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The effects of fasting in Ramadan

1. Serum uric acid and lipid concentrations

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1. The changes in serum levels of uric acid and lipids during 1 month of starvation-refeeding were measured in sixteen male volunteers.

2. Uric acid levels increased linearly with the duration of the experiment. The increase was positively correlated with the increase in serum triglycerides but not with cholesterol or phospholipids.

3. Triglycerides increased at a faster rate than uric acid implying that the increase in uric acid was secondary to that of the lipid.

4. It was concluded that the purine and lipid synthetic pathways are linked through a common small-molecular-weight effector rather than through the sharing of a common enzyme.

Throughout the holy lunar month of Ramadan, moslems are expected to abstain from food and drink daily between dawn and sunset. The incidence of renal colic or of angina pectoris increases noticeably during this Islamic month especially when the latter coincides with the hot, dry summer in the Sudan. The question whether these complaints are due to increases of risk factors predisposing to renal calculi and to coronary vascular disease consequent upon the dietary pattern during Ramadan remained to be answered.

When breaking their fast at sunset, Sudanese moslems consume large volumes of sugar-sweetened juices to quench thirst, and foods rich in carbohydrates are eaten from sunset till dawn. Nicholls & Scott (1972) reported that energy restriction leads to a decrease in the plasma level of uric acid and attributed this partly to the relative hydration state associated with weight loss. Increased carbohydrate intake, especially sucrose, is known to increase the triglyceride concentration in serum (Anderson, Grande, Matsumoto & Keys, 1963; Nestel, Carrol & Haverstein, 1970; Fry, Spector, Connor & Connor, 1973; Roberts, 1973; Sacks, Castelli, Donner & Kass, 1975).

The present study reports the changes in the serum levels of uric acid and lipids during daily starvation–refeeding over a period of 28 d in an attempt to test their relationship to the associated complaints of renal colic or angina. Correlation studies were used to test the relation between uric acid and lipid metabolism during periods of maximal dehydration and rehydration throughout the 28 d.

MATERIALS AND METHODS

The present investigation took place in the Facuty of Medicine, University of Khartoum, Sudan. Sixteen male students aged between 20 and 22 years volunteered for the study, which was to span the one month of Ramadan. All volunteers were healthy as evident from a general medical examination and none was receiving any medication.

Venous blood was collected into clean tubes and allowed to clot at room temperature.

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Table 1. *Protocol for sampling blood for uric acid and lipid levels in healthy adult male volunteers*

Day ...	0		1			4	5		6	7		11	12		13	14		18	19		20	21		25	26		27	28	
Period ...	A	B	A	B	T	B	A	T	B	A	T	B	A	T	B	A	T	B	A	T	B	A	T	B	A	T	B	A	T
Volunteer																													
1	+	+	+	+	+	.	.	.	+	+	+	.	.	.	+	+	+	.	.	.	+	+	+	.	.	.	+	+	+
2	+	+	+	+	+	.	.	.	+	+	+	.	.	.	+	+	+	.	.	.	+	+	+	.	.	.	+	+	+
3	+	+	+	+	+	.	.	.	+	+	+	+	+	+	+	+	+	.	.	.	+	+	+	.	.	.	+	+	+
4	+	+	+	+	+	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5	+	+	+	+	+	+	+	+	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
6	+	+	+	+	+	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
7	+	+	+	+	+	.	.	.	+	+	.	.	.	.	+	+	+	.	.	.	+	+	+	.	.	.	+	+	+
8	+	+	+	+	+	+	+	+	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
9	+	+	+	+	+	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
10	+	+	+	+	+	.	.	.	+	+	+	.	.	.	+	+	+	.	.	.	+	+	+	.	.	.	+	+	+
11	+	+	+	+	+	.	.	.	+	+	+	.	.	.	+	+	+	.	.	.	+	+	+	.	.	.	+	+	+
12	+	+	+	+	+	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
13	.	.	.	.	.	+	+	+	.	.	.	+	+	+	.	.	.	+	+	+	.	.	.	+	+	+	.	.	.
14	.	.	.	.	.	+	+	+	.	.	.	+	+	+	.	.	.	+	+	+	.	.	.	+	+	+	.	.	.
15	.	.	.	.	.	+	+	+	.	.	.	+	+	+	.	.	.	+	+	+	.	.	.	+	+	+	.	.	.
16	.	.	.	.	.	+	+	+	.	.	.	+	+	+	.	.	.	+	+	+	.	.	.	+	+	+	.	.	.

A, 18.00 hours; B, 06.00 hours; T, 19.00 hours.

Table 2. *Levels of serum uric acid and lipids (mmol/l) during period A (sampled at 18.00 hours) for healthy adult male volunteers during fasting–refeeding in Ramadan*†

(Mean values with their standard errors; values were obtained by transforming the corresponding mean log. The number of observations for each measurement is given in Table 1).

Day	Uric acid		Triglycerides		Cholesterol		Phospholipids		Total lipids	
no.	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
0	0·255	0·014	0·856	0·098	4·22	0·097	1·55	0·059	7·99	0·396
1	0·254	0·009	0·298	0·086***	4·45	0·087	1·52	0·121	8·36	0·255
5	0·268	0·003	0·384	0·034***	3·47	0·188***	2·35	0·059***	9·10	0·440
7	0·238	0·019	0·496	0·053**	4·14	0·334	2·22	0·150***	8·62	0·847
12	0·273	0·014	0·645	0·106	3·37	0·255**	2·49	0·144***	8·94	0·255
14	0·243	0·026	0·670	0·098	3·91	0·073*	1·77	0·089	9·31	0·424*
19	0·309	0·021*	0·707	0·210	4·56	0·410	2·34	0·214***	9·29	0·231*
21	0·311	0·013**	0·918	0·067	3·89	0·205	1·89	0·184	9·28	0·544
26	0·323	0·017**	0·980	0·149	4·92	0·166***	2·10	0·039***	9·44	0·871
28	0·311	0·014**	1·091	0·263	3·83	0·121*	1·88	0·158	9·77	0·910

Mean values statistically different from those for day 0: * $P < 0·050$, ** $P < 0·010$, *** $P < 0·005$.
† For details, see p. 575 and Table 1.

Table 3. *Levels of serum uric acid and lipids (mmol/l) during period B (sampled at 06.00 hours) for healthy adult male volunteers during fasting–refeeding in Ramadan*†

(Mean values with their standard errors; values were obtained by transforming the corresponding mean log. The number of observations for each measurement is given in Table 1)

Day	Uric acid		Triglycerides		Cholesterol		Phospholipids		Total lipids	
no.	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
0	0·255	0·014	0·856	0·098	4·22	0·097	1·55	0·059	7·99	0·396
1	0·209	0·008*	0·372	0·066**	4·07	0·109	0·09	0·099***	8·18	0·344
4	0·238	0·010	0·446	0·065***	3·83	0·247	2·58	0·151***	6·86	0·474
6	0·236	0·025	0·980	0·073	3·26	0·192***	2·35	0·242***	8·34	0·385
11	0·232	0·010	0·781	0·214	3·94	0·266	1·91	0·115*	8·07	0·359
13	0·228	0·027	1·166	0·158	3·60	0·106***	1·55	0·118	10·08	1·182
18	0·296	0·009*	1·128	0·063*	4·38	0·392	2·35	0·120***	8·82	1·420
20	0·257	0·015	1·128	0·282	4·04	0·190	3·00	0·429***	10·86	0·968*
25	0·292	0·021	1·190	0·236	4·01	0·318	1·57	0·262	9·29	0·768
27	0·263	0·015	1·414	0·290	3·83	0·118*	1·69	0·149	8·38	0·720

Mean values statistically different from those for day 0: * $P < 0·050$, ** $P < 0·010$, *** $P < 0·005$.
† For details, see p. 575 and Table 1.

When the clot retracted, serum was transferred to plastic tubes and stored at −18° until subsequent analysis. Each student served as his own control by comparing his Ramadan with his pre-Ramadan serum levels of uric acid and lipids. Sampling was performed at 06.00 hours (period B), 18.00 hours, just before breaking the fast (period A), and at 19.00 hours, after breaking the fast (period T) according to the scheme shown in Table 1.

The serum uric acid levels were determined by the method of Caraway (1955). Total cholesterol was determined by the method of Levine & Zak (1964). Phospholipids were determined by the method of Bartlett (1959). The triglycerides were determined after extraction and transesterification (Royer & Ko, 1969) by the Hantzch condensation reaction using the method of Soloni (1971). Total lipids were determined colorimetrically by the sulphophosphovanillic reaction (Zollner & Kirsch, 1962). Serum 3-hydroxybutyrate was measured by the method of Williamson, Mellanby & Krebs (1962).

Table 4. *Levels of serum uric acid and lipids (mmol/l) during period T (sampled at 19.00 hours) for healthy adult male volunteers during fasting-refeeding in Ramadan*†

(Mean values with their standard errors; values were obtained by transforming the corresponding mean log. The number of observations for each measurement is given in Table 1)

Day no.	Uric acid		Triglycerides		Cholesterol		Phospholipids		Total lipids	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
0	0·255	0·014	0·856	0·098	4·22	0·097	1·55	0·059	7·99	0·396
1	0·279	0·010	0·285	0·077***	4·43	0·113	1·45	0·100	8·75	0·320
5	0·290	0·009*	0·645	0·084	2·82	0·239***	2·26	0·384	7·88	0·710
7	0·294	0·024	0·818	0·153	4·12	0·296	2·18	0·311	8·01	0·440
12	0·315	0·010***	0·868	0·238	3·34	0·152***	2·32	0·342*	9·29	0·272*
14	0·292	0·036	1·054	0·137	4·12	0·210	1·89	0·131*	7·96	0·448
19	0·330	0·023*	0·942	0·235	4·53	0·452	2·84	0·301***	8·73	1·064
21	0·323	0·018**	1·190	0·026***	3·65	0·094***	1·46	0·237	7·88	0·176
26	0·341	0·017***	0·980	0·145	4·30	0·304	1·98	0·163*	11·25	1·933
28	0·332	0·020	1·091	0·208	4·12	0·150	2·34	0·277	7·55	0·289

Mean values statistically different from those for day 0: * $P < 0·050$, ** $P < 0·010$, *** $P < 0·005$.
† For details, see p. 575 and Table 1.

Table 5. *Correlations between the mean logs of serum uric acid and lipid levels and the duration of fasting–refeeding for healthy adult male volunteers during Ramadan*†

Period	Uric acid	Triglycerides	Cholesterol	Phospholipids	Total lipids
A	0·8177**	0·9725**	0·2497	0·0741	0·8826**
B	0·7923**	0·8449**	0·3172	0·1680	0·5238
C	0·9185**	0·7700*	0·2865	0·1278	0·1978

A, 18.00 hours; B, 06.00 hours; T, 19.00 hours.
* $P < 0·050$, ** $P < 0·010$.
† For details, see p. 576 and Table 1.

Statistical analysis

All results were analysed for significant difference from the values obtained on day 0 of the experiment by Student's t test. Values of $P > 0·05$ were considered not significant.

RESULTS

The small size of the groups studied precluded the investigation of the type of distribution of serum lipids and of uric acid. Berkowitz (1966); Gunther, Knapp & Siller (1968) and Mielants, Veys & De Weerdt (1973*a*) reported that the distribution of serum uric acid and lipids is of the log-normal type.

The serum levels of uric acid, triglycerides, cholesterol, phospholipids and of total lipids are shown in Tables 2–4 for the sampling periods A, B and T respectively; the tabulated means were derived by transforming their corresponding log values (Snedecor & Cochran, 1974).

Uric acid

There was no change in serum uric acid level in period A of the first 2 weeks of fasting–refeeding (Table 2). During the subsequent 2 weeks the uric acid level increased significantly ($P < 0·05$–$< 0·01$) by 21–27% compared with the previous value for period A. On the other hand, during period B the serum uric acid level initially decreased significantly ($P < 0·05$) by 18% and subsequently increased gradually towards the prefasting level

Table 6. *Correlations between serum uric acid and lipid levels for healthy adult male volunteers during Ramadan*†

Period ...	A	B	C
Uric acid *v.* triglycerides	+0·724*	+0·658	+0·690*
Uric acid *v.* total lipids	+0·694*	+0·278	+0·390
Total lipids *v.* triglycerides	+0·856**	+0·637	−0·075

A, 18.00 hours; B, 06.00 hours; T, 19.00 hours.
* $P < 0{\cdot}050$, ** $P < 0{\cdot}010$.
† For details, see p. 577 and Table 1.

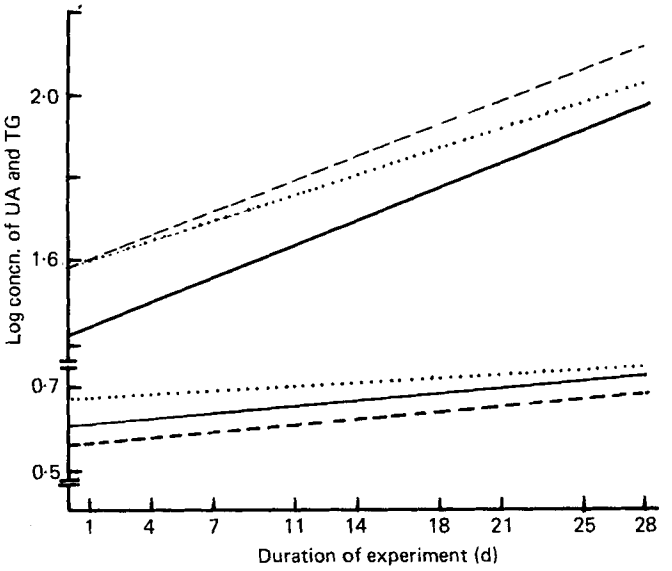

Fig. 1. Regression lines for log concentrations of serum uric acid (UA) and triglycerides (TG) *v.* duration of experiment (d) for healthy adult male volunteers during fasting–refeeding in Ramadan (for details, see p. 577 and Table 1). ——, Period A, 18.00 hours; – – –, period B, 06.00 hours; ·····, period T, 19.00 hours. Correlation coefficients: TG: A 0·0195; B, 0·0185, T 0·0155; UA: A 0·0044, B 0·0043, T 0·0031.

(Table 3). In contrast, there was a gradual significant increase to a maximum of 34% during period T (Table 4). The increases in the serum levels of uric acid correlate positively with the duration of the experiment (Table 5), and with the triglycerides (Table 6).

Triglycerides

In all three periods, after an initially significant decrease in the level of serum triglycerides, there was a gradual increase to levels higher than the mean prefasting level. However, the increase was not statistically significant except for period B of the 27th day. The lack of statistical significance can be attributed to the large range of levels encountered and the small size of the groups. The increase in the level of serum triglycerides correlates positively with the duration of the experiment (Fig. 1) and with the total lipids during period A (Table 6).

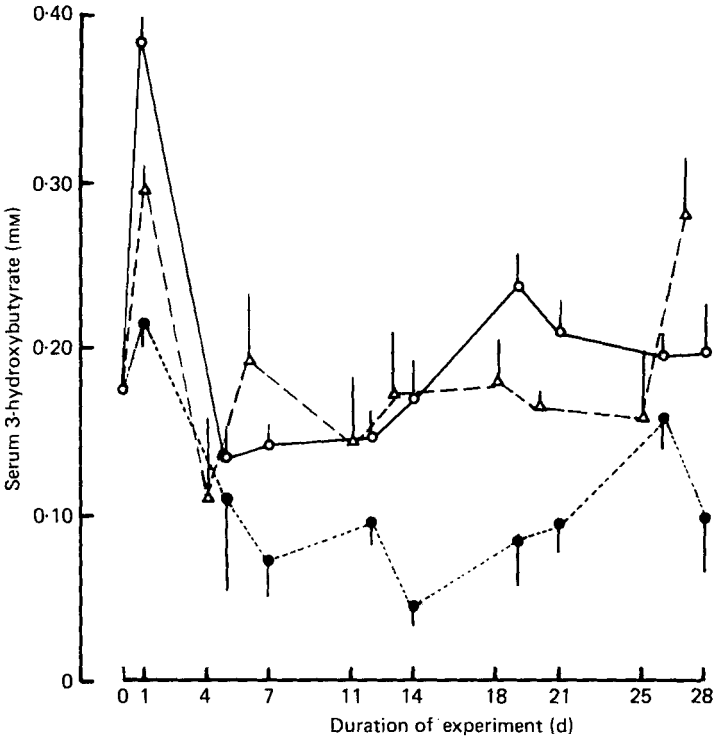

Fig. 2. The changes in the serum concentration of 3-hydroxybutyrate (mM) during fasting–refeeding in Ramadan for healthy adult male volunteers (for details, see p. 578 and Table 1). ——, period A, 18.00 hours; – – –, period B, 06.00 hours; ·····, period T, 19.00 hours. Vertical bars represent the standard errors of the means.

Cholesterol

During period A there was an average decrease of 4% in the level of serum cholesterol. In periods B and T the decrease was 8 and 7% respectively. No particular pattern for the decrease was noted in any of the three periods.

Phospholipids

The serum level of phospholipids increased significantly by 30–34% during the three periods, but like cholesterol there was no particular pattern for the increase. It was noted that the level of phospholipids was approximately 50% of the level found in the controls by Mielants *et al.* (1973*a*), but was in keeping with values for normal subjects studied in this laboratory.

Total lipids

The level of serum total lipids showed a tendency to increase throughout the duration of the experiment. The largest increase was for period A, 14%, while in periods B and T values increased by 10 and 7% respectively. The increase during period A was statistically significant ($P < 0.05$).

3-*Hydroxybutyrate*

The level of serum 3-hydroxybutyrate increased during the first day of the experiment and subsequently returned to prefasting level for periods A and B (Fig. 2). However, in period T, after an initial increase, the level of serum 3-hydroxybutyrate decreased below the prefasting level.

DISCUSSION

Weight loss through restriction of energy intake was reported to be associated with a significant decrease in serum uric acid levels which was not accompanied by an increased excretion of urate in the urine (Nicholls & Scott, 1972). These authors proposed that their findings could be partly due to the relative hydration associated with weight loss and to a decreased rate of purine synthesis when energy intake is restricted. In support of those findings, Semple, Henderson & Boyle (1974) demonstrated that fasting decreased the rate of purine synthesis *de novo* by the possible feedback inhibition of the enzyme formyl glycinamide ribonucleotide amidotransferase (*EC* 6.3.5.3) by nucleotides derived from the catabolism of RNA (Wyngaarden & Ashton, 1959; Munro, 1968) consequent on fasting.

The present study revealed that intermittent fasting and refeeding is associated with an increase in the serum level of uric acid which correlates positively with the duration of the experiment for all three periods, A, B and T (Table 5). In contrast with the low-carbohydrate diet used by Nicholls & Scott (1972) to decrease body-weight, the diet consumed by the subjects in the present study was rich in carbohydrates, mainly sucrose, as a sweetener for the massive amounts of juices consumed at sunset to break the fast. Since the highest levels of serum uric acid were observed in period T, the increase in serum uric acid level cannot be attributed to dehydration. This increase in the level of serum uric acid may have either been due to increased *de novo* synthesis of purines concomittant on refeeding, or from increased breakdown of RNA in tissues during fasting (Munro, Naismith & Wikramanayake, 1953). The increasing concentration of serum uric acid coupled to the oliguria from dehydration (K. Y. Mustafa, N. A. Mahmoud, K. A. Gumaa, & A. M. A. Gader unpublished results) may predispose to the crystallization of the acid within the urinary tract to produce dysuria and the attacks of renal colic often encountered during this month of fasting. Scott, McCallum & Holloway (1964) showed that starvation ketosis decreases the rate of uric acid excretion. In the present study, except for a small increase in serum 3-hydroxybutyrate level in the first day of fasting (Fig. 2), there was no ketosis to explain the observed increase in the level of serum uric acid.

The kinetics of serum triglycerides revealed that after the initial significant decrease in its concentration the increase was linearly correlated with the duration of the experiment (Table 5). This would be expected in view of the increased carbohydrate intake, mainly in the form of sucrose, throughout the duration of the experiment (Anderson *et al.* 1963; Nestel *et al.* 1970).

The increase in the serum concentration of triglycerides correlated significantly ($P < 0{\cdot}001$) with the increase in serum uric acid concentration ($r + 0{\cdot}91$, $+0{\cdot}89$ and $+0{\cdot}90$ for periods A, B and T respectively). Although this correlation is in agreement with the findings of many workers, the mechanism responsible for this relationship is still not clear. Mielants, Veys & De Weerdt (1973*b*) postulated that lipid and purine metabolism are genetically linked through a hypothetical enzyme which is defective in gout. In the present study the slopes of the regression lines for uric acid and triglycerides *v.* duration of experiment (Fig. 1) differed widely for all three periods of the experiment. The greater slopes for the triglyceride correlations with the duration of the experiment relative to those for uric acid implied that the change in purine metabolism may be consequent upon the change in lipid metabolism. The link between the two pathways is more likely to be a small-molecular-weight effector, the redox state or the energy charge than a common enzyme. In this context, it is interesting to note that Jakovcic & Sorensen (1967) postulated that in Type I glycogen-storage disease, the deficiency of the enzyme glucose-6-phosphatase (*EC* 3.1.3.9) leads to an intracellular accumulation of glucose-6-phosphate which acts as a substrate for *de novo* purine synthesis via the pentose phosphate pathway, and the reducing equivalents generated, i.e. $NADPH_2$,

promote lipogenesis. The observation that there is a simultaneous decrease of both the triglycerides and uric acid in the serum of gouty patients treated with lipid-lowering drugs (Berkowitz, 1965), and a decrease in serum triglycerides in gouty patients treated with uric acid-lowering drugs (Bluestone, Lewis & Mervart, 1971) can be attributed to feedback control of one pathway of synthesis on the other.

Gout was reported to be associated with hypercholesterolaemia (Becker, 1960), but Gibson & Grahame (1974) could not confirm this association. In the present study with normal subjects, no correlation was observed between the increasing serum uric acid level and cholesterol, in agreement with observations on gouty patients (Mielants *et al.* 1973*b*). Similarly there was no correlation between levels of phospholipids and uric acid in the present study. On the other hand, uric acid levels were positively correlated with levels of total lipids, the correlation being of border-line significance. This may be in part due to the correlations already observed between the levels of serum total lipids and one of its components, the triglycerides, which as noted previously were closely correlated with levels of serum uric acid (Table 6).

The evidence linking hyperuricaemia with ischaemic heart disease (Dawber, Moore & Mann, 1957; Hall, 1965) has been attributed to the association of hyperuricaemia with hypertriglyceridaemia, the latter being associated with coronary vascular disease (Charlson & Bottiger, 1972). The increase in serum triglycerides during fasting–refeeding with a high-carbohydrate diet is not necessarily a risk factor predisposing to coronary heart disease since it was recorded that a slow adaptation to the high-carbohydrate diet occurs and leads to low serum triglycerides levels (Antonis & Bersohn, 1960, 1961).

It is concluded that prolonged fasting and refeeding leads to increases of both serum uric acid and triglycerides. The association between hypertriglyceridaemia and hyperuricaemia is unlikely to be through a common enzyme (Mielants *et al.* 1973*b*), but rather through feedback interaction between the pathways of metabolism mediated through small-molecular-weight effectors or similar modulators.

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