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# Normoglycemic ketonemia as biochemical presentation in ketotic glycogen storage disease

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**Abbreviations:** FI, fasting intolerance; GSD, glycogen storage disease; KB, ketone bodies.

**Abstract**

**Background:** According to the textbooks, the ketotic glycogen storage disease (GSD) types O, III, VI, IX and XI are associated with fasting ketotic hypoglycemia and considered milder as gluconeogenesis is intact.

**Methods:** Retrospective cohort study of biochemical profiles from supervised clinical fasting studies performed in ketotic GSD patients in our metabolic center. For data analysis, hypoglycemia was defined as plasma glucose concentration <2.6 mmol/L. Total KB was defined as the sum of blood acetoacetate and β-hydroxybutyrate concentrations. If the product of glucose and KB concentrations was greater than 10, a ketolysis defect was suspected.

**Results:** Data could be collected from 13 fasting studies in 12 patients with GSD III (n=4), GSD VI (n=3) and GSD IX (n=5). Six patients remained normoglycemic with median glucose concentration of 3.9 mmol/L [range: 2.8-4.6 mmol/L] and median total KB concentration of 1.9 mmol/L [range: 0.6-5.1 mmol/L]. The normoglycemic patients included type VI (3 out of 3) and type IX (3 out of 5) patients. All type III patients developed ketotic hypoglycemia. Interestingly, in five patients (1 GSD III, 1 GSD VI and 3 GSD IX), the biochemical profile suggested a ketolysis defect.

**Conclusion:** Normoglycemic ketonemia is a common biochemical presentation in patients with GSD types VI and IX and ketonemia can precede hypoglycemia in all studied GSD types. Therefore, GSD VI and IX should be added to the differential diagnosis of ketotic normoglycemia and KB concentrations should be routinely measured in ketotic GSD patients.

## Compliance with Ethics Guidelines

**Conflict of Interest:** Francjan J van Spronsen has received research grants and consultancy and speaker's fees from Merck Serono and Danone Nutricia. He is a member of the scientific advisory board of Merck Serono and chair of the scientific advisory board of Danone Nutricia. In the last 5 years, Terry GJ Derks has received speaker's fees from Danone Nutricia, Vitaflo and Recordati and research fees from Sigma Tau and Vitaflo. Irene J Hoogeveen, Rixt M van der Ende, Foekje de Boer, and M Rebecca Heiner-Fokkema declare that they have no conflict of interest to disclose.

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**Contributions of individual authors:** Irene J Hoogeveen and Rixt M van der Ende collected and analyzed data from supervised clinical fasting studies, performed the data analysis, drafted the first version of the manuscript, and wrote the final manuscript.
Francjan J van Spronsen was involved in clinical management and monitoring and critically reviewed and revised the manuscript, and approved the final manuscript as submitted.
Foekje de Boer was involved in dietary management, critically reviewed and revised the manuscript, and approved the final manuscript as submitted.
M Rebbeca Heiner-Fokkema supervised the data analysis of the fasting studies, critically reviewed and revised the manuscript, and approved the final manuscript as submitted.
Terry G J Derks initiated this study, was involved in clinical management and monitoring, drafted the first version of the manuscript, critically reviewed and revised the manuscript, and wrote the final manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. All authors confirm the absence of previous similar or simultaneous publications.

**Informed Consent:** All procedures followed were in accordance with the ethical standards of the institutional responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000. Since all data were retrieved retrospectively and analyses anonymously, no informed consent was needed.

## Introduction

Fasting intolerance (FI) is biochemically associated with hypoglycemia and/or metabolic acidosis, the latter often caused by increased concentrations of lactate and/or ketones. The differential diagnosis of childhood FI includes many endocrine disorders and inborn errors of metabolism, among which several types of glycogen storage disease (GSD).

There are at least 13 types of GSD, which are classified according to the protein defect and organ distribution (Laforet et al 2012). The ketotic GSD types 0, III, VI, IX and XI are associated with fasting ketotic hypoglycemia and considered relatively mild compared to GSD type I because gluconeogenesis is intact. Traditionally ketotic *hypo*glycemia is considered the common diagnostic biochemical phenotype upon fasting in patients with ketotic GSD types (Laforet et al 2012), although cohort studies have demonstrated that this is not always the case (Beauchamp et al 2007a; Beauchamp et al 2007b). It has recently been reported that ketotic GSD types can be easily misinterpreted as idiopathic ketotic hypoglycemia (Brown et al 2014).

Regular monitoring of ketone bodies (KB) is recommended to titrate dietary management in ketotic GSD patients (Dagli et al 2010; Dagli and Weinstein 2009, Goldstein et al 2011), but experimental data are lacking. Therefore, we have performed this retrospective study of supervised clinical fasting studies in patients with ketotic GSD.

## Patients and Methods

Subjects - The Section of Metabolic Diseases, Beatrix Children's Hospital, University Medical Center Groningen is a tertiary metabolic center and a reference center for hepatic GSD patients. In the period 1993-2012, 539 supervised clinical fasting studies have been performed in 476 patients. From this cohort all patients with ketotic GSD have been identified to perform a retrospective study of the biochemical profiles of their supervised clinical fasting studies. Data were anonymously retrieved from both the paper and electronic medical files.

Fasting studies - Supervised clinical fasting studies were performed as described elsewhere (Bonnefont et al 1990; Van Veen et al 2011), for either diagnostic or therapeutic reasons, i.e. to titrate dietary management. Most diagnostic studies were performed before 2003, when plasma acylcarnitine profiling became available in our laboratory. Fasting studies were only performed in healthy patients in good nutritional condition. Subjects were admitted one day before the fasting test when they were <8 years of age. There was no limitation in water intake. After the last meal and an individually tailored period of fasting, an intravenous catheter was inserted for blood sampling at hourly intervals. Carefully supervised fasting was continued until glucose concentrations dropped below 2.6 mmol/L or until development of symptoms or signs of hypoglycemia.

Statistical analysis - SPSS Statistics version 22.0 (IBM Corp., Armonk New York, USA) was used to calculate median and range for concentrations of glucose and KB. For data analysis, hypoglycemia was defined as plasma glucose concentration <2.6 mmol/L (Koh et al 1988). Total KB was defined as the sum of blood acetoacetate and β-hydroxybutyrate concentrations. If the product of glucose and KB concentrations was greater than 10, a ketolysis defect was suspected (Touati et al 2012).

## Results

Table 1 presents patients characteristics from 12 patients with GSD type III (n=4), type VI (n=3) and type IX (n=5), in whom a total of 13 supervised clinical fasting studies were performed. A fasting study was performed twice in patient 2 due to therapeutic reasons. For patient 2 and 12 no confirmatory molecular studies were available, however diagnosis was confirmed enzymatically, in leukocytes and erythrocytes, respectively. Patient 2 died at the age of 27 years by a car accident, his sister was homozygous for the c.2039G>A AGL founder mutation from the island of Aruba.

Table 2 presents biochemical data during the fasting studies in the individual patients. Six patients showed normoglycemia during fasting, i.e. median blood glucose concentration in these patients were 3.9 mmol/L [range: 2.8-4.6 mmol/L] with median total KB concentration of 1.9 mmol/L [range: 0.6-5.1 mmol/L]. The *normo*glycemic patients included type VI (3 out of 3) and type IX (3 out of 5) patients. All type III patients developed ketotic hypoglycemia, but interestingly, a remarkable increase in KB preceded hypoglycemia in these patients. Patient 4 displayed hypoglycemia at the end of the fasting study, although her glucose concentration was not below 2.6 mmol/L during the last combined KB and glucose measurement. Patient 9 developed hypoglycemia very quickly without clinical manifestations. In patient 11 the fasting study was terminated because of abdominal pain, nausea and vomiting, although plasma blood glucose concentrations were normal. At the moment of terminating the blood KB concentration was 3.3 mmol/L. For patient 12 only one combined measurement of blood glucose and KB concentration could be obtained, however it showed an elevated KB concentration of 0.6 mmol/L already after three hours of fasting. Interestingly, the product of glucose and KB

suggested a ketolysis defect in 5 patients. One of these 5 patients underwent a fasting study for diagnostic purposes.

Figure 1 presents concentrations of glucose and KB longitudinally in time for all fasted GSD type VI patients, demonstrating normoglycemia despite remarkable increase of KB concentrations.

## Discussion

This study demonstrates that normoglycemic ketonemia is a common biochemical phenotype in GSD type VI and IX and that ketonemia can precede hypoglycemia in all studied GSD types. This is important from both a diagnostic and management point of view.

In this study normoglycemic ketonemia was presented by half of the GSD patients. Five out of twelve patients displayed a biochemical phenotype suggestive of a ketolysis defect (Bonnefont et al 1990). It was recently reported that especially GSD IX is an unappreciated cause of idiopathic ketotic hypoglycemia (Brown et al 2014). As this study also included diagnostic fasting studies, to our opinion it emphasizes the potential risk of underdiagnosing ketotic GSD. Ketotic GSD should therefore be included in the differential diagnosis of childhood FI associated normoglycemic ketonemia.

Previously, supervised clinical fasting studies have played a central diagnostic role as an informative functional *in vivo* test (Bonnefont et al 1990), but nowadays these studies are considered obsolete. Moreover, fasting studies are relatively time-consuming, expensive, invasive and potentially dangerous. These fasting studies have merely been replaced after the introduction of new laboratory techniques, like acylcarnitine profiling (Millington et al 1990). More recently next generation sequencing and/or exome sequencing have developed into powerful diagnostic confirmatory tests (Wang et al 2012). In our experience there are few indications for the traditional clinical fasting studies, under exceptional circumstances and well-controled conditions, to characterize the clinical *in vivo* implications for patients with unknown variations in the metabolome or genome.

Several factors complicate the recognition of patients with ketotic GSD. During ‘quick’ physical examination at an emergency room, both the soft hepatomegaly (like in GSD types VI and IX)

and failure to thrive may be easily overlooked. Simple laboratory tests in blood are not routinely requested in stress samples from patients with FI. In untreated GSD patients, (a specific combination of) plasma concentrations of lactate, transaminases, uric acid, triglycerides and cholesterol is usually abnormal. In contrast, the traditional hormonal and secondary metabolic tests (like analysis of plasma acylcarnitines and urinary organic acids) are usually normal, even when samples are obtained under critical conditions. The above-mentioned investigations are important first-line tests in patients with FI to select candidates for confirmatory molecular and/or enzymatic testing for GSD.

It is not known why some ketotic GSD patients display hypoglycemia and some do not. This variation is especially observed in GSD VI; hepatic phosphorylase deficiency, encoded by the *PYGL* gene (OMIM #232700) and GSD IX; hepatic phosphorylase b kinase deficiency, encoded by the *PHKA2* gene (OMIM #300798; X-linked GSD IX), the *PHKB* gene (OMIM #172490), and *PHKG2* gene (OMIM #172471) respectively. Beauchamp et al reported hypoglycemia in 5 out of 13 GSD VI patients on either fasting or glucose loading tests (Beauchamp et al 2007a), while in GSD IX Beauchamp et al reported hypoglycemia as a presenting sign in 5 out of 15 GSD IX patients (Beauchamp et al 2007b). The hypoglycemia in GSD IX patients included those with mutations in the *PHKG2* gene, which is in line with Bali et al, who reported fasting hypoglycemia in all 5 patients with *PHKG2* mutations (Bali et al 2014). This finding may be very well explained by the fact that mutations of the PHKG2 gene contains the catalytic site of hepatic phosphorylase b kinase.

Uncooked cornstarch and protein are the keystones of dietary management in ketotic GSD, the latter serving as an alternative source for gluconeogenesis to maintain normoglycemia (Derks and Smit 2015). In ketotic GSD types, increased KB concentrations reflect increased

mitochondrial fatty acid oxidation, which is associated with activation of gluconeogenesis and secondary endogenous proteolysis from muscle tissue. Instead of maintenance of normoglycemia, prevention of increasing KB concentrations could therefore be regarded as a more relevant aim in optimizing metabolic control.

At a relatively young age, one GSD III patient (patient 4) displayed a decrease in both KB and glucose concentrations with prolonged fasting. Hypoketosis has been reported before in GSD III patients (Seigel et al 2008; Clemente et al 2010), in whom exogenous carbohydrate requirements are still relatively high (Derks and Van Rijn 2015). We speculate that, as a consequence of dietary management with frequent high carbohydrate meals, there may have been a relatively high plasma insulin state together with high intracellular malonyl-CoA levels, physiologically inhibiting long-chain mitochondrial fatty acid oxidation at the level of carnitine palmitoyltransferase type I.

This study has several limitations. First, data have retrospectively been retrieved from electronic and paper files, from fasting studies that have mostly been performed at least ten years ago. Second, fasting studies have been conducted in only a subset of our GSD patients, which could have introduced a selection bias. Third, these fasting studies originate from a period, in which the general opinion on dietary management and outcome parameters for ketotic GSD types was different. Last, the definition of hypoglycemia is debatable in several ways. We have defined hypoglycemia as a *plasma* glucose concentration <2.6 mmol/L, measured by calibrated meters with a constant factor of 1.11 for conversion between blood glucose and plasma glucose concentrations (D'Orazio et al 2005). Therefore, the plasma glucose concentrations are on average 11% higher compared to blood concentrations, depending on the hematocrit and the water component in blood. Also, hypoglycemia defined by a single number does not distinguish

the difference values at which an individual starts to compensate for inadequate glucose supply to the brain (Cornblath et al 2000).

To date, in contrast with GSD III (Derks and Smit 2015; Kishnani et al 2010), there are no formal diagnostic and management guidelines for GSD VI and IX. Based on expert opinion, caregivers are advised to titrate dietary management, aiming at normoglycemia and maintenance of blood β-hydroxybutyrate concentrations lower than 0.3 mmol/L, measured by a portable blood ketone meter (Dagli et al 2010; Dagli and Weinstein 2009; Goldstein et al 2011). This study provides short-term, indirect biochemical evidence substantiating these management advices, but there is a lack of data on long-term clinical outcome parameters, like growth, liver size, laboratory studies, hepatic complications and bone density.

## Conclusion

This is the first study that critically analyzed blood glucose and KB concentrations during fasting in ketotic GSD patients. Normoglycemic ketonemia is a common biochemical presentation in patients with GSD types VI and IX and ketonemia can precede hypoglycemia in all studied GSD types. Therefore, GSD VI and IX should be added to the differential diagnosis of ketotic normoglycemia and KB concentrations should be routinely measured in ketotic GSD patients.

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**Legends Figures**

**Figure 1. Longitudinal course of fasting in GSD type VI**

Legend: • Glucose concentration, ◆ Ketone Bodies concentration, - - - Cut off point hypoglycemia.

342 **Table 1. Patient characteristics**

| **Case** | **Age**[a] ($Y^{m}$) | **Sex**[b] | **GSD type** | **Molecular defect** | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | *Gene* | *Exon nr* | *Nucleotide change allel 1* | *Coding effect allel 1* | *Exon nr* | *Nucleotide change allel 2* | *Coding effect allel 2* |
| 1 | $18^{0/12}$ | F | IIIa | AGL | 17 | c.2039G>A | p.Trp680X | 17 | c.2039G>A | p.Trp680X |
| 2 (1)* | $11^{0/12}$ | M | IIIa | - | - | - | - | - | - | - |
| 2 (2)* | $16^{6/12}$ | M | IIIa | - | - | - | - | - | - | - |
| 3* | $22^{5/12}$ | F | IIIa | AGL | 17 | c.2039G>A | p.Trp680X | 17 | c.2039G>A | p.Trp680X |
| 4 | $1^{5/12}$ | M | III | AGL | 13 | c.1571G>A | p.Arg524His | - | - | - |
| 5 | $3^{3/12}$ | M | VI | PYGL | 3 | c.385G>A | p.Asp129Asn | 20 | c.2446C>T | p.Arg816* |
| 6 | $4^{10/12}$ | M | VI | PYGL | 3 | c.418C>G | p.Leu140Val | 11 | c.1366G>A | p.Val456Met |
| 7 | $1^{10/12}$ | M | VI | PYGL | 1 | c.131G>A | p.Arg44His | 16 | c.1900G>C | p.Asp634His |
| 8 | $4^{4/12}$ | M | IX | PHKA2 | 33 | c.3614C>T | p.Pro1205Leu | | | |
| 9 | $1^{7/12}$ | F | IX | PHKA2 | 33 | c.3614C>T | p.Pro1205Leu | | | |
| 10 | $2^{6/12}$ | M | IX | PHKA2 | - | DelXp22.13 | - | | | |
| 11 | $7^{10/12}$ | M | IX | PHKB | 14 | c.1265dup | - | 27 | c.2316-2A>C | p.Asn422fs |
| 12 | $2^{3/12}$ | M | IX | - | - | - | - | - | - | - |

343 Legend: [a]: age during the fasting study in years and months, [b]: M=male, F=female, -:

344 mutation unknown, *: patients are siblings.

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**Table 2. Biochemical data of the fasting studies**

| Case | Purpose test [a] | Duration of Fasting | Glucose | KB[b] | FFA | FFA/KB | KBxGlucose[c] |
|---|---|---|---|---|---|---|---|
| | (D/T) | (hh:mm) | (mmol/L) | (mmol/L) | (mmol/L) | | |
| 1 | T | 11:30 | 3.5 | 1.4 | 0.9 | 0.6 | 4.9 |
| | | 18:30 | 2.4 | 4.0 | 1.2 | 0.3 | 9.6 |
| 2 | T | 10:30 | 2.1 | 4.8 | 1.8 | 0.4 | 10.1 |
| | | 11:30 | 2.0 | 6.9 | 1.3 | 0.2 | 13.8 |
| 2 | T | 11:00 | 3.3 | 3.8 | 1.2 | 0.3 | 12.5 |
| | | 17:00 | 1.7 | 4.8 | 1.6 | 0.3 | 8.2 |
| 3 | T | 11:00 | 3.2 | 2.6 | 0.9 | 0.3 | 8.3 |
| | | 16:30 | 1.7 | 3.2 | 0.8 | 0.3 | 5.4 |
| 4 | D | 04:00 | 4.8 | 2.0 | 1.2 | 0.6 | 9.6 |
| | | 05:00 | 4.4 | 1.5 | 0.8 | 0.5 | 6.6 |
| 5 | D | 12:30 | 5.1 | 1.5 | 1.0 | 0.7 | 7.7 |
| | | 15:15 | 3.0 | 3.5 | 1.1 | 0.3 | 10.5 |
| 6 | D | 08:45 | 4.1 | 0.7 | 0.6 | 0.9 | 2.9 |
| | | 14:45 | 3.5 | 0.8 | 0.8 | 1.0 | 2.8 |
| 7 | D | 09:00 | 2.7 | 1.4 | - | - | 3.8 |
| | | 12:00 | 3.0 | 1.9 | - | - | 5.7 |
| 8 | T | 02:00 | 4.6 | 1.6 | 0.9 | 0.6 | 7.4 |
| | | 08:15 | 3.8 | 5.1 | 1.2 | 0.2 | 19.4 |
| 9 | T | 03:00 | 3.7 | 0.6 | - | - | 2.2 |
| | | 07:00 | 2.3 | 3.3 | 1.1 | 0.3 | 7.6 |
| 10 | T | 08:30 | 3.5 | 1.8 | 1.4 | 0.8 | 6.3 |
| | | 14:15 | 2.5 | 6.1 | 1.6 | 0.3 | 15.3 |
| 11 | T | 07:50 | 4.1 | 1.4 | 0.9 | 0.6 | 5.7 |
| | | 14:50 | 3.8 | 3.3 | 0.9 | 0.3 | 12.5 |
| 12 | D/T | 03:10 | 4.3 | 0.6 | 0.6 | 1.0 | 2.6 |
| | | | - | - | - | - | - |

Legend: [a]:D=diagnostic, T=therapeutic, [b]:KB is the sum of acetoacetate and β-hydroxybutyrate, [c]:suspect ketolysis defect is defined as a product of glucose and KB greater than 10 (Touati et al 2012).