Correction of Leukocyte Adhesion Deficiency Type II With Oral Fucose

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We describe a simple, noninvasive, and effective therapy for leukocyte adhesion deficiency type II (LAD II), a rare inherited disorder of fucose metabolism. This disorder leads to an immunodeficiency caused by the absence of carbohydrate-based selectin ligands on the surface of neutrophils as well as to severe psychomotor and mental retardation. The fucosylation defect in LAD II fibroblasts can be corrected by addition of L-fucose to the culture medium. This prompted us to initiate dietary fucose therapy on a patient with LAD II.

Oral supplementation of fucose in this patient induced the expression of fucosylated selectin ligands on neutrophils and core fucosylation of serum glycoproteins. During 9 months of treatment, infections and fever disappeared, elevated neutrophil counts returned to normal, and psychomotor capabilities improved.

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cerebrospinal fluid (CSF) cultures were always sterile and did not identify any bacterial origin of the infection. Coronavirus was isolated from stool samples on several occasions and was the only infectious agent ever isolated from the patient. Systemic antibiotic treatment with cefotaxime or clindamycin was initiated on several occasions and normalized body temperature within 2 days. Even in the intervals between the febrile episodes, low-dose cephalosporins were administered in an attempt to reduce the frequency of these events.

We report here on the successful treatment of this patient by oral supplementation of fucose. In addition to the re-expression of selectin ligands on neutrophils, the drastically elevated peripheral neutrophil counts could be reduced to normal levels, no episodes of fever occurred after beginning therapy, and psychomotor capabilities and growth of the patient improved. Although expression of selectin ligands was rescued, fortunately, fucose therapy did not lead to the re-expression of the α1,2-fucosylated H-antigen, avoiding complications due to the patient’s low-titer anti-H antibodies.

MATERIALS AND METHODS

Materials. L-Fucose (fucose) from Kaden Biochemicals (Hamburg, Germany) and from Pfannstielh Laboratories (Waukegan, IL) was manufactured by crystallization of acid hydrolyzed fucoydan. Anti-P-selectin glycoprotein ligand-1 (PSGL-1) monoclonal antibody (MoAb) PLI,15 was from Coulter-Immunotech (Hamburg, Germany). Anti-α-Le4 mouse IgM (CSLEX-1) was obtained from ATCC (Manassas, VA). Anti-H-antigen was from Mast Diagnostica (Reinfeld, Germany). L-Selectin (LCA) and Histopaque 1077 and 1119 were manufactured by Sigma Chemical Co (St Louis, MO). E-selectin–IgG and P-selectin–IgG fusion proteins contained the first 4 and 5 domains, respectively, of human E-selectin and P-selectin, respectively, in frame with IgG. 16 The VE-cadherin-IgG fusion protein, used here as negative control, contained the complete extracellular part of mouse VE-cadherin and was constructed as described.16 In certain experiments, cells were preincubated for 10 minutes with 40 µg/mL of anti-PSGL-1 MoAb PLI.12 Incubations with purified selectin-IgG fusion protein or VE-cadherin-IgG were performed at 25 µg/mL. Cells were washed in the same buffer and binding was detected with either 10 µg/mL B-phycocerythrin–conjugated anti-human IgG or 30 µg/mL fluoresecin isothiocyanate (FITC)-conjugated rabbit anti-mouse antibody. As negative control, cells were incubated with an irrelevant IgM control antibody. After washing, the detection was performed using an FITC-conjugated rabbit anti-mouse IgM antibody. All antibodies were incubated in saturating concentrations.

Flow cytometry. Fluorescence-activated cell sorting (FACS) analysis of peripheral blood leukocytes was performed as described.16 E-selectin–IgG and P-selectin–IgG fusion proteins contained the first 4 protein domains of the respective mouse selectin (lectin domain, epidermal growth factor [EGF] repeat, first 2 consensus repeats) fused to the hinge region of human IgG1, followed by the 2 constant Ig domains, as described.15 The VE-cadherin-IgG fusion protein, used here as negative control, contained the complete extracellular part of mouse VE-cadherin and was constructed as described.16 In certain experiments, cells were preincubated for 10 minutes with 40 µg/mL of anti-PSGL-1 MoAb PLI.12 Incubations with purified selectin-IgG fusion protein or VE-cadherin-IgG were performed at 25 µg/mL. Cells were washed in the same buffer and binding was detected with either 10 µg/mL B-phycocerythrin–conjugated anti-human IgG or 30 µg/mL fluoresecin isothiocyanate (FITC)-conjugated rabbit anti-mouse antibody. As negative control, cells were incubated with an irrelevant IgM control antibody. After washing, the detection was performed using an FITC-conjugated rabbit anti-mouse IgM antibody. All antibodies were incubated in saturating concentrations.

Measurement of serum fucose concentrations. Serum samples were obtained before and after therapy, normal human control sera, and purified human IgM standard at different concentrations were individually diluted in PBS and coated on the wells of a microtiter plates. The wells were blocked with 3% BSA in PBS overnight at 4°C, washed, and incubated with anti-human IgM alkaline phosphatase conjugate for 2 hours at room temperature. This was followed by development using p-nitrophenyl phosphate substrate. Serum IgM levels were quantitated using regression analysis from the reactivity of purified human IgM.

RESULTS

Fucose corrects defective fucosylation in cultured LAD II fibroblasts. To determine whether defective fucosylation in LAD II cells could be corrected by exogenous fucose, we cultured fibroblasts from a healthy control and from the patient in Dulbecco’s modified Eagle’s medium (DMEM) containing 1 or 10 mmol/L fucose. After 5 to 7 days in culture, cells were analyzed by flow cytometry for binding of LCA, a lectin that recognizes α-glucose and α-mannose with low affinity and α1,6-core fucosylated N-linked oligosaccharides with high affinity. LAD II cells incubated with 1 mmol/L fucose showed increased LCA binding (Fig 1, lower panel, thin, green line), and incubation with 10 mmol/L fucose resulted in LCA binding even greater than that seen in control cells (Fig 1, lower panel, bold, blue line). This is in agreement with fucose supplementation studies of cultured fibroblasts of the first identified LAD II patients, analyzed for binding to Lotus tetragonolobus agglutinin (LTA), another fucose-dependent lectin.9 Fucose supplementation did not change LCA binding in control cells (Fig 1, upper panel). Although GDP-mannose can be converted into GDP-fucose, the addition of 1 mmol/L mannose to the culture
medium had no effect on the synthesis of fucosylated molecules of either cell line (data not shown). We conclude that exogenous fucose can rescue the LAD II phenotype in fibroblasts and therefore decided to treat the patient with a fucose-containing diet.

**Fucose treatment of the LAD II patient.** At the time we considered fucose therapy, there were no data on the kinetics of fucose absorption in humans. We determined the free fucose concentration in the serum of healthy children and adults by GC/MS and found it to be less than the detection level of 5 µmol/L (data not shown). Oral administration of fucose to healthy volunteers (50 to 100 mg/kg body weight [BW]) increased serum fucose concentrations, which reached a maximum of 110 to 210 µmol/L after 60 minutes (Fig 2). Fucose was
cleared from the serum with a half time of 100 minutes. After 24 hours, fucose in the serum was still greater than basal levels.

The LAD II patient was treated with 5 doses of fucose per day, starting at 25 mg/kg BW. A single dose of fucose was dissolved in 10 mL water and administered by gastrointestinal tube 20 to 30 minutes before feeding the child. Single doses were slowly increased to a maximal dose of 492 mg/kg BW after 277 days. Peak fucose concentrations in the blood were monitored once weekly 60 to 90 minutes after ingestion and ranged from 39 to 358 µmol/L during the course of therapy. Fucose doses and measured serum fucose concentrations over the full course of therapy are given in Table 1.

**Fucose therapy restores selectin binding.** The effect of fucose therapy on selectin ligand expression in neutrophils was determined by FACS analysis using the MoAb CSLEX-1 against sLeα and 2 selectin-IgG fusion proteins. These proteins contained the N-terminal C-type lectin domain, the EGF-like domain, and 2 consensus repeats of E- or P-selectin fused to the Fc part of human IgG1. Before fucose therapy, neutrophils did not bind to either P- or E-selectin (Fig 3/I). After 40 days of therapy and gradually increasing the dosage to 5 doses/day of 140 mg fucose/kg BW, P-selectin–IgG chimera binding reached approximately 50% of that of control cells (Fig 3B/II).

Because selectins are Ca²⁺-dependent cell adhesion molecules, we tested the specificity of the observed binding by incubating the cells with P-selectin–IgG in the presence of EDTA. As shown in Fig 3B/II, EDTA blocked binding demonstrating selectin specificity of the FACS signal. As an additional control, we preincubated the cells with the MoAb PL-112 against PSGL-1, the major P-selectin ligand on human leuko-

### Table 1. Serum Fucose Concentrations Determined Over the Full Course of Therapy

<table>
<thead>
<tr>
<th>Day of Treatment</th>
<th>mg Fucose/kg BW (single dose)</th>
<th>Serum Fucose Concentration (µmol/L)</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>&lt;5</td>
</tr>
<tr>
<td>10</td>
<td>55</td>
<td>39</td>
</tr>
<tr>
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<td>153</td>
</tr>
<tr>
<td>277</td>
<td>492</td>
<td>234</td>
</tr>
</tbody>
</table>

Blood samples were taken 60 to 90 minutes after ingestion. Treatment was started with 25 mg/kg BW (single dose); the first determination of serum fucose concentration was performed at day 10.
GDP-fucose can either be synthesized from fucose (salvage pathway) or from GDP-mannose (de novo pathway). GDP-fucose that is metabolized by fucosyltransferases needs to be transported into the Golgi from the cytosol.
cytes. This treatment blocked P-selectin–IgG binding as effectively as the EDTA control (Fig 3C/II), demonstrating that it was PSGL-1 specific. In contrast, therapy did not improve E-selectin–IgG chimera binding (Fig 3A/II), and sLe\(^\text{a}\) expression increased only slightly as monitored with the MoAb CSLEX-1 (Fig 3D/II).

E-selectin–IgG binding was not detectable during the first 100 days of therapy, during which fucose doses had been increased to 5 doses/day of up to 207 mg/kg BW (not shown). Doses were further increased within the next 100 days to 5 doses/day of 333 mg/kg BW each. After a total of 200 days from the start of therapy, FACS analysis was repeated. As seen in Fig 3A/III and 3D/III, prolonged administration of higher doses of fucose resulted in restoration of E-selectin–IgG binding along with good recovery of sLe\(^\text{a}\). E-selectin–IgG binding was sensitive to EDTA treatment (Fig 3A/III) and resulted in signals that were 20% of those observed on healthy neutrophils. Similarly, sLe\(^\text{a}\) recovered to 20% and P-selectin–IgG binding to 72% that of healthy cells, respectively (Fig 3B/III). Results of the FACS analysis for P- and E-selectin binding could be reproduced in nonstatic rotation adhesion assays with E- and P-selectin–IgG immobilized in 96-well microtiter plates (data not shown). Our results demonstrate that re-expression of E-selectin ligands required higher doses of fucose than the restoration of P-selectin ligands.

LAD II patients have the Bombay phenotype blood group, because they lack the \(\alpha_1,2\)-fucosylated H-antigen.\(^4,10\) Therefore, we had to consider the possibility that fucose supplementation therapy could lead to synthesis of the H-antigen, possibly causing unwanted autoimmune side effects due to anti-H-antigen antibodies. Fortunately, the H-antigen did not appear on the patient's erythrocytes at any time during the entire 280 days of fucose therapy, as was tested by FACS analysis. Figure 4 shows that the FACS signal for the H-antigen was negative both before therapy and after 280 days of therapy at doses of 492 mg/kg BW. Similarly, no signal greater than that of the second antibody alone or a control IgM antibody was detected on erythrocytes of Bombay phenotype. For comparison, the mean fluorescence of the H-antigen signal on healthy erythrocytes was 400-fold more intense than that of the negative controls (Fig 4). While incubations with anti-H antibodies were performed in the course of FACS analysis, no sign of cell agglutination was observed with LAD II cells. Measuring hemoglobin, reticulocytes, lactic acid dehydrogenase (LDH), and haptoglobin levels in blood samples during the course of the therapy gave no indication for hemolysis during therapy. Thus, even at fucose doses that led to the re-expression of E-selectin ligands, the H-antigen was still undetectable. We conclude that different levels of fucose are required for the biosynthesis of different fucosylated glycoconjugates.

**Fucose therapy corrects core-fucosylation of serum glycoproteins.** To verify that fucose therapy also affected other glycoproteins, we analyzed \(\alpha_1,6\)-core fucosylation of N-linked oligosaccharides on serum glycoproteins using an MoAb (CAB4) that is highly specific for fucose linkage in this structure.\(^3\) Ig heavy chains (\(\gamma\) and \(\mu\)) are the major core fucosylated serum glycoproteins. Western blots of sera from 4 different normal individuals detected a major protein of approximately 72 kD that corresponds to purified human IgM (\(\mu\) chains). This band was absent from the pretherapy sample of the patient (Fig 5, lane 1). However, within 1 week of starting fucose therapy, core fucosylation of IgM \(\mu\) chains was detectable and reached 35% of normal by 32 days (Fig 5). Serum IgM levels, on the other hand, showed little variation at all time points, as was determined by enzyme-linked immunosorbent assay (ELISA) using antihuman IgM antibodies that recognize IgM independently of its glycosylation. Thus, the increase in core fucosylation was not due to a corresponding increase in IgM. A band at 53 kD (not shown) corresponds to IgG \(\gamma\) chains and also showed improved core fucosylation during therapy. These results also demonstrate that fucose linked in a different way than in selectin ligand structures was restored by fucose therapy. In addition, the fucose detected on IgM was incorporated in N-linked carbohydrates, in contrast to the O-linked carbohydrates preferentially found on most selectin ligands.
These results demonstrate that fucose therapy is sufficiently robust to partially correct impaired fucosylation of major serum glycoproteins and is not restricted to the fucosylated selectin ligands, which are quantitatively minor glycoproteins. Moreover, the results show that fucose corrects glycosylation of both N- and O-linked species.

Fucose therapy reduces peripheral neutrophil counts to normal levels. Before beginning fucose therapy, this patient had serious recurrent infections and high fever that required continuous low-dose antibiotic treatment. Peripheral neutrophil counts before therapy were consistently high (10,000 to >50,000/µL blood). Within 10 days of starting fucose therapy, neutrophil levels returned to the normal range of 1,500 to 8,500 cells/µL blood (Fig 6). Consistent with this effect, there were no further infections and antibiotic prophylaxis was discontinued. However, lymphocyte counts were not normalized by fucose therapy (mean before therapy, 11,632/µL; mean during therapy, 14,144/µL; normal, 4,000 to 10,000/µL).

Psychomotor development during fucose therapy. Psychomotor development improved during fucose therapy. The widely administered Griffiths Test measured changes in psychomotor functioning in the areas of head and body motor control, eye-hand coordination, speech and language, and social interaction. A score of 100 EQ is equivalent to the 50th percentile. Before therapy, the patient showed a severe psychomotor retardation as evidenced by a total score of 28.5 EQ. Reassessment after 3 months of fucose therapy showed a significant increase in psychomotor functioning, with a total score of 45 EQ. Equal improvement was found across all of the assessed domains. Fucose concentrations in the CSF were measured (n = 2) at approximately 25% of the serum fucose concentrations, indicating that fucose crosses the blood-brain barrier.

At present, it cannot be decided whether the marked improvement is a consequence of the generally improved clinical condition of the child without recurrent episodes of high fever or whether fucose treatment has a specific effect on the psychomotor and mental development of the child. At 2 years of age, the boy is still severely retarded. He does not speak yet, but is able to actively turn around when lying on his back, takes toys that are presented in his hands, and starts to sit briefly without support.

**DISCUSSION**

We have shown that the defect in fucose metabolism in an LAD II patient can be partially corrected by oral fucose substitution therapy. Peripheral neutrophil counts decreased to normal values, and the frequently observed recurrent episodes of infections and high fever did not occur again after the onset of therapy.

LAD II is based on an as yet undefined genetic defect in fucose metabolism. No fucosylated glycoconjugates have yet been identified in these patients. The most significant consequence of this defect is the absence of α1,3-fucosylated sLe^a^-like selectin ligands, which causes an immunodeficiency.
due to impaired leukocyte migration into sites of infection in these patients. Other fucosylated glycoconjugates, such as the α1,2-fucosylated H-antigen on erythrocytes and the α1,6-core fucosylated N-glycans on serum and cell surface proteins, are also missing. Because all of these glycoconjugates are synthesized by different fucosyltransferases, Etzioni et al. suggested that LAD II is probably caused by a defect in the synthesis of the common donor substrate, GDP-fucose.

GDP-fucose is synthesized by 2 different pathways, a de novo and a salvage pathway (Fig 7). The de novo pathway starts from GDP-mannose, which itself originates from glucose or mannose. The 2 enzymes that catalyze the conversion of GDP-mannose to GDP-fucose are GDP-mannose-4,6-dehydratase (GMD) and the FX protein, a homodimer that has epimerase as well as reductase activity. The salvage pathway starts from fucose that is taken up into the cell or derived from degraded glycoconjugates and is converted into GDP-fucose via a fucose-kinase followed by a GDP-L-fucose-pyrophosphorylase.

In cultured mammalian cells, the flux through the salvage pathway is thought to contribute only approximately 10% to the synthesis of the total GDP-fucose20; however, high concentrations of exogenous fucose were sufficient to partially rescue expression of α1,6-core fucosylated N-glycans on fibroblasts of the patient. This is in agreement with results by Karsan et al.20 for cells of the other LAD II patients. These results lead to the conclusion that the defect in LAD II is based on an insufficient amount of GDP-fucose. This could be due to a mutation in one of the enzymes in the de novo GDP-fucose biosynthetic pathway or a mutation that affects the efficiency of the transport of GDP-fucose from the cytosol, where it is synthesized, to the Golgi, where it is used. The mammalian GDP-fucose transporter has not yet been purified or cloned.

Despite these encouraging in vitro results, there were 2 major concerns that argued against using fucose supplementation therapy for the patient. First, fucose ingestion studies had never been performed in humans. It was discouraging that 1 mmol/L fucose in the cell culture medium only partially restored α1,6-core fucosylated N-glycans on fibroblasts and that 10 mmol/L fucose was necessary for complete rescue. Second, we had to expect that re-expression of fucosylated glycoconjugates would include the expression of the α1,2-fucosylated H-antigen. Although titers of anti-H antibodies were very low and only undiluted serum of the patient could agglutinate healthy erythrocytes, we had to consider the possibility of complications due to hemolysis. For these reasons, we started the therapy with low doses of fucose that were gradually increased, while we carefully monitored for any signs of hemolysis. Fortunately, low levels of sLex expression and a 50% recovery of P-selectin binding of neutrophils was observed as early as 40 days after beginning therapy, without any sign of H-antigen re-expression on the erythrocytes. Even after 280 days of therapy using 5 doses/day of up to 492 mg fucose/kg BW, H-antigen was undetectable. This may suggest that different levels of GDP-fucose are necessary for the synthesis of α1,3-fucosylated selectin ligands and α1,2-fucosylated H-antigen. It is possible that the α1,2-fucosyltransferase that generates the H-antigen requires higher concentrations of GDP-fucose for its activity than the α1,3-fucosyltransferases that generate selectin ligands.

Alternatively, erythrocyte progenitors might have a quantitatively insignificant or inefficient salvage pathway for GDP-fucose synthesis.

The differences in the expression kinetics of the P- and E-selectin ligands on neutrophils during fucose therapy were even more surprising. Using 5 daily doses of 140 mg/kg, P-selectin–binding of neutrophils was re-established to 50%, whereas no binding was seen with E-selectin. Even treatment with 5 doses/day of 207 mg/kg BW E-selectin ligands were still undetectable. Continuing the same regimen and increasing the doses to 333 mg/kg produced E-selectin binding that was 20% of the intensity of healthy control cells. We conclude that different levels of GDP-fucose are necessary to express P- and E-selectin ligands. Because 2 different α1,3-fucosyltransferases, Fuc-TIV and Fuc-TVII, are expressed in myeloid cells, it would be possible that E- and P-selectin ligands differ in their dependence on each of these enzymes and that each of the 2 enzymes differs in its Kₘ for GDP-fucose. Alternatively, P-selectin ligands could require lower levels of fucosylation for selectin-binding than for E-selectin ligands. The latter explanation would be in agreement with studies on activated T cells, in which PSGL-1 binds well to P- and E-selectin shortly after antigen-specific activation, but only retains its ability to bind to P-selectin at later stages of activation.21 These results could be explained by different levels of fucosylation of PSGL-1 possibly caused by different levels of fucosyltransferase expression at different time points of activation. In the present study, different levels of fucosylation might have been caused by re-establishing different levels of GDP-fucose during therapy. Indeed, it has been shown that PSGL-1 has only few fucosylated O-linked oligosaccharides, and it is possible that only one site is sufficient for binding to P-selectin,22,23 whereas more sites might be necessary for binding to E-selectin.

Other fucosylated glycoconjugates were also partially restored during fucose therapy. The recovery of core α1,6-fucosylated N-glycans on serum IgM heavy chains is significant, because it shows that treatment is sufficiently robust to drive the fucosylation of major serum glycoproteins. The half life of IgM in serum is 5 to 10 days, which may explain why we could detect this change very early in the therapy. Much lower levels of fucose were necessary to restore core fucosylation of IgM in the patient than to normalize core fucosylation of N-linked oligosaccharides of fibroblasts in culture. As discussed above, the variable effectiveness of fucose therapy suggests that correction may be cell-type and glycoconjugate specific.

Despite the successful correction of immunodeficiency-related defects in LAD II, correcting the delayed psychomotor development was expected to be more difficult to achieve. However, the patient showed significant psychomotor improvement while on fucose therapy. Fucose crosses the blood-brain barrier, resulting in elevated free fucose levels in the CSF during therapy. It is a topic of further investigation whether fucosylation of glycoproteins produced in the central nervous system and found in the CSF is influenced by fucose therapy. A long-term follow-up of different LAD II patients will be needed to decide whether fucose treatment will have a beneficiary effect in avoiding the severe psychomotor and mental retardation in these children.
Fucose ingestion studies have not been performed in humans; therefore, we need to consider potential side effects of dietary fucose. Fucose is a potent inhibitor of myoinositol transport (Ki, 3 mmol/L).\textsuperscript{24} Neuroblastoma cells exposed to 1 to 30 mmol/L fucose decrease incorporation of myoinositol into phospholipids.\textsuperscript{25} Rats fed high amounts of fucose (10% to 20% of total weight of food) showed nerve conduction velocity that is much lower than those used on cultured cells. Third, humans can synthesize myoinositol, whereas rats and mice might not. We found that motor nerve conduction velocities in the patient were normal after 5 and 9 months of therapy (Marquardt and Kurlermann, unpublished observations). Future studies need to determine whether increasing the level of fucose substitution is beneficial.

In cells, fucose is found in N- and O-linked oligosaccharides and in glycosphingolipids. Consequently, the genetic defect in LAD II leads to a multisystemic disorder. The list of diseases resulting from inherited glycosylation defects may be growing in the future.\textsuperscript{28,30} Several of these genetic defects cause multisystemic disorders. Well-studied examples are the carbohydrate-deficient glycoprotein syndromes (CDGS) that are characterized by hypoglycosylation of glycoproteins. Oral mannose supplements were successfully used to reverse clinical and biochemical symptoms in a patient with a recently identified subtype of these syndromes, CDGS type 1b.\textsuperscript{31} Since then, this therapy has been effectively used in other patients with the same disorder. We show here that another simple monosaccharide effectively alleviates the major symptoms caused by a glycosylation defect. Needless to say, the simplicity of an oral substitution therapy is superior to a bone marrow transplantation or some form of gene therapy. In addition, fucose substitution allowed us to successfully treat the patient without precisely knowing the gene that is affected in LAD II.

**ACKNOWLEDGMENT**

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