# Sugar nucleotide concentrations in red blood cells of patients on protein- and lactose-limited diets: effect of galactose supplementation[1–3]

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**ABSTRACT** Uridine diphosphate (UDP) galactose, a pivotal compound in the metabolism of galactose, is the obligate donor of galactose in the formation of complex glycoconjugates. The cellular UDPgalactose concentration has been thought to be maintained by the interconversion of UDPglucose and UDPgalactose by UDPgalactose-4-epimerase. However, recent findings of lower average red blood cell (RBC) UDPgalactose concentrations in galactose-1-phosphate uridyltransferase–deficient patients suggest that other factors play a role in determining its concentration. To test the hypothesis that the amount of galactose traversing the Leloir pathway contributes to the cellular UDPgalactose pool, we determined RBC UDPgalactose in patients with maple syrup urine disease (MSUD), phenylketonuria (PKU), and other metabolic diseases who were treated with a low-protein, and consequently, low-lactose diet. Six patients with MSUD were also supplemented with 19 g galactose/d and their UDPhexose concentrations were measured at intervals. We show that young patients with MSUD or PKU have decreased average RBC UDP-galactose concentrations when compared with similarly aged healthy subjects. Galactose supplementation of MSUD patients significantly increased their UDPgalactose concentrations in both RBCs and white blood cells (WBCs) from 29.5 ± 1.5 to 42.3 ± 5.8 nmol/g hemoglobin and from 69.0 ± 7.5 to 193.0 ± 49.0 nmol/g protein, respectively. Discontinuation of supplementation was associated with a return to basal values in RBCs and a reattainment of the pretreatment ratio of UDPglucose to UDPgalactose in WBCs. These observations demonstrate that dietary galactose is a factor in establishing the steady state concentrations of the uridine sugar nucleotides and imply that galactose metabolism modulates the achievement of an epimerase-mediated equilibrium. *Am J Clin Nutr* 1996;63:704–8.

**KEY WORDS** Galactose, uridine diphosphate galactose, maple syrup urine disease

## INTRODUCTION

The sugar nucleotides uridine diphosphate (UDP) galactose and UDPglucose are important intermediates in many metabolic pathways. UDPgalactose assumes a dual importance as a pivotal compound in the metabolism of galactose and as the obligate donor of galactose in the formation of complex glycoconjugates. Although the cellular concentration of UDP-galactose has been thought to be maintained by the interconversion of UDPglucose and UDPgalactose by the enzyme UDPgalactose-4-epimerase, with an equilibrium ratio of ≈3:1 (1), recent findings have suggested that other factors play a role in red blood cell (RBC) UDPgalactose concentrations. This stems from the observation that as a group, galactosemic subjects with defective galactose-1-phosphate uridyltransferase who are treated with low-galactose diets have a significantly lower than normal average RBC concentration of the galactose-containing nucleotide sugar (2–5). The idea that normal amounts of galactose traversing the Leloir pathway contribute to the UDPgalactose pool was bolstered by the fact that non-galactosemic persons on a low-lactose diet may also exhibit lower than normal RBC UDPgalactose concentrations (3, 5).

In an effort to determine whether RBC UDPgalactose is regulated by increasing ambient galactose, we orally administered large quantities of the sugar to healthy subjects and found that there was an increase in RBC and white blood cell (WBC) UDPgalactose (6). The elevation lasted ≈4 h, the interval in which plasma galactose was detected. In contrast, glucose loading, resulting in an increase in plasma glucose, did not affect the RBC nucleotide sugar concentration. Also, altered concentrations were not observed in RBCs of diabetic patients with high plasma glucose concentrations (6). The data indicate that acute oral intake of galactose promotes increased cellular UDPgalactose.

In the present studies we focused on the relations of diets and RBC UDPhexose content, namely the effect of limited lactose intake, which results from diets limited in protein. Our previous evaluation of patients on such diets, involving a smaller number of subjects examined as a group, suggested that lactose restriction may influence RBC UDPgalactose and UDPglucose contents. To more clearly elucidate the role of dietary lactose on UDPhexose concentrations, three groups of patients were examined: those with maple syrup urine disease (MSUD), phenylketonuria (PKU), and other metabolic diseases such as organic acidurias and urea cycle enzyme defects. As a group, patients with MSUD had the

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[2] Supported by NIH grant PO1-HD-29847 and by the Daland Fellowship from the American Philosophical Society (to JBG).

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Received July 19, 1995.

Accepted for publication December 4, 1995.

 

lowest average erythrocyte UDPgalactose content and the highest ratio of UDPglucose to UDPgalactose, which nearly corresponded to the values observed in the RBCs of galactosemic patients. There was no correlation between the degree of protein limitation and UDPgalactose concentrations. A daily galactose intake < 3 g was associated with a lower than normal RBC UDPgalactose concentration. The feeding of a supplemental galactose equivalent in three glasses of milk a day (19 g) to six MSUD patients for 28 d resulted in increases in both RBC and WBC UDPgalactose with a lowering of the ratio of UDPglucose to UDPgalactose. These data suggest that normal amounts of dietary galactose play a role in the maintenance of UDPhexose pools of circulating blood cells in subjects with intact galactose metabolism.

## SUBJECTS AND METHODS

### Patient population

The study population was 53 patients with inborn errors of amino acid metabolism for which limitation of protein intake is a portion of the therapeutic management. The diagnoses were made by biochemical analysis of plasma and/or urine with confirmation by enzymatic or molecular biologic studies when possible. Eighteen (nine males and nine females) of the patients had classical MSUD due to deficient branched-chain ketoacid dehydrogenase (EC 1.2.1.25) activity. They ranged in age from 2 wk to 13.5 y. Nineteen patients had PKU as a result of deficient phenylalanine hydroxylase (EC 1.14.16.1) activity. This group comprised 10 males and 9 females ranging in age from 2 to 32 y. The third group included 16 patients ranging in age from 10 mo to 22 y with diagnoses of urea cycle defects in 4, branch-chain aminoacidopathies (other than classical MSUD) in 6, cobalamin defect in 1, glutaric aciduria type 1 in 1, homocystinuria in 2, and variant MSUD in 2.

The blood specimens were obtained at selected follow-up visits when the patient was judged to be clinically well. Laboratory confirmation of this status, of dietary compliance, and of good metabolic control, was obtained in all of the patients with MSUD because plasma leucine concentrations were < 450 μmol/L (< 6 mg/dL). In 16 of the patients with PKU, compliance was judged to be good to excellent with plasma phenylalanine concentrations measured at 485 μmol/L (< 8 mg/dL). In the other three patients with PKU, phenylalanine concentrations were 720-1150 μmol/L (12–19 mg/dL). In the third group of patients, metabolic control was determined by combinations of factors including recent prospective dietary records, blood ammonia concentrations < 50 μmol/L, individualized basal concentrations of disease-specific urinary metabolites, and normal plasma amino acid analysis.

Diet therapy forms a main component of the treatment for each of these patients. In all cases, protein limitation is used to prevent the presentation of excessive substrate, decreasing the amount of catabolism and resultant accumulation of abnormal compounds. The diets were designed and adjusted to provide adequate nitrogen and energy for growth. In many cases, synthetic amino acid mixtures were used as supplements to very restrictive native protein intakes. The total amount of amino acid mixture and natural protein ingested ranged from 0.6 to 2.4 $g \cdot kg\ body\ wt^{-1} \cdot d^{-1}$ with 90% of the subjects on diets containing < 1.8 $g \cdot kg\ body\ wt^{-1} \cdot d^{-1}$. Because several of the major sources of protein in the typical diet of American children are dairy products, such as milk and cheese, protein-limiting therapies have a relative or absolute proscription on these foods. These dairy products are the major source of dietary galactose with 250 mL (8 oz) milk supplying 6 g galactose (7).

Consequently, patients with inborn errors of amino acid metabolism have diets with a galactose content lower than average for their age. The galactose content of the diets for 21 patients, 14 with MSUD and 7 with metabolic disorders other than PKU, was estimated from dietary records and average galactose contents of individual foodstuffs (8, 9). The patients were segregated into two groups on the basis of their galactose intake. The first group comprised 17 patients with an intake ranging from 10 to 600 mg/d (average 130 mg/d), 16 of whom had an intake < 250 mg. The medical food products used with these patients are made with sucrose, tapioca, and corn solids as the carbohydrate sources. The second group comprised seven patients who were receiving formula that contained galactose; their galactose intake ranged from 1 to 6 g/d (average 2.9 g/d), six of whom had an intake < 3.5 g.

Both the supplementation study and survey of patients were done under protocols approved by the Children's Hospital of Philadelphia Institutional Review Board for the use of human subjects in research.

### Protocol

After written, informed consent, blood was obtained for measurement of erythrocyte and leukocyte UDP sugars via venipuncture at the conclusion of a routine clinic visit. The specimens were taken at random times, but in subjects older than 1 y they were generally taken several hours after a meal.

In six patients aged 1.3–7 y (three males and three females) with classical MSUD, supplemental galactose was given. Their parents were given packets containing 6.5 g galactose (Pfanstiehl Co, Waukegan, IL), which was added to their MSUD formula three times a day. Blood specimens were obtained at weekly intervals for 4 wk in all six and at 9 wk in two of the subjects. A final specimen was collected at the next clinic visit 4–10 wk after galactose supplementation ended to demonstrate restoration of baseline UDP sugar concentrations.

Specimen preparation and analysis were conducted as described previously (10, 11). Statistical analysis of the population data was done by comparing the UDPhexose concentrations in the groups with each other and with a previously studied healthy population (5). The previous analysis had shown a significant decrease in UDPgalactose and UDPglucose concentrations in erythrocytes in children older than 10 y (5). Thus, each of the patient groups was also analyzed after this simple age stratification (≤ 10 y and > 10 y).

### Statistical analysis

A two-tailed Student's *t* test was used to analyze the data for the population and repeated-measures analysis of variance (ANOVA) followed by a Bonferroni multiple-comparison test were used for the experimental group. SPSS software (version 6.1; SPSS Inc, Chicago) was used for the analysis. Significance was assumed at $P < 0.05$.

## RESULTS

### Nucleotide sugars in erythrocytes

The mean (± SD) of the RBC UDPhexoses of the three groups of patients compared with normal subjects with age stratification (5) are shown in **Table 1**. The average concentration of UDPgalactose of 27.9 ± 6.5 nmol/g hemoglobin in the MSUD patients aged < 10 y was significantly lower than that of the healthy subjects of the same age ($P < 0.01$). The ratio of UDPglucose to UDPgalactose, which we found to be more useful in discriminating galactosemic from normal subjects (5), was also significantly higher in the younger MSUD patients. The mean RBC UDPgalactose concentration, UDPglucose content, and ratio of UDPglucose to UDPgalactose in PKU patients aged ≤ 10 y were also lower than normal ($P < 0.05$). However, neither the UDPhexose concentration nor the ratio of UDPglucose to UDPgalactose in RBCs of patients aged > 10 y in both the PKU and MSUD groups were not significantly different from age-matched healthy subjects. The patients with other disorders had RBC UDPhexose contents that were not statistically different from those of age-matched healthy groups.

Because the number of patients examined with each diagnosis is relatively small compared with the historical control group of 36 healthy subjects aged ≥ 10 y, we also contrasted UDPgalactose concentrations in the 35 younger patients as one cohort with those of the age-matched control subjects. When this was done the average UDPgalactose content was 28.2 ± 7.8 nmol/g hemoglobin, a value significantly lower than the value for the healthy subjects (*36.6 ± 12.4*, $P < 0.01$) but similar to the value for the smaller metabolic patient cohort examined previously (5).

### RBC UDPhexoses and nitrogen and galactose intakes

Because the primary dietary manipulation in all of these patients is protein limitation, the RBC UDPhexose concentrations were examined in relation to daily nitrogen intake. There was no correlation of UDPgalactose concentration to the amount of dietary nitrogen over the intake range of 0.6–2.4 $g \cdot kg\ body\ wt^{-1} \cdot d^{-1}$ in any of the three groups of patients.

The limited protein intake resulted in a low galactose intake. The estimation of dietary galactose revealed two groups of patients, those consuming special formulas and foods that contain little galactose and those consuming some milk or infant formula containing lactose. In the first group, who had a mean (± SEM) average daily galactose intake of 130 ± 50 mg, the RBC UDPgalactose concentration was 29.4 ± 2.0 nmol/g hemoglobin. In the second group, who had a galactose intake of 2.9 ± 0.64 g, the RBC UDPgalactose concentration averaged 27.0 ± 3.4 nmol/g hemoglobin. Thus, within this restricted range of galactose intake there was no significant difference in the RBC UDPgalactose concentration between a severe restriction and ≤ 3 g in the diet.

### Effect of galactose supplementation on red cell UDPhexoses

All six patients showed an increase in RBC UDPgalactose values ranging from 2.0 to 28.0 nmol/g hemoglobin. The increase was first seen at different times of feeding, with the highest value observed at 28 d of the supplement. In one subject for whom the study was extended to 64 d, the highest value was reached at that time. The average initial RBC UDPgalactose concentration for the six subjects was 29.5 ± 1.5 nmol/g hemoglobin (**Table 2**), which was similar to the concentration in the larger group of 15 MSUD patients (Table 1). The average increase to the maximum observed value was 12.5 nmol/g hemoglobin. The maximum content was significantly different from the prefeeding concentration at the $P < 0.001$ level. When the galactose supplement was stopped, the average RBC UDPgalactose concentration returned to the baseline value. On the other hand, there was no significant change in the RBC UDPglucose concentration although there was a trend toward a lower concentration.

The ratio of UDPglucose to UDPgalactose in RBCs was elevated above the norm in this subgroup of MSUD patients as it was in the larger group shown in Table 1. With galactose feeding, the ratio fell below the normal average to 2.10 and returned to the prefeeding ratio when galactose feeding ceased (Table 2).

### Effect of galactose feeding on WBC UDPhexoses

The changes in WBC nucleotide sugars after galactose administration are shown in Table 2. The average UDPgalactose concentration of 69.0 nmol/g protein was increased to a maximum of almost threefold higher ($P < 0.01$). In general, the increase in WBCs was not synchronous with the increase in RBCs and occurred earlier in the study. There was no significant change in WBC UDPglucose content during the period of augmented galactose ingestion. In contrast with the RBC compounds, the WBC

**TABLE 1**
Erythrocyte uridine diphosphate (UDP) hexoses in patients with metabolic diseases[1]

| Disease and age | UDPgalactose | UDPglucose | Ratio |
|---|---|---|---|
| | *nmol/g hemoglobin* | *nmol/g hemoglobin* | |
| MSUD ≤ 10 y ($n$ = 15) | 27.9 ± 6.5[2] | 90.1 ± 16.2 | 34.0 ± 9.2[2] |
| MSUD > 10 y ($n$ = 3) | 17.7 ± 6.5 | 53.0 ± 25.7 | 29.0 ± 6.3 |
| PKU ≤ 10 y ($n$ = 12) | 30.2 ± 7.1[3] | 80.4 ± 14.2[3] | 29.8 ± 4.4[3] |
| PKU > 10 y ($n$ = 7) | 26.9 ± 6.7 | 69.8 ± 14.6 | 26.2 ± 1.8 |
| Other diseases ≤ 10 y ($n$ = 8) | 29.6 ± 9.2 | 85.2 ± 19.9 | 30.0 ± 6.3 |
| Other diseases < 10 y ($n$ = 8) | 27.1 ± 7.9 | 86.8 ± 26.3 | 32.3 ± 7.3 |
| All patients ≤ 10 y ($n$ = 35) | 28.2 ± 7.8[2] | 83.1 ± 19.1 | 30.6 ± 7.4[2] |
| All patients > 10 y ($n$ = 18) | 25.5 ± 7.9 | 74.5 ± 25.0 | 29.4 ± 6.1 |
| Normals ≤ 10 y ($n$ = 36) | 36.6 ± 12.4 | 92.1 ± 19.9 | 26.5 ± 5.4 |
| Normals > 10 y ($n$ = 81) | 25.4 ± 8.0 | 73.5 ± 17.0 | 30.2 ± 6.4 |

[1] $\bar{x}$ ± SD. MSUD, maple syrup urine disease; PKU, phenylketonuria.
[2,3] Significantly different from normal subjects of the same age: [2] $P < 0.01$, [3] $P < 0.05$.

**TABLE 2**
Alterations in uridine diphosphate (UDP) hexoses by galactose feeding in patients with maple syrup urine disease[1]

| | Red blood cells | White blood cells |
|---|---|---|
| | *nmol/g hemoglobin* | *mmol/g protein* |
| UDPgalactose | | |
| Initial | 29.5 ± 01.5 | 69. ± 08. |
| Maximum | 42.3 ± 05.8[2] | 194. ± 49.[3] |
| Off | 27.2 ± 01.8 | 136. ± 08.[3] |
| UDPglucose | | |
| Initial | 94.3 ± 05.0 | 241. ± 56. |
| Maximum | 85.5 ± 08.4 | 307. ± 43. |
| Off | 87.2 ± 08.0 | 407. ± 13.[3] |
| Ratio | | |
| Initial | 3.20 ± 0.06 | 3.4 ± 0.6 |
| Maximum | 2.07 ± 0.11[2] | 1.9 ± 0.5[3] |
| Off | 3.22 ± 0.16 | 3.0 ± 0.2 |

[1] $\bar{x}$ ± SEM.
[2,3] Significantly different from initial values (Bonferroni's multiple-comparison test): [2] $P < 0.001$, [3] $P < 0.01$.

UDPgalactose content did not return to baseline and the WBC UDPglucose concentration was significantly higher than the pretreatment value when galactose supplementation was discontinued. Thus, the average ratio of UDPglucose to UDPgalactose declined from 3.4 to 2.5 during the study but returned toward the prefeeding value with cessation of galactose supplementation.

## DISCUSSION

Patients on protein-limited diets for treatment of metabolic diseases have a diminished intake of galactose because of the absence of milk and dairy products. We find that these children, in whom no lactose-containing formulas are used, ingest an average of 130 mg galactose/d. This is within the range of the daily intake of galactose by patients with galactosemia (12). When some milk or lactose-containing formula is used as part of the dietary prescription, metabolic patients consume ≈3 g galactose/d, an amount still far below the 12–19 g galactose (equivalent to two to three glasses of milk a day) ingested by children aged ≤ 10 y on normal diets.

The examination of RBC and WBC UDPhexose contents in these metabolic patients is an opportunity to examine the dietary factors that contribute to the regulation of their cellular concentration. In patients with galactosemia, the average RBC UDPgalactose concentration is significantly lower than normal (2–5) and the ratio of UDPglucose to UDPgalactose is abnormally high (2–5). These observations have led to the hypothesis that the maintenance of cellular UDPgalactose pools at normal amounts requires the flux of galactose through the Leloir pathway: phosphorylation to galactose-1-P, which reacts with UDPglucose catalyzed by galactose-1-phosphate uridyltransferase to form UDPgalactose. It is the latter reaction that is blocked in patients with transferase-deficient galactosemia (whose treatment requires a lactose-free diet). Thus, the examination of cellular UDPhexose concentrations in patients whose galactose intake has been documented to be low affords the opportunity of testing this hypothesis.

Measurement of UDPhexoses in RBCs of the three studied groups indicates that the average UDPgalactose content is significantly lower than normal in patients aged < 10 y with MSUD and PKU and the ratio of UDPglucose to UDPgalactose is significantly higher than normal. This same conclusion is reached when all the subjects are analyzed together. Our analysis shows that the low average RBC UDPgalactose concentration occurs in MSUD patients who ingest either 130 mg or even 3 g galactose/d. These data suggested that a normal concentration would depend on the intake of > 3 g/d and influenced us in the provision of a much larger amount in our galactose-administration protocol.

Although the average RBC UDPgalactose concentration in patients on the low-protein, galactose-limited diets was significantly less than normal, the values did not differ from the average RBC UDPgalactose concentration of 26.1 ± 9.3 nmol/g hemoglobin observed in 51 galactosemic patients aged ≤ 10 y that we reported previously (5). This is particularly relevant to the report by Kirkman (13) that the RBC UDPgalactose content of classic galactosemic patients does not differ from that of a group of control subjects consisting of PKU patients. Indeed, we confirmed this finding in our group of PKU patients (30.2 ± 7.1 nmol/g hemoglobin) when compared with galactosemic patients.

The data suggest that there is no correlation between moderately limited protein intake and RBC UDPhexose concentration. There are data, however, from animal studies that a high protein intake stimulates uracil nucleotide synthesis, thus making protein intake a positive affector of uridine synthesis and tissue UDPglucose content (14). It may be that the protein intake of our subjects was below a threshold for a stimulatory effect, which could take place at the usual protein intake in normal children, ≥ 2.5 g · kg body $wt^{-1} \cdot d^{-1}$ (15). The question arises whether galactosemic patients who have low RBC UDPgalactose concentrations, as a consequence of their low galactose intake, are limiting their protein intake below that of normal. There appears to be no published data on this point.

Of the complex factors that control steady state concentrations of uridine sugar nucleotides in erythrocytes, subject age is clearly important. The values for both UDPgalactose and UDPglucose are lower in normal subjects aged > 10 y (4, 5). A lower daily protein and galactose intake in normal adults might be considered an explanation but these phenomena are observed in older galactosemic patients in whom galactose and possibly protein had been limited in childhood. These same phenomena of age-related decreases in RBC UDPhexoses, however, do not occur in other metabolic patients with limited protein and galactose intakes; the RBC UDPgalactose concentrations are essentially the same as those of healthy persons aged > 10 y and the difference seen between these patients and healthy persons aged < 10 y is obliterated.

Galactose intake is a factor in both RBC and WBC concentrations of UDPgalactose, as shown by the effect of administering the galactose equivalent of three glasses of milk to patients with MSUD. The 19.5 g galactose fed, which far exceeds the usual galactose intake of these patients, raised the average RBC UDPgalactose content from below to above the normal average concentration during the period of supplementation. The higher than normal ratio of UDPglucose to UDPgalactose decreases with galactose supplementation and returns to the pretreatment value when galactose supplementation ends. These findings mimic the observations we made after giving acute loads of galactose to normal adult subjects in whom changes in UDPhexose concen-

trations persist only as long as plasma galactose is elevated (6). The response of chronic galactose feeding also mimics the UDPhexose response of WBCs observed during acute galactose administration. In both protocols the WBC UDPgalactose response is much greater than that seen in RBCs and in contrast with RBCs, the response involves an increase in total cell UDPhexose content that appears to persist after galactose feeding is stopped (6).

Our observations clearly demonstrate that dietary galactose is a factor in establishing the steady state concentration of RBC UDPgalactose and the maintenance of a normal ratio of UDPglucose to UDPgalactose. A vexing question is why such metabolic alterations occur in both these patients and in galactosemic patients with diminished galactose flux through the Leloir pathway. Because the sugar nucleotide interconversion is an equilibrium reaction of UDPgalactose-4-epimerase, even in the absence of UDPgalactose formation from the metabolism of galactose, its concentration should be determined from normal UDPglucose concentrations. The findings imply that there is an alteration in the ability to achieve epimerase-mediated equilibrium between UDPglucose and UDPgalactose. The etiology of this disequilibrium is unknown.

The effect of low UDPgalactose concentrations in the patients as well as in galactosemic patients, is open to speculation. Whether, the moderate reduction in concentration of RBC UDPgalactose, the obligate donor of galactose, observed in galactosemic patients and these metabolic patients reflect a defective glycoconjugate formation in brain or ovary is unknown. Our data suggest that, in metabolic patients with galactose-restricted diets, supplementation with galactose may prevent the lowered UDPgalactose concentration. Conclusive demonstration of long-term systemic effects of UDPhexose manipulation remains a scientific challenge.

We thank the families and patients without whom these studies could not have been performed, and Chris Boardman for statistical assistance. The assistance of Kelly Green and Jule Ann Henstenburg in the analysis of diet records is appreciated. Harvey L Levy was especially generous, contributing the specimens and clinical information on many of the patients with PKU.

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