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The fasting test in paediatrics: application to the diagnosis of pathological hypo- and hyperketotic states

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Abstract. A 24-h fasting test was performed in 48 control children, in 9 hypoketotic patients with inherited defects of fatty acid oxidation and in 2 hyperketotic patients with inherited defects of ketolysis. The control group was then divided into three age groups on the basis of different adaptation to fasting. Concentrations of blood glucose, lactate, free fatty acids (FFA), 3-hydroxybutyrate, acetoacetate and carnitine were measured after 15 h, 20 h and 24 h of fasting. Significant negative correlations were found in the control group between plasma total ketone bodies (KB) and plasma glucose ($P < 0.001$), plasma carnitine ($P < 0.005$) and the amplitude of glycaemic response to glucagon at the end of the fast ($P < 0.01$). FFA/KB ratio and the product of final fasting values of glucose and ketones were useful to differentiate between hypoketotic or hyperketotic patients and normal subjects. In children with a suspected or definite hyperketotic or hypoketotic disorder, a fasting test must only be performed in healthy patients, in good nutritional condition with non-diagnostic basal biochemical investigations. Carefully supervised fasting should be continued sufficiently to allow ketogenesis and ketolysis to become activated.

Key words: Fasting test – Fatty acid oxidation – Hypoketosis – Hyperketosis

Introduction

During fasting, a complex interaction of hormonal and metabolic mechanisms produces significant variations in the blood concentration of hormones and metabolic components. Haymond et al. [11] established differences in circulating substrates among fasting men, women and children, and others have studied the child's adaptation to fasting [3, 4, 9, 12, 13, 17, 22] but little is known about fasting tests in the study of pathological states [17, 20]. The interpretation of fasting tests in the paediatric population is difficult because of the variability of blood parameters at a given time during the fast, even in normal subjects. Differences in nutritional state and age render it difficult to establish control values and the definition of pathological hypo- and hyperketosis using absolute values will probably be misleading.

In the last decade, pathological hypoketosis in inherited defects of fatty acid oxidation has been extensively studied [2, 7, 10, 19, 21] but little is known about hyperketotic states due to inherited defects of ketolysis. The present work was undertaken to study variations in blood parameters during fasting in control subjects and in genetically determined hypo- and hyperketotic states in paediatrics in order to identify children with defects of fatty acid oxidation and of ketolysis using the most discriminatory parameters with the shortest period of fasting.

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Abbreviations: FFA = free fatty acids; KB = ketone bodies

Materials and methods

Subjects

Our control group consisted of 48 children and adolescents of both sexes (21 girls and 27 boys). They were retrospectively selected from patients referred for metabolic evaluation of suspected hypoglycaemia, cardiomyopathy or myopathy after a complete metabolic evaluation failed to detect any metabolic or endocrine abnormality.

Previous studies had demonstrated different responses to fasting between children younger than 7–8 years, and older children [12, 13]. On this basis, we divided our control population into group C ($n = 9$), aged 7–15 years, and group B ($n = 27$) aged 1–7 years. A third group, A, consisted of infants aged 1–12 months ($n = 12$) whose nutrient intake differed either in quality or frequency with respect to children from groups B and C. For some comparisons, six normal subjects, aged 8–13 years were included.

The hypoketotic group was composed of nine subjects referred for evaluation of hypoketotic hypoglycaemia. These patients were only fasted when not acutely ill and in the absence of a massive abnormal organic acid excretion; their ages ranged from 9 months to

Table 1. Blood values at the end of the fast in hypo- and hyperketotic patients

	Hypoketotic patients									Hyperketotic patients	
	Case									Case	
	1 [2, 5]	2 [5]	3 [16]	4	5	6	7	8	9	10 [18]	11 [18]
Diagnosis	CPT	CPT	SCD	MCAD	MCAD	MCAD	MAD.M	LCFA	LCFA	SCT	SCT
Age	9 months	1 year 7 months	9 years	3 years	2 years 2 months	1 year 9 months	2 years 8 months	15 years 6 months	6 years	2 years	1 year
Time (h)	20	20	24	24	17	24	18	32	24	24	20
Glucose (mmol/l)	2.2	1.5	4.2	4.2	2.7	3.1	2.3	2.6	3.7	4.4	3
Lactate (mmol/l)	1.1	–	0.2	3.4	–	2.7	1	10.3	3.8	1.1	1.3
Free fatty acids (mmol/l)	2.1	4	1.1	3.6	4.6	3.9	3.8	3.6	2.3	1.35	3
Ketone bodies (mmol/l)	0.3	0.1	0.3	1.4	0.8	0.5	0.3	0.2	0.3	4.8	10.3
3-OH-B (mmol/l)	< 0.1	< 0.1	0.2	0.9	0.6	0.3	0.2	< 0.1	0.1	3.5	6
FFA/KB	7	40	3.7	2.6	5.7	7.8	12.7	18	7.7	0.3	0.3
FFA/3-OH-B	> 20	> 40	5.5	4	7.7	13	19	> 36	23	0.4	0.5
3-OH-B/AcAc	< 1	< 1	2	1.5	3	1.5	2	< 1	0.5	2.7	1.4
Free carnitine (μmol/l)	–	–	1.1	13	18	18	19	38	–	25	–
KB × glucose	0.7	0.1	1.3	5.9	2.2	1.5	0.7	0.5	1.1	21.1	30.9

3-OH-B = 3-hydroxybutyrate; AcAc = acetoacetate
CPT = carnitine palmitoyl transferase deficiency; SCD = idiopathic systemic carnitine deficiency; MCAD = medium chain acyl CoA dehydrogenase deficiency; MAD.M = multiple acyl CoA dehydrogenase deficiency mild form; SCT = succinyl CoA transferase deficiency; LCFA = long-chain fatty acid oxidation defect in fibroblasts

16 years. Patients 1–7 were subsequently diagnosed as having congenital defects of fatty acid oxidation (Table 1). Patients 1, 2, 3 have been previously reported [2, 5, 16]. Patients 8 and 9 had an abnormal long chain fatty acid oxidation in cultured fibroblasts, but the specific enzymatic deficit is still unknown.

The hyperketotic group was formed by two patients aged 1 and 2 years, respectively, who were studied because of ketoacidotic episodes. Both were deficient in fibroblast succinyl-CoA transferase activity, with abnormal KB utilisation [15, 18].

Test procedures

In all cases, informed parental consent was obtained. The subjects were in good health and were studied after 3 days on a normal diet. None had received supplements of carnitine for at least 15 days before the test. The last meal was taken at 6 pm and a 24-h fast was then begun with no limitation in water intake. The test was interrupted if blood glucose fell below 2 mmol/l (36 mg/dl), or if prolonged drowsiness or acidosis (bicarbonate level < 15 mmol/l) developed.

Blood was sampled after the 6 pm meal (0 h), and then after 15 h, 20 h, and 24 hours of fasting. Three (group C) control children and one hypoketotic patient, older than 10 years, were fasted for a 30-h period. Blood samples at 0, 15, 20, 24 and 30 h were collected from an indwelling needle maintained with saline. A 500 μl aliquot was promptly mixed with 1 ml of perchloric acid 1 mol/l for assay of glucose, lactate, acetoacetate and 3-hydroxybutyrate. Another 1.5 ml aliquot was collected in a heparin-containing tube, centrifuged at 4°C and the supernatant stored at −20°C for assay of free fatty acids (FFA) and carnitine. Determinations of glucose, lactate, acetoacetate, 3-hydroxybutyrate and FFA were performed by standard enzymatic methods [8]. Plasma carnitine was determined by radioisotopic assay [14]. The statistical differences between data at specific times within each control group were analysed by a paired-Student's t test, and differences between groups at a specific time by a non-paired Student's t test. All data are expressed as mean, 10th and 90th percentiles.

Results

Control subjects

Concentrations of blood parameters in the three control groups during a 24-h fasting test are presented in Table 2. As previously recognized [3, 11, 12], concentrations of many circulating compounds changed during fasting as a result of metabolic and hormonal adaptation. Comparing the 15-h and 24-h fasting values showed that plasma glucose, free carnitine concentrations and the FFA/KB ratio significantly decreased ($0.001 < P < 0.01$) while ketonaemia, the 3-hydroxybutyrate/acetoacetate ratio and FFA concentrations significantly increased ($0.001 < P < 0.05$). Final lactate concentrations were not statistically different from the 15-h values.

Significant differences in the measured blood parameters existed between groups B and C (Table 2). Children from 1 to 7 years had higher values of KB (Fig. 1) ($0.001 < P < 0.02$), 3-hydroxybutyrate/acetoacetate ratio, FFA and lactate concentrations ($0.02 < P < 0.05$), and lower values of glucose concentration and FFA/KB ratio (Fig. 2) ($0.001 < P < 0.02$) than older children. Intermediate substrate levels were found in the fasted group A, especially for ketones and FFA, although these differences were not significant. Fasting plasma KB levels were

Table 2. Control groups blood values during fasting

	Age group								
	A = 1–12 months (n = 12)			B = 1–7 years (n = 27)			C = 7–15 years (n = 9)		
	Time of fasting (h)			Time of fasting (h)			Time of fasting (h)		
	15	20	24	15	20	24	15	20	24
Glucose (mmol/l)	3.9–5.3 (4.7)	3.5–4.6 (3.9)	2.7–4.5 (3.6)	3.5–4.8 (4.4)	2.8–4.3 (3.5)	2.8–3.8 (3.3)	4.4–4.9 (4.7)	3.8–4.9 (4.3)	3.0–4.3 (3.8)
Lactate (mmol/l)	1.1–2.3 (1.8)	0.85–1.8 (1.3)	0.8–2.0 (1.4)	0.8–1.5 (1.0)	0.5–1.7 (1.1)	0.7–1.6 (1.2)	0.6–0.9 (0.9)	0.6–0.9 (0.7)	0.4–0.9 (0.7)
Free fatty acids (mmol/l)	0.5–1.6 (1.0)	0.6–1.3 (0.9)	1.1–1.6 (1.3)	0.6–1.5 (1.1)	0.9–2.6 (1.7)	1.1–2.8 (2.1)	0.2–1.1 (0.7)	0.6–1.3 (1.0)	1.0–1.8 (1.4)
Ketone bodies (mmol/l)	0.1–1.5 (0.4)	0.6–3.2 (1.6)	1.5–3.9 (2.7)	0.15–2.0 (0.8)	1.2–3.7 (2.4)	2.2–5.8 (3.5)	< 0.1–0.5 (0.2)	0.1–1.3 (0.6)	0.7–3.7 (1.3)
3-OH-B (mmol/l)	0.1–1.0 (0.4)	0.5–2.3 (1.1)	1.1–2.8 (1.8)	< 0.1–0.9 (0.6)	0.8–2.6 (1.8)	1.7–3.2 (2.5)	< 0.1–0.3 (0.1)	< 0.1–0.8 (0.4)	0.5–1.3 (0.9)
FFA/KB	0.6–5.2 (2.3)	0.3–1.4 (0.8)	0.3–0.7 (0.5)	0.7–4.0 (2.2)	0.4–1.5 (0.8)	0.4–0.9 (0.6)	1.9–10 (5.4)	0.7–4.6 (2.5)	0.5–2 (1.5)
FFA/3-OH-B	0.9–4.3 (3.5)	0.5–1.9 (1.1)	0.6–0.9 (0.7)	0.9–12.7 (5.4)	0.5–2.0 (1.1)	0.5–1.2 (0.8)	3.7–29 (13.1)	1.7–8.5 (5.8)	1.2–2.4 (2.3)
3-OH-B/AcAc	1.4–2.6 (2.2)	1.9–3.1 (2.5)	2.5–2.7 (2.6)	1.2–3.2 (2.4)	2.7–3.3 (2.8)	2.7–3.5 (2.9)	0.5–2.3 (1.6)	1.3–2.8 (2.0)	1.6–3.1 (2.6)
Free carnitine (μmol/l)	15–39 (27)	15–26 (19)	13–23 (17)	18–37 (28)	16–27 (21)	11.5–18 (15)	31–43 (37)	24–46 (34)	18–30 (25)
Glucose × KB	–	3–11 (6.1)	7.6–11.5 (9.5)	–	4.8–11.5 (8.2)	8.3–13 (11.3)	0.2–1.6 (0.9)	0.4–4.6 (2.7)	2.4–7.3 (4.7)

3-OH-B = 3-hydroxybutyrate; AcAc = acetoacetate
Results are expressed as 10–90 percentiles (mean)

negatively correlated with glucose ($P < 0.001$) (Fig. 3) and free carnitine ($P < 0.005$).

Hypoketotic subjects

Blood parameters at the end of the fast are presented in Table 1. The fast was of variable length according to age, clinical tolerance and glycaemic control. Four tests were interrupted because of hypoglycaemia (patients 1, 2, 5 and 7). Despite normal blood glucose levels, patients 6 and 8 became drowsy. As a group, the hypoketotic patients had lower blood glucose levels (2.8 ± 0.98) than controls at the time when fasting was interrupted. Blood lactate concentrations were variable, but many patients developed a hyperlactacidaemia during the fast. The mean KB value was 0.5 mmol/l by the end of the fast, one-third of the mean value for the entire control group. Moreover, when individual values were separated by time of fasting and age, all but one value was lower than 10th percentile of control levels (Fig. 1). Before the 20th hour of fasting, one of the three hypoketotic patients aged from 1 to 7 years did not differ from controls, suggesting that at least for this age group, fasting must be extended for at least 20 h. For children older than 7 years, 24-h fasting may be not sufficient. A useful parameter for the evaluation of patients is the FFA/KB ratio, which was never lower than 2.6 at the end of the fast (Fig. 2) as well as the FFA/3-hydroxybutyrate ratio, which was never lower than 4. It is puzzling to note that in two patients this ratio fell as the fast progressed which was clearly unexpected. This fact cannot be easily explained but may account for the delay in the initiation of ketogenesis in patients affected with only partial enzymatic deficiency as described in some previous papers [1, 6]. Another useful parameter is given by plotting KB values against simultaneous plasma glucose levels (Fig. 3). When blood glucose was under 3 mmol/l, KB values were always over 1.8 mmol/l in controls and always under 0.8 mmol/l in patients affected with a fatty acid oxidation defect, irrespective of the age and the duration of fast. Apart from patient 3 (primary carnitine deficiency), plasma free carnitine levels were approximately or over 10th percentile of the control range.

Hyperketotic subjects

Fasting parameters in this group are shown in Table 1. The relevant features are the high levels of ketonaemia relative to blood glucose and hours of fasting, especially in patient 11 whose test had to be interrupted because of ketoacidosis. The FFA/KB ratio was extremely low

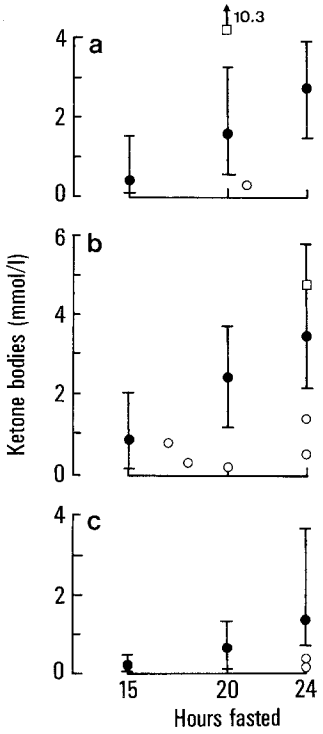

Fig. 1. Plasma ketone body concentrations during fasting according to the age. **a** 1 month–1 year; **b** 1–7 years; **c** 7–15 years. Control values are expressed as a mean (●), 10th and 90th percentiles. Only one value obtained at the end of the fast is shown for each patient (○, fatty acid oxidation defect, □, ketolysis defect)

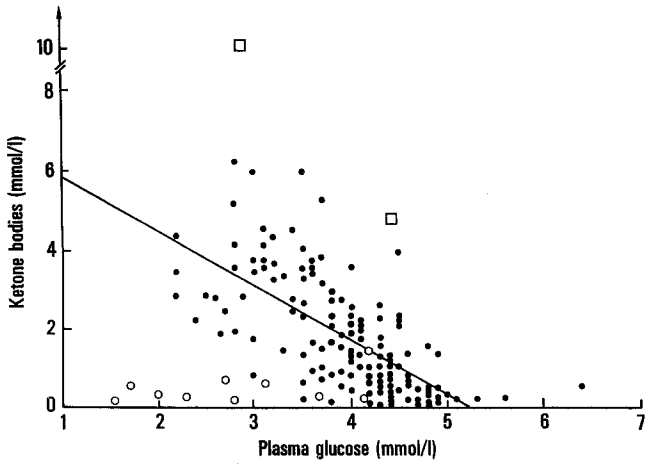

Fig. 3. Correlation between blood ketone bodies and plasma glucose during fasting. Controls (●) and patients (○, fatty acid oxidation defect, □, ketolysis defect) have been pooled irrespective of the age and the duration of fasting. Only the value obtained at the end of the fast is shown for each patient. Regression line given as slope and intercept (± confident limit). *y*, represents blood ketone bodies (mmol/l); *x*, represents plasma glucose (mmol/l); *n* number of aparied couples; *r*, coefficient of correlation. $n = 134$; $r = 0.69$; $y = -1.38 \times (\pm 0.25) + 7.2\ (\pm 1)$

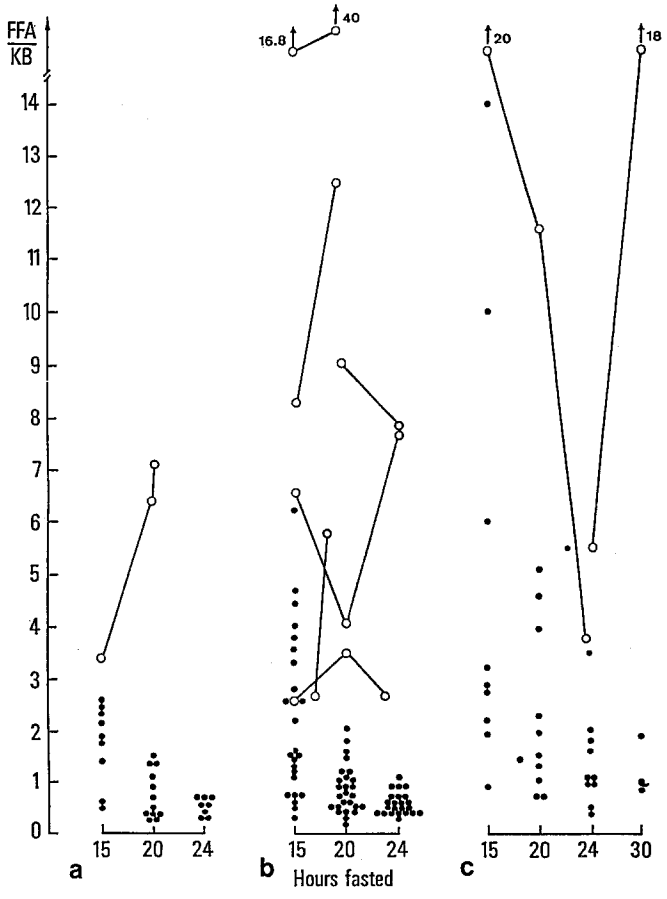

Fig. 2a–c. Free fatty acid/ketone body ratios (FFA/KB) during fasting according to the age (●, controls; ○, hypoketotic patients)

in both cases during the entire fasting period: case 11 showed a value close to 1 in the post-prandial state.

Discussion

In the last decade, an increasing number of inherited defects of ketogenesis [2, 7, 10, 19, 21] and ketolysis [18] have been described. Many of these conditions show only intermittent clinical and biochemical abnormalities. Decompensation of such disorders can be triggered by catabolic states produced by febrile illnesses, vomiting or prolonged fasts. A controlled fasting test was considered the first approach to the study of these disorders. Recently, other biochemical investigations have replaced fasting to characterize hypo- and hyperketotic states. Measurement of fatty acid derived metabolites in urine, of plasma and urinary carnitine levels, of urinary acyl carnitine esters, and functional and enzymatic investigations on cultured cells in vitro are useful, accurate, and non-dangerous approaches to diagnosis. However, these techniques are not universally available, and a detailed interpretation of their results requires experienced professionals possessing complete clinical and biochemical information. Therefore, in children at risk for defects in ketogenesis or ketolysis, the fasting test remains a useful tool.

Accurate interpretation of fasting parameters in pathological states requires the knowledge of age-dependant hormonal and metabolic changes during starvation in normal individuals. Our choice of three control age groups was based on the findings that children older than 7 years (group C) have a better glucose homeostasis and later onset of fatty acid mobilization as a consequence of more important glycogen and glyconeogenic substrate

stores [12, 13]. By contrast, younger children show an early decreased glucose availability with an active ketogenesis after 15 h of fasting. Of group B, 70% had FFA/KB ratios lower than 1 between 15 h and 20 h of fasting. The intermediate blood fasting substrate levels found in group A probably result from larger glycogen reserves derived from frequent and high caloric feeding in infants. Even when age and time of fasting are controlled, there is a wide range of normal values, especially for ketones, causing difficulties in distinguishing hypo- and hyperketotic states using individual pathological values. This is the case for one patient in group B (1–7 years) (Fig. 1), in whom the last fasting value of ketonaemia was superior to the 10th percentile of controls. For the diagnosis of a hypoketotic state, if a cutoff value of 1.5 mmol/l is chosen (sensitivity 100%), specificity of the test is respectively 80% and 100% at 20 h and 24 h of fast in patients aged less than 7 years. In children over 7 years, specificity markedly decreases, even when fasting is extended for 24 h or 30 h. However, when we plotted ketone values against simultaneous glucose levels (Fig. 3), most patients could be distinguished from controls. A few patients still remain in the control range, due to the variability in control values. When blood glucose is under 3 mmol/l, KB values are always over 1.8 mmol/l in controls and always under 0.8 mmol/l in our patients irrespective of the age and the fasting time. According to these values, KB levels are clearly discriminative between patients with a fatty acid oxidation defect and controls when glycaemia is under 3 mmol/l (Fig. 3) with 100% specificity and sensitivity. However, this test is uninformative if the blood sugar remains over 3 mmol/l at the end of the fast. It is therefore justified to continue the fast for a sufficient time with careful monitoring.

Plasma free carnitine decreases during fasting [9] as a result of acylcarnitine formation, which, in normal subjects, mainly consists of acetylcarnitine. We found a weak negative correlation between KB and free carnitine in controls (data not shown). Hypoketotic patients had lower levels of plasma free carnitine than controls, although their KB levels remained low.

3-Hydroxybutyrate/acetoacetate ratio was usually low by the end of the fast in hypoketotic patients but did not appear to be very sensitive. Interesting information can be obtained from the FFA/KB ratio (Fig. 2). This ratio in hypoketotic patients was >2.5 at the end of the fast, significantly different from controls. From Fig. 2, it appears that FFA/KB does not discriminate between patients and controls, when duration of fasting is restricted to 15 h. In patients under 7 years, a 20-h fast seems to be discriminant when a cut off value of 2.2 is taken for the FFA/KB ratio, with a sensitivity and a specificity of 100%. This data requires confirmation by further measurements in a larger number of patients. In patients aged over 7 years, FFA/KB may not discriminate patients from controls at 20 h or even at 24 h of fast. Kinetic data are always necessary for the assessment of such pathological processes. In hyperketotic patients, FFA/KB reached a very low value, approximately 0.3, very early in the fast. Another parameter for the evaluation of hypoketosis is the product of the plasma KB and glucose levels at the end of the fast [7]. While normal children reach values between 8 and 13, with older children slightly lower (Table 2), hypoketotic patients had very low values, usually below 2 (Table 1). Conversely, both hyperketotic patients reached values much higher than controls (Table 1). When a ketolysis defect is suspected, a valuable investigation to separate hyperketotic patients from controls would appear to be an injection of 1 mg glucagon at the end of the fast: in one of our two patients, glucagon administration produced a significant rise in the glucose level, in spite of a marked hyperketonaemia (data not shown).

In summary, if it has been decided to perform a fasting test in a child suspected of having a defect in ketogenesis or ketolysis, it must be sufficiently long to allow activation of fatty acid oxidation and ketogenesis. Simultaneous determinations of blood substrates, carnitine and urinary organic acids must be performed. For diagnostic purposes, the fast must only be performed in healthy patients in a good nutritional state, and whose basal urinary organic acid analysis and serum carnitine values have been non-diagnostic. In patients with an identified metabolic defect, a carefully supervised fasting test may help to determine optimal modes of therapy.

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