 - 7.5) 6.3 ± 0.6	6.6 ± 1.2
Serum bicarbonate (24 - 32 mmol/L)	(17 - 24) 21.0 ± 2.5	(16 - 23) 20.2 ± 2.6	20.7 ± 2.5

Mean serum bicarbonate level was 20.7 mmol/L for all patients with the mean for males as 21.0 mmol/L and that for females as 20.2 mmol/L.

Comparison between patients with high fetal haemoglobin and those with normal fetal haemoglobin is shown in Table 8(a) and (b). Patients whose haemoglobin electrophoresis showed a wide haemoglobin F band or had estimated quantity of more than 6% haemoglobin F were categorised as having high haemoglobin F. Other patients were categorised as having normal or low haemoglobin F (15,22).

Table 8: Effect of haemoglobin F on serum uric acid, BUN and serum creatinine levels in SCD

(a) Males

Mean	High Haemoglobin F	Norma /Low Haemoglobin F	t Test
Serum uric acid mg/dL	5.4 ± 1.8	9.3 ± 3.5	t = 3.5531 p $<$ 0.01
BUN mmol/L	3.2 ± 1.5	4.3 ± 2.7	t = 1.13041 p = 0.20
Serum creatinine µmol/L	65.9 ± 15.0	77.7 ± 23.2	t = 1.4446 p $<$ 0.20 $>$ 0.10

Table 8. Effect of haemoglobin F on Serum Uric acid BUN and Serum Creatinine levels in SCD

(b)

Mean	High Haemoglobin F	Normal/low Haemoglobin F	't' Test
Serum Uric acid Mg/dL	6.6 1.8	8.5 3.4	t = 0.90261 P∠0.50>0.20
BUN MMol/L	2.9 1.4	3.2 1.2	t = 0.4875 P = 0.50
Serum Creatinine Umol/L	55.1 12.0	63.7 22.0	t = 1.00 P > 0.20

Low haemoglobin F was associated with higher levels of mean serum Uric acid, Serum Creatinine and BUN. The difference was statistically significant for the Uric acid in Males where t = 3.5531, P∠0.01.

Hyperuricaemia did not have any demonstrable effect on the frequency of sickle cell crisis as shown in table 9.

Table 9. Effects of sickle cell crisis on serum uric acid

Sickle cell state		Uric acid 7mg %	Uric acid 2 - 7mg %	Total
IN CRISIS	No.	(6)	(9)	(15)
	%	40%	60%	100%
IN STEADY STATE	No.	(17)	(16)	(33)
	%	51.5%	48.5%	100%
ALL PATIENTS	No.	(23)	(25)	(48)
	%	47.9%	52.1%	100%

DISCUSSION

In this study, the majority of patients studied were less than 25 years old. Only 10.8% of them were aged above 25 years. Although the study was based in Nairobi which is 320 Kilometers from the areas with the highest prevalence of sickle cell disease in the country, it does suggest that survival rate for persons with this disorder is still very low (23).

Factors which may be responsible for the low survival rate include severity of the disease, environmental factors which predispose the patients to infections and hence crisis, and ignorance of the availability of medical management that would give some chance of longer survival (Pg.33). The low survival rate for sickle cell disease patients has resulted in the age distribution of the patients shown in Table I and Figure A. The low proportion of patients in the age group 10-15 years results from the fact that sicklers in the paediatric age group are followed in the Paediatric haematology clinic until the age of 13 years when they are referred to the adult haematology clinic.

In this study it appears that less severe disease associated with high levels of haemoglobin F (15,24,25,26,35) resulted in longer survival. This is suggested by the high levels of haemoglobin F in the 3 patients aged more than 30 years. Their haemoglobin F levels were as follows:-

One male aged 42 years had haemoglobin F level of 12%,
Another male aged 35 years was reported to have a broad haemoglobin F band on electrophoresis.

Progressively increasing prevalance of high haemoglobin F levels with age was demonstrated as follows:- The percentage of patients with high haemoglobin F among those aged less than 20 years was 32.5% while for those aged more than 20 years, the prevalence of high haemoglobin F was 53.8%.

This does strongly suggest preferential survival of patients with elevated haemoglobin F.

SERUM URIC ACID

Uric acid is derived from purine metabolism. The purines adenine and guanine are structual units in nucleic acids. When nucleic acids are being broken down, the purines are liberated by the action of nucleoside phosphorylase and then converted to xanthine. Xanthine is oxidised, in the presence of xanthine oxidase, to uric acid. Conditions associated with increased cell turnover will thus be associated with increased uric acid production from the degradation of nuclear material (17,27).

The prevalence of hyperuricaemia in this study was 47.9% and is comparable with 42% obtained by Gold M.S. et al (1). Only one patient had urate arthropathy which gave an incidence rate for urate arthropathy among sickle cell disease patients as 2.1%. This is in agreement with observation that the majority of persons with either primary or secondary hyperuricaemia never develop urate arthropathy (1).

Hyperuricaemic states can result from one or two mechanisms which are:- (a) increased production and (b) decreased excretion (16).

The following are some of the conditions associated with hyperuricaemia:-

(i) Over -production - Myeloproliferative disorders
- Infectious monocucleosis
- Psoriasis
- Malignancy
- Cytotoxic therapy

(ii) Under-excretion - Chronic renal failure
- Diuretic therapy
- Hypertension
- Diabetic Ketoacidosis
- Hypothyroidism
- Toxaemia of pregnancy

None of the patients in this study had any of the above conditions. All patients in the study were normotensive and none was on diuretic therapy (18). Hyperuricaemia was found both in patients admitted in sickle cell crisis and those in the steady state and the frequency of admissions to hospital was not higher in the hyperuricaemic patients than those with normal serum uric acid levels - (Table 9, Figure B).

This means that the sickle cell crisis are not directly related to the hyperuricaemia observed. One patient had elevated BUN of 11.9mmol/L with normal creatinine level - 97 µmol/L and hyperuricaemia of 18.6 mg/dL. It is unlikely that the hyperuricaemia in this patient was due to renal insufficiency as the creatinine level is not consistent with chronic renal failure. Renal damage may have resulted from the hyperuricaemia. Renal failure is known to occur in sickle cell disease frequently past the age of 30 years. As the majority of patients in this study, were under 30 years of age, this could explain the low incidence of renal insufficiency found in this study (4,6,7,28).

Chronic haemolytic anaemias are known to be associated with hyperuricaemia which results from urate over production (1,2,6,16). The haematological parameters were consistent with persistent haemolysis in this study. The reticulocyte counts were quite high with mean counts of 11.8 ± 8.1% for males and 13.6 ± 6.5% for females (29). White blood cell counts were also quite elevated with mean counts of 15.1 ± 5.1 x 10^9/L for males and 14.5 ± 5.6 x 10^9/L for the females. This elevated WBC count gives rise to a state similar to leukaemia (30). This state of increased cell turnover due to persistent haemolysis definitely contributes to the hyperuricaemia observed in these patients. The mechanism for the hyperuricaemia is as follows:- Red blood cells develop from the nucleated stem cell (haemocytoblast). During the maturation process, the nucleus becomes pyknotic and is extruded during the late normoblast stage. The nuclear material is broken down creating a large purine pool among other metabolites. Metabolism of these purines as described above results in production of large quantities of uric acid. On loosing the nucleus the normoblast becomes a reticulocyte (31).

The leukocytosis contributes to hyperuricaemia through increasing the free purine pool as above.

Figures C and D show a tendency for the reticulocyte and WBC count to increase with rising serum uric acid thus confirming the contribution of these cells to the hyperuricaemia.

It was however noted that in the age group 10-15 years, although the reticulocyte and WBC counts were high, the mean serum uric acid level was low.

It has been reported that in sickle cell disease patients, there is increased renal urate clearance matching the increased effective renal plasma flow (ERPF) initially. This is associated with normal serum uric acid levels despite the over production. Hyperuricaemia develops with age as the ERPF decreases with advancing renal lessions secondary to the sickling phenomenon (6), Figure E. Possibly this late stage reflects a defect of the renal tubular secretion of uric acid which can develop alongside other renal tubular function defects known to occur in sickle cell disease patients as a result of the abnormal haemoglobin S.

Ischaemic insults resulting from repeated intravascular sickling and eventual interstitial and peritubular fibrosis cause impairment of tubular functions. Urate secretion which is one of the tubular functions is unlikely to be spared in this process and becomes deranged with time. It appears that besides the overproduction of uric acid in sickle cell disease, diminished tubular secretion - secondary to ischaemic tubular injury plays a role in serum uric acid elevation past the age of 15 years. This requires to be demonstrated by suitable experiments.

It was found that patients with high levels of haemoglobin F tended to have lower serum uric acid levels. This confirms the protective effects of haemoglobin F against sickling and hence results in reduced hemolysis associated with lower cell turnover and lower serum uric acid (15,24,25,26). Mean MCV for

patients with hyperuricaemia was found to be greater than that for those with normal serum uric acid levels. This tendency towards larger MCV could result from one of the following:-

(a) Folate deficiency due to chronic hemolysis.

(b) Large proportion of young cells in the erythrocyte population.

Folate deficiency is unlikely since all sickle cell disease patients followed in the hospital are maintained on folic acid 5 mg daily for life. The other alternative of a large population of young red blood cells is more likely and is in agreement with increased erythropoiesis as major factor behind the hyperuricaemia of sickle cell disease. (21)

BUN and Serum Creatinine Levels

In this study one patient had elevated BUN of 11.9 mmol/L. This patient also had urate arthropathy of the distal interphalangeal joint of the right middle finger. Other patients had normal BUN levels and no tendency to increase with age was observed.

Walker B.R. et al (22) observed that renal function tests did not reflect glomerular lessions in sickle cell disease as shown on histology. Other workers have observed that glomerular function is intact or even supranormal during the earlier years of life, then progressively deteriorates after 30 years (5,6,7,8). The majority of patients in this study were less than 30 years old. Only 5.4% were aged more than 30 years. It appears that the maintenance of normal BUN in the patients studied was a result of the low mean age. The absence of abnormal

biochemical parameters does not rule out glomerular lessions as pointed out by Walker, B.R. et al (32). The medical management of sickle cell disease is prophylactic against sickling crisis It comprises of malaria prophylaxis, folate supplements to avert severe anaemia, prompt treatment of ifentions, proper hydration and advice to avoid physical factors likely to precipitate sickling crisis such as strenuous exercise or exposure to cold. As the management shown above has improved the chances of survival for sicklers, it is likely that renal failure, with uraemia, in sickle cell disease, will become an important problem as more patients survive longer (5, 23).

The mean serum creatinine level remained normal in all age groups. Two patients had minimally elevated serum creatinine levels of 114 umol/L and 123.7 umol/L (5,6,7,8). There was a tendency for the mean serum creatinine level to rise with age (fig.F). This most likely reflects a progressing subclinical glomerular lession resulting in worsening glomerular filtration with time (32). This interpretation has to be taken with caution as the number of patients aged more than 25 years was very small in this study. A larger series of patients requires to be studied locally before a definite conclusion about the pattern of serum creatinine levels can be made.

Urine Concentration.

Urine specific gravity was low in all patients in whom this test was done (table 7). The mean urine specific gravity was 1.014 $\pm$ 0.0013 which is much less than would be expected in a normal person fasted overnight.

Statius van Eps, C.P. Veels, G.H. de Vries, J.de Koning (11) observed that a urine concentrating defect was the commonest renal manifestation of sickle cell disease. The defect which is due to the presence of haemoglobin S in circulation was fixed at 400-450 m Osmol/kg and was irreversible after the age of 10 years. Structural changes have been demonstrated in the renal medulla on microscopy with the main finding as very diminished numbers of vasa recti. This is a direct result of recurrent sickling, vascular occlusion and ischaemia which is followed by fibrosis with obliteration or distortion of vasa recti. The hypertonic environment in the renal medulla most likely promotes sickling (9).

The osmolality of the urine produced in these patients of 400-450 m Osmol /kg reflects lack of function of the juxtamedullary nephrons whose loops dip into the renal medulla and papillae to produce concentrated urine by the counter current multiplication phenomenon (8, 9, 10). This level of osmolality is equivalent to a specific gravity of 1.015.

Other workers have demonstrated similar urine concentration defects. H.G. Keitel et al (8) found a urine concentrating defect with maximum urine specific gravity of 1.010-1.020 in adult patients with sickle cell disease.

Omolo (10) studied paediatric patients with sickle cell disease and confirmed the urine concentrating defect. The mean maximum urine concentration was 422 $\pm$ 35 m Omol/kg and no other impairment of renal function was demonstrated.

The findings in the present study are in agreement with those of other investigators in that a universal urine concentrating defect does exist in sickle cell disease.

Urine pH and Serum Bicarbonate

Urine pH in all the patients studied was elevated the minimum recorded pH being 5.5.

Since no acid loading tests were done it was not possible to conclude from this study that acid excretion is diminished. The mean pH was 6.8 $\pm$ 1.3 for males and 6.3 $\pm$ 0.5 for females. Ping Kong and Alleyne demonstrated diminished urinary acid secretion with acid load (34). Serum bicarbonate was low in all the patients where the test was done with a range 16-24 mmol/L and a mean of 20.7 $\pm$ 2.5 mmol/L.

These observations are suggestive of a disorder of H^+ and HCO_3^- metabolism. Possibly this reflects a tubular disorder with inability to maintain (H^+) gradient or bicarbonate wasting (17). These two abnormalities (diminished urinary acid excretion and low serum bicarbonate concentration) are likely to occur along with other tubular dysfunctions, discussed above, secondary to ischaemic insults associated with the presence of intravascular sickling in renal tissue especially the hypertonic medulla (9).

CONCLUSION

1. Hyperuricaemia is a common complication of sickle cell disease. Increased erythropoiesis is the main factor responsible for the hyperuricaemia but it appears that diminished tubular uric acid secretion plays a role as well.

   Some of the painful episodes in sickle cell disease may result from the hyperuricaemia as opposed to sickling.

2. Hyposthenuria is confirmed in this study.

3. Protective role of high fetal haemoglobin level against hyperuricaemia in sickle cell disease is demonstrated.

4. Renal failure in sickle cell disease is uncommon in the young but serum creatinine level increases with age.

RECOMMENDATION

Sickle cell disease patients who show poor response to management for painful crisis should have their serum uric acid determined to exclude hyperuricaemia.

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Laboratory and Clinical data for Sicklers (Males)

M-	Age (years)	Uric acid mg%	BUN mmol/L	Creatinine µmol/L	Bicarbonate mmol/L	Urine SG	Urine pH	Hb Electrophoresis	Hb level gm/dL	WBC x10^9/L	RBC x1012/L	MCV fl	Retic Count %	Admissions (1 yr)
M1	19	18.6	11.9	97	-	1.014	6	SS	6.7	16.0	2.61	98	6	3
M2	17	10.0	2.8	73	-	1.012	6.5	SS	8.4	19.1	2.7	91	25	2
M3	18	8.0	-	-	-	1.014	8	SS	9.6	16.8	3.34	83	17	2
M4	15	8.9	3.4	72	-	-	-	SS	8.9	10.2	3.17	87	9	1
M5	20	7.5	-	-	-	-	-	SS	9.6	13.6	3.86	85	14	0
M6	18	9.0	6.1	77	22	-	-	SF	9.6	12.5	4.12	79	11	1
M7	17	8.6	4.4	79	-	-	-	SF	9.9	12.5	3.1	-	8	2
M8	18	11.0	4.7	114	-	-	-	SS	8.4	18.5	2.7	91	25	2
M9	21	9.7	0.9	62	-	-	-	SF	6.6	20.8	1.88	106	16	1
M10	22	9.7	-	-	-	-	-	SS	8.7	11.7	2.94	95	11	2
M11	30	8.5	3.9	66	-	-	-	SS	7.0	13.1	2.63	89	6	0
M12	12	6.3	2.2	38	-	-	-	SF	9.3	12.9	2.59	100	9	1
M13	18	6.22	-	67	19	-	-	SF	10.4	10.6	4.47	75	2	2
M14	12	5.6	2.7	47	21	-	-	SS	6.7	13.6	2.27	88	22	1
M15	10	5.4	2.1	63	23	-	-	SF	8.6	23.6	3.1	85	6.0	3
M16	13	5.9	2.7	44	-	-	-	SF	8.6	7.1	3.06	86	9.0	1
M17	17	6.9	3.2	-	-	-	-	SS	7.2	8.0	4.59	60	1	1
M18	19	5.0	5.1	94	-	-	-	SF	10.6	20.4	4.12	85	20	4
M19	16	3.9	3.1	45	-	-	-	SF	8.8	14.1	3.18	84	5	2
M20	35	5.8	-	83	20	-	-	SF	14.7	5.4	6.16	71	2	0
M21	42	5.3	4.0	93	17	-	-	SF	10.0	12.3	3.76	83	6	0
M22	13	4.4	1.9	57	23	-	-	SF	8.8	19.0	3.66	76	-	1
M23	19	4.5	5.2	69	-	1.015	6	SF	11.2	14.5	3.96	91	13	4
M24	17	5.8	1.6	40	-	1.016	6.5	SS	7.1	16.9	2.87	82	19	2
M25	19	3.0	2.2	60	-	1.014	9	SF	5.5	14.5	2.63	79	-	2
M26	15	5.5	3.4	78	24	1.014	6.5	SF	8.8	16.0	4.34	65	15	3
M27	14	2.5	2.8	72	17	1.012	5.5	SF	8.0	13.2	3.43	76	2.5	2
M28	13	-	-	-	-	-	-	SS	7.3	31.0	2.82	88	6.5	3
M29	15	-	4.6	97	24	1.014	9	SS	12.8	16.5	4.01	98	8	2
M30	17	-	-	-	-	1.012	6	SS	2.6	18.0	2.89	92	13.5	3

Laboratory and Clinical data for Sicklers (Females)

F-	Age (years)	Uric acid mg %	BUN mmol/L	Creatinine µmol/L	Bicarbonate mmol/L	Urine SG	Urine pH	Hb Electrophoresis	Hb level gm/dL	WBC $\times 10^9$/L	RBC $\times 10^{12}$/L	MCV fl	Retic count %	Admissions
F1	19	7.3	5.3	63	-	-	-	SF	6	18	1.67	87	15	
F2	16	7.9	2.3	52	-	-	-	SS	7.5	12.7	2.41	100	15	
F3	16	15.6	3.2	72.9	-	-	-	SS	8.2	13.1	2.61	96	9	
F4	23	23.1	6.6	123.7	-	-	-	SS	6.6	26.6	2.38	92	13	
F5	17	7.2	2.2	47	23	-	-	SS	7.2	8.6	2.50	92	13	
F6	26	7.3	-	-	-	-	-	SS	8.7	13.0	2.48	112	12	
F7	11	7.3	2.8	53	19	1.013	6	SF	5.8	16.0	2.44	85	20	
F8	22	9.4	4.9	68.9	-	1.016	6.5	SF	9.7	6.6	4.15	75	-	
F9	25	7.3	2.7	76	-	1.014	7	SF	9.9	10.8	3.3	83	1	
F10	20	7.2	1.3	60	-	1.014	7.5	SS	6.2	13.5	1.89	110	10	
F11	16	7.7	2.2	43	-	1.018	6	SS	8.0	9.7	2.75	88	14	
F12	23	9.5	2.7	74	-	1.015	6	SS	9.2	4.8	2.95	94	-	
F13	20	4.1	3.2	55	-	-	-	SS	11.2	19	4.05	84	15	
F14	17	6.2	1.1	39	20	-	-	SF	7.8	17.9	2.36	96	2.0	
F15	17	7.0	2.0	49	23	-	-	SS	8.2	8.4	3.19	74	-	
F16	20	6.33	4.1	77	16	-	-	SS	8.1	10.4	4.07	73	14	
F17	13	4.5	3.3	41	-	-	-	SF	8.7	17.4	2.84	86	3	
F18	16	3.2	3.2	52	-	-	-	SS	10.3	19.9	2.92	-	10	
F19	22	6.5	2.2	46	-	1.012	5.5	SF	10.1	12.1	3.23	87	20	
F20	21	2.7	3.2	55	-	1.016	6.5	SS	7.9	24.6	3.05	85	2.5	
F21	21	3.2	2.1	49	-	1.014	6	SF	9.6	13.3	2.94	100	11.5	
F22	27	-	-	-	-	-	-	SF	7.4	19.8	2.68	89	8	
F23	18	-	-	-	-	-	5.5	SS	8.9	10.6	3.13	89	-	
F24	15	-	-	-	-	-	-	SF	6.4	22.3	2.58	94	29	
F25	12													
F26	40													

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