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Lower Insulin Secretory Response to Glucose Induced by Artificial Nutrition in Children: Prolonged and Total Parenteral Nutrition

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ABSTRACT: Long-term parenteral nutrition (TPN) in children is associated with sustained hyperinsulinemia due to a high nutriment infusion flow 12 h/24 h, with plausible lipotoxicity secondary to repeated lipid infusions and with changes in incretin hormone release. The aim of this study was to test whether long-term TPN can lead to an alteration in β-cell function. Thirteen children (age 9.5 ± 3.9 y) on total TPN without obvious alternation in glucose tolerance were included. β-Cell function was quantified with an intravenous glucose tolerance test (IVGTT) and a graded glucose infusion. First phase insulin release (FPIR) was low in five patients. The same demonstrated a lower insulin release under graded glucose infusion, although plasma glucose reached values as high as 15 mM. These data emphasize that metabolic conditions induced by TPN can lead to lower insulin secretory response to glucose. Patients who remain dependent on TPN are at risk of developing glucose tolerance disorders. **(*Pediatr Res* 62: 624–629, 2007)**

Risk factors for type 2 diabetes have been well identified for years. Among them, lipotoxicity, chronic hyperinsulinemia, and alteration in the enteroinsular axis have been debated (1–3). Clinical situations, such long-term long-term parenteral nutrition (TPN), encompassing these metabolic conditions are not frequently studied. In theory, they could lead to alteration in glucose homeostasis or insulin release. In one pediatric cohort followed in two children's hospitals in Paris, the appearance of some cases of chronic and unremitting hyperglycemia during infusion, requiring insulin, suggested that TPN could promote glucose homeostasis disorders.

In examples like intestinal mucosa deficiency or neonatal extended intestinal resections, TPN has dramatically changed the prognosis (4,5). Adequate nutrition is now provided to these children as daily home care. However, TPN is a nonphysiologic route of nutrient delivery. Nutrient mixtures are infused nightly over 10–14 h in sick children in whom caloric needs are equal or greater than in healthy children. High glucose and insulin secretagogue nutrients induce chronic hyperinsulinemia lasting approximately 12 h per day (6). High lipid infusion rates could promote peripheral and central lipotoxicity. Moreover, some intestinal diseases have been shown to be associated with an alternation in incretin hormone release (7).

Insulin release in children on TPN was evaluated in one study 10 y ago (8). It was measured during an intravenous glucous tolerance test (IVGTT) and a hyperglycemic clamp. No obvious alterations in insulin release were observed. Patients had an insulin response to IVGTT similar to that of control children of the same age. Insulin release was greater than that in healthy young adults during a hyperglycemic clamp. However, patients were not observed among standardized metabolic conditions. Many of them were not totally dependent on TPN. Indeed, β-cell failure could not be reported there.

The aim of the study was to test whether metabolic conditions associated with long-term TPN could lead to an alteration β-cell function before any obvious alteration in glucose tolerance.

METHODS

Patients. Thirteen children on long-term TPN were included. Inclusion criteria were the following: children on PN since birth and for at least 5 y, >80% of their daily caloric intake *via* the parenteral route, no obvious alternation in glucose tolerance as defined by fasting glycemia (before the beginning of TPN) <6.93 mM and Hb A_{1C} level <6% at the time of the study, and no drugs known to affect glucose tolerance.

Patients were hospitalized for 4 d in the Clinical Investigation Unit at the Robert Debré Hospital. TPN was infused between 1600 h and 0400 h. Tests began 6 h after the end of infusion. Glucose and insulin were infused in the central venous catheter used for parenteral infusion (superior vena cava). Written informed consent from parents and assent from children were obtained. The study protocol was reviewed and approved by the ethical committee of Paris-St. Louis University.

Insulin sensitivity. Insulin sensitivity was measured with a 2-h euglycemic hyperinsulinemic clamp as described by de Fronzo and Beckles (9). First, a bolus of insulin was followed by a continuous infusion rate of 40 mU/m^2/min. Plasma glucose was clamped at 5.5 mM with a variable rate of 30% glucose solution. Peripheral insulin sensitivity was determined from the amount of

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Abbreviations: FFM, fat-free mass; **FPIR,** first phase insulin release; **GDI,** glucose disposal index; **IVGTT,** intravenous glucose tolerance test; **TPN,** long-term parenteral nutrition

Table 1. *Characteristics of the patients*

Patient	1	2	3	4	5	6
Age, y	10	6	6	6	18	16
Sex	M	M	F	F	F	M
Tanner stage	I	I	I	I	IV	IV
Weight, kg (SD)	30 (+0.5)	20 (0)	21.0 (+0.5)	20.9 (+1.0)	50.0 (0)	58.4 (−0.8)
Height, cm (SD)	131 (−1)	112 (−0.5)	115 (+0.5)	102 (−2.5)	163 (+0.3)	169 (−0.7)
BMI, kg/m^2 (SD)	7.5 (1.7)	15.9 (0.5)	15.9 (0.5)	20.1 (3.3)	18.8 (0.1)	20.4 (0.2)
FM, %	26.7	18.1	19.6	38.9	29.1	18.5
1st + 2nd generation family history	N	Y	N	Y	N	Y
Hb A_{1C}	5.4	4.5	4.9	4.4	5	5.5
Fasting glycemia, mmol/L	4.9	4.6	5.0	5.6	6.0	5.6
Fasting serum insulin, mUI/L	2.9	2.1	2.9	4.1	4.9	16.5
Fasting HGO, mg/kg/min	2.8	4.9	2.6	3.8	6.9	3.1
Intestinal disease	Neonatal volvulus	Hirschsprung disease	Chronic intestinal pseudo obstruction syndrome	Epithelial dysplasia	Chronic intestinal pseudo obstruction syndrome	Chronic intestinal pseudo obstruction syndrome
Small intestine (cm)	41	80	27	Intact	180	Intact

FM, fat mass; N, no; Y, yes.

glucose required to maintain euglycemia over the final 40 min at steady state reported for glycemia at the steady state.

Hepatic glucose output (HGO) was measured with [^{2}H]-glucose administered as a bolus (5 mg/kg) starting 240 min before starting insulin infusion followed by a constant infusion rate until the end of the test. Isotopic enrichment was determined 3, 4, and 6 h after the end of the parenteral infusion and at steady state. We could then check that glucose output was constant and at a fasting equivalent rate before the beginning of the clamp.

IVGTT. The acute insulin response was determined by IVGTT (10). After obtaining baseline samples, an IV bolus of glucose was injected (0.5 g/kg body weight). Blood samples for glucose and insulin were obtained at 1, 3, 5, and 10 min after the bolus. Glucose disposal index (GDI) was calculated as logarithm of product of insulin sensitivity and sum of 1 and 3 min of serum insulin.

Graded IV glucose infusion. Insulin secretion was measured using a graded IV glucose stimulation. Glucose was infused over 40-min periods at infusion rates of 4, 8, 12, 16, and 30 mg/kg/min, respectively. Blood samples were taken every 10 min to measure plasma glucose and at 30, 40, 70, 80, 110, 120, 150, 160, 190, and 200 min to measure insulin and C peptide concentrations. The test was stopped if the plasma glucose concentration was >22 mM.

GLP-1 release. GLP-1 (7-36 amide) release response to enteral stimulation was determined using an oral load of glucose (50 g). Blood samples were collected at baseline and at 30 and 120 min. GLP-1 release is maximum at 30 min and returns to baseline values at 120 min.

Analytical methods. Plasma glucose concentrations were measured by the glucose oxidase method (Glucose Analyzer GM9, Analox, London, UK). Free fatty acids were measured by an enzymatic colorimetric method (NEFA C, Wako Chemicals GmbH, Neuss, Germany). Serum insulin concentrations were measured using an immunoradiometric assay (Bi-Insulin IRMA, CIS Bio International, Gif sur Yvette, France). The cross-reactivity with proinsulin and des 31,32 split proinsulin was <1%. The detection limit was 0.5 mU/L. The interassay coefficient of variation was <8%. Serum GLP-1 (7-36) amide concentrations were measured using an immunoradiometric assay (Linco Research, St. Charles, MO). Alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transferase, and alkaline phosphatase levels were determined by enzymatic methods using an ADVIA analyzer (Bayer Diagnostics, Puteaux, France). Anti–glutamic acid decarboxylase (GAD) autoantibodies and anti–tyrosine phosphatase (IA-2) autoantibodies were determined by radioimmunossays (GAD-AB and IA2-AB, CIS Bio International). Body composition was assessed by dual energy x-ray absorptiometry (GE Medical Systems, Prodigy Lunar Radiation, Madison, WI).

Statistical considerations. This was an exploratory study. Data were analyzed with SAS software version 8-02 (SAS, Cary, NC). Data are expressed as mean ± SE. We compared groups using the nonparametric Wilcoxon rank test. A p value <0.05 was considered statistically significant.

RESULTS

Subjects. Characteristics of the subjects are shown in Table 1. Thirteen children and adolescents (eight girls and five boys) were included. Median of age was 9.5 y (range, 6.2–18.2). Children were either prepubertal or at the end of puberty. Median body mass index (BMI) was + 0.45 SD (range, −0.29 to +3.28). One patient was obese (BMI, 3.28 SD). The mean percentage of fat mass was 25.8% (range, 18.5%–38.9%). Hb A_{1C} was normal in all patients (median, 5%) except one boy in whom it reached 6.0%. Eight had second-generation family history of type 2 diabetes. One had first-generation family history.

Liver function was assessed on hepatic enzymes concentration. Both ALT and AST were increased in four patients (AST: 77, 110, 266, 96 UI/L, respectively, in patients 3, 4, 11, 13; normal range, 5–45 UI/L; ALT: 47, 65, 241, 59 UI/L, respectively, in patients 3, 4, 11, 13; normal range, 5–45 UI/L). AST was elevated in another patient (AST: 58 UI/L in patient 2). Alkaline phosphatase blood concentration was normal in all patients. Gamma-glutamyl transpeptidase (GGT) blood concentration was elevated in eight patients (157, 95, 116, 42, 54, 41, 373, 58 UI/L, respectively, in patients 1, 2, 3, 4, 5, 7, 11, 13; normal range, 7–25 UI/L).

To exclude an ongoing autoimmune process, autoantibodies associated with type 1 diabetes were measured. Anti-GAD and anti-IA2 were negative in all patients, except in one girl in whom anti-IA2 was positive (patient 12; IA2: 2.1).

Children were on TPN because of extended intestinal resection or mucosal dysfunction. TPN was infused nightly in all children over 10–14 h. Characteristics of TPN are summarized in Table 2. Mean glucose and lipid flows were 13.6 and 2.0 mg/kg · min^{-1} (range, 8.0–18.5 and 0–3.3), respectively.

Insulin secretion. Results of IVGTT could separate two groups of patients: patients with a high first phase insulin release (FPIR) and patients with a lower one. Despite a similar increase in plasma glucose, five patients demonstrated a lower FPIR evaluated by the sum of insulin release at 1 and 3 min. It was below or around the first tertile of 1 + 3 min (first tertile = 68.1 mIU/L, second tertile = 151.6 mIU/L). Mean 1 + 3 min insulin sum was 55.3 ± 6.09 in these patients in contrast to 189 ± 22.5 mIU/L in the remaining patients (p = 0.002) (Fig. 1). It suggests us that if insulin secretion reached

Table 1. *Continued*

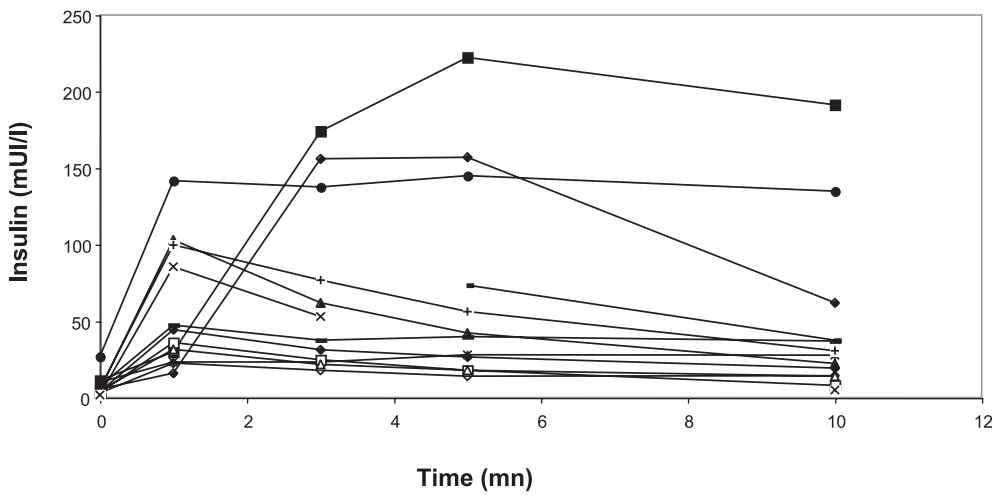
7	8	9	10	11	12	13
11	12	13	9	6	7	6
F	F	F	M	M	F	F
I	I	I	I	I	I	I
33.1 (0)	32.2 (−1.1)	41.1 (−1.0)	25.2 (−0.8)	17.5 (−2.5)	27.5 (+1.5)	20.2 (0)
128 (−2.0)	136 (−3.0)	149 (−1.0)	127 (−1.0)	108 (−2.0)	125 (+0.5)	113 (−0.5)
20.2 (1.8)	17.4 (−0.2)	18.5 (0.2)	15.6 (−0.3)	15.0 (−0.2)	17.7 (1.7)	15.7 (0.5)
39.4	31.5	27.7	15.7	21.1	29.0	19.7
N	Y	Y	Y	Y	Y	Y
5.3	4.7	5.1	6.0	4.9	4.9	5.0
4.7	4.9	4.5	5.4	4.3	5.3	4.1
6.8	2.7	4.8	5.4	0.8	5.3	5.5
3.7	2.8	2.9	4.8	11.0	4.0	4.4
Epithelial dysplasia	Syndromic diarrhea	Chronic intestinal pseudo obstruction syndrome	Neonatal volvulus	Epithelial dysplasia	Hirschsprung disease	Hirschsprung disease
Intact	Intact	Intact	15	Intact	Intact	Intact

physiologic values in these patients, they could have a lower insulin secretory response to glucose. A graded IV glucose infusion was then performed to assess this lower β-cell sensitivity to glucose stimulation.

Graded glucose infusion showed two different patterns of insulin release similar to ones found by IVGTT. The mean maximum glucose concentration achieved was similar in children with low FPIR and in those with higher FPIR (15.14 ± 0.65 mM *versus* 16.01 ± 0.11 mM, $p = 0.59$). By contrast, insulin secretion was almost 2.6-fold lower in patients with low FPIR. Insulin release only reached a mean value of 67.8 mIU/L ± 23.8 in patients with an alteration in FPIR, although it reached a mean value of 176.4 ± 38.1 mIU/L in patients without any alteration ($p = 0.028$) (Fig. 2). These

Table 2. *Characteristics of TPN*

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13
Parenteral nutrition duration (y)	10	6	6	6	18	16	11	12	13	9	6	7	6
Infusion duration per day (h)	12	12	12	12	12	14	12	14	10	12	13	12	12
Glucose intake (g/kg/d)	6.6	7.3	14.6	13.0	6.0	7.9	10.5	7.2	9.8	9.1	12.5	9.8	13.5
Lipids intake (g/kg/d)	1.5	2.5	1.9	1.9	0	1.7	0.8	0.9	1.7	1.8	2.3	1.4	1.5
Amino acid intake (g/kg/d)	1.5	4.5	2.0	1.8	1.1	2.1	1.8	2.1	1.9	1.6	2.3	1.6	1.4
Caloric intake (kcal/kg/d)	39.8	51.9	75.9	69.3	21.9	43.7	42.3	28.5	38.9	52.4	50.3	39.3	53.4
Glucose infusion rate (mg/kg/min)	9.1	10.3	20.3	18	7.6	10.9	14.6	8.5	16.2	12.6	16.1	13.6	18.5
Lipid infusion rate (mg/kg/min)	2	3.3	3.3	2.5	0	2.3	1.0	1.0	2.8	2.7	3.19	2.0	2.05



Patient	1	2	3	4	5	6	7	8	9	10	11	12	13
1+3 (mUI/l)	172	NM	165	40.4	46.6	279.4	176.6	204	85	75.6	60.6	53.1	138.2

Figure 1. IVGTT: FPIR (mIU/L) release. Sum of insulinemia at 1 and 3 min is summarized in the table.

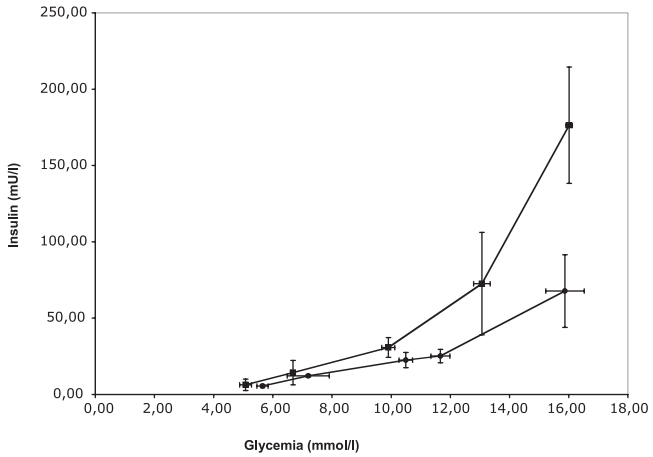


Figure 2. Insulin (mU/L) release during graded IV glucose infusion in patients with normal FPIR and patients with low FPIR. ■: 1 + 3 > 80 mUI/L; ●: 1 + 3 < 80 mUI/L.

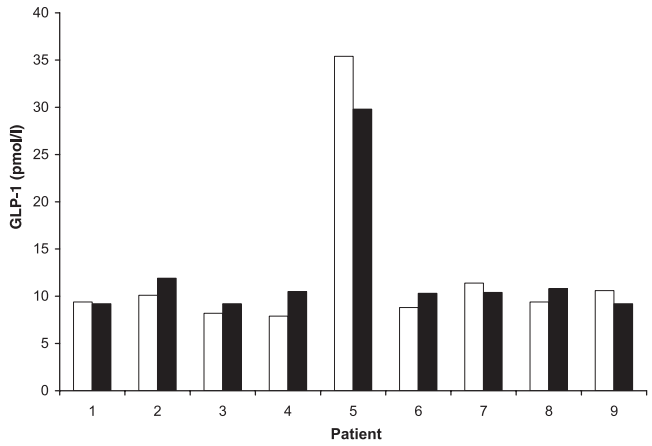


Figure 3. Fasting (*open columns*) and oral stimulated (60 min post-glucose oral load; *solid columns*) GLP-1 (pmol/L) active form release.

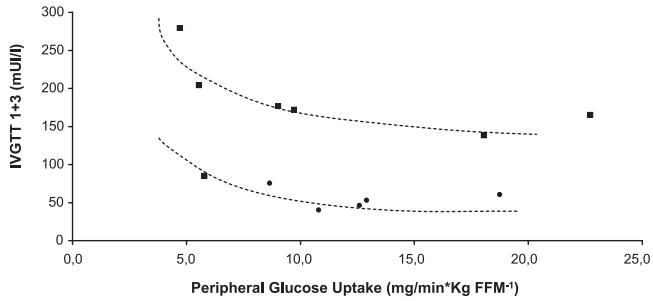


Figure 4. GDI. Relationship between insulin sensitivity (mean adjusted for FFM and glycemia) and FPIR (insulinemia 1 + 3 during IVTT). ■: patients with normal FPIR; ●: patients with low FPIR.

patients demonstrated then a lower insulin secretory response to glucose.

Insulin sensitivity. Peripheral glucose uptake (mean) adjusted for fat-free mass (FFM) was measured during euglycemic hyperinsulinemic clamp. Most of the patients had normal or high insulin sensitivity using previously reported values in healthy children (11). Mean peripheral glucose uptake was 10.7 mg/min · kg FFM^{-1} ± 1.6 mg/min · kg FFM^{-1} in girls and 12.1 ± 3.2 in boys. There was no difference between patients irrespective of whether they had low or high insulin secretion during IVGTT or graded IV glucose infusion (12.7 ± 1.5 *versus* 11.8 ± 2.3, $p = 0.95$). Decreased insulin sensitivity was found only in one boy (mean = 4.7 mg/min · kg FFM^{-1}).

All patients had normal or increased fasting hepatic glucose output after 6 h of cessation of infusion 4.4 ± 2.3 mg/kg/min. It was not statistically different between children with or without low FPIR (6.07 ± 1.2 mg/kg/min *versus* 3.4 ± 0.3 mg/min/kg, $p = 0.28$). HGO was abolished at clamp steady state in all patients. Hepatic insulin sensitivity was normal.

GLP-1 release. To assess whether there was stimulation of the enteroinsular axis even in children with poor oral intake, the active form of circulating GLP-1 was measured after an oral glucose load. In healthy adult subjects, a test meal is followed by a threefold increase in GLP-1 (12).

This test was performed in nine patients. The remaining patients had a complete intolerance of oral feeding. There were no increases in GLP-1 in any patients after the oral load (Fig. 3), indicating that the enteroinsular axis was not at all stimulated.

Relationship between FPIR and insulin sensitivity. To correlate FPIR, insulin sensitivity, and β-cell function, we calculated the GDI. GDI is the product of insulin sensitivity and FPIR. It has been shown to be constant in subjects with no β-cell failure (13). A decrease in insulin sensitivity is then physiologically compensated by a higher insulin release in healthy subjects, whereas subjects with higher insulin sensitivity demonstrate a lower FPIR. There is a hyperbolic relationship between FPIR and insulin sensitivity. By contrast, subjects with nonappropriated β-cell function (prediabetic or diabetic patients) have a loss of insulin release compensation. GDI is then lower, and subjects are plotted on lower hyperbolic graphs.

Indeed, in this study, patients with lower FPIR have lower GDI than patients with higher FPIR (GDI: 3.6 ± 0.06 *versus* 3.9 ± 0.1; $p = 0.03$). Patients with lower FPIR were plotted on lower graphs, although the other patients were plotted on higher hyperbolic graphs (Fig. 4).

DISCUSSION

Among 300 children on long-term TPN followed in two pediatric gastroenterology units, three children developed chronic hyperglycemia without any other risks factors than TPN. This incidence of glucose metabolism disorder, higher than in the general population, suggests that TPN could alter insulin secretion. The aim of the present study was to assess whether a lower insulin secretory response to glucose could be detected in children on TPN. Five children demonstrated a low first phase of insulin. A reduced first phase has been shown to be a risk factor for progression to type 2 diabetes even though the rate of insulin release is still in physiologic values and if glycemia during infusion is still normal. It is the earliest detectable defect of β-cell function (14). In first-degree relatives of patients with type 1 diabetes, a low FPIR associated with antibodies against pancreatic antigens has been demonstrated to be predictive of progression to diabetes (15).

Insulin release was further investigated with a graded IV glucose infusion that has been shown to be a very sensitive test to measure insulin release in response to glucose in subjects with no alternation in insulin release. It has been used, for example, in healthy subjects with heterozygous mutation of glucokinase or in subjects exposed to diabetes *in utero* to demonstrate whether lower insulin secretion can be assessed (16–18). This test has a high sensitivity to measure β-cell response to glucose stimulus. Children with lower FPIR demonstrated lower insulin release under sustained and graded glucose infusion despite high levels of blood glucose (15.3 mM). Insulinemia in children with low FPIR were 2.6-fold lower than values in patients without alteration in FPIR. Graded glucose infusion could attest to a lower insulin secretory response to glucose in these patients, as previously described in others groups of healthy patients with different risk factors (16,17). Patients with low FPIR demonstrated simultaneously a lower GDI. When FPIR were plotted with insulin sensitivity, patients with mild or high insulin release fitted the same hyperbolic graphs. Taken together, these data point to an altered secretory response to glucose in some patients even if insulin release still reaches physiologic values. This group of patients could be at risk of developing β-cell failure and glucose tolerance abnormalities.

Insulin sensitivity was normal in all our patients except one patient who demonstrated decreased insulin sensitivity compensated by a high insulin release. This patient was the only one studied during puberty (Tanner stage 4).

At least three risk factors of glucose homeostasis disorders can be found in these children. Here we can eliminate an autoimmune process, as children with lower insulin secretory response to glucose had no autoantibodies against pancreatic antigens.

TPN exposes children to high glucose and nutrient flow rates 12 h/d from birth onward. High insulin concentrations surrounding β cells could inhibit glucose-mediated insulin secretion pathways *via* overstimulation of its own receptor on the β-cell membrane (19,20). Indeed, it is difficult to assess the direct effect of hyperinsulinemia in such patients, although it seems to be an important risk factor.

Peripheral insulin resistance induced by lipotoxicity associated with lipid infusion does not seem to be involved. It is been demonstrated that in healthy patients, lipid infusion induces a decrease in insulin sensitivity (21). Here insulin sensitivity was altered only in one patient. In other patients, insulin sensitivity was in the normal range or even increased with regard to values previously reported in healthy children (11). Insulin sensitivity was similar in patients with low or normal FPIR (mean, 12.7 *versus* 11.7).

Moreover, these patients do not show alteration in hepatic insulin sensitivity under insulin infusion. TPN has been reported to be frequently associated with mild to severe steatosis induced by glucose and lipid infusions, even with normal blood liver tests (22). It appears early after the beginning of TPN and may contribute, along with other risks factors, to fibrosis and later cirrhosis (23). It is thought that steatosis may induce modifications of insulin sensitivity similar to these reported in nonalcoholic steatosis associated with obesity (24). Indeed, it has been demonstrated to be an inflammatory state that disturbs insulin effects on hepatic glucose output *via* such cytokines like interleukin-6 (25). In patients in this study, hepatic glucose output was suppressed by insulin infusion.

Alteration in β-cell function induced by lipid infusion may be expected. Free fatty acid accumulation in β-cell could inhibit insulin secretion pathway. It could inhibit K^+-dependent channels *via* the mitochondrial expression of decoupling proteins like UCP-2 (26). It increases malonyl-coenzyme A and induces ceramide production that could enhance cellular apoptosis (3).

Low GLP-1 release could be involved in the disorders reported here. Even in patients with poor oral intake, GLP-1 secretion is not stimulated. This has been observed irrespective of the nature of the original disease, the nutritional pattern or the length of the residual small bowel. Alteration in GLP-1 release has been previously reported in adult patients with an intestinal resection (7). We can hypothesize that GLP-1 secretion has not been stimulated from birth in these children because of intestinal resection, mucosal dysfunction, or lack of oral intake. The role of this incretin in enhancing insulin release and hepatic glucose uptake has been well documented (27,28). GLP-1 has also been implicated in the postnatal maturation and trophicity of β cells, at least in rodent models (29–31). GLP-1 infusion together with TPN could improve insulin secretion in children on TPN with lower insulin secretory response to glucose.

Because of the small size of the study population, it is difficult to identify clinical factors associated with the lower insulin secretory response to glucose. Interestingly, a family history of type 2 diabetes was frequently observed in patients with a low FPIR. Three of five patients with alteration in insulin release had a second-degree family history and one a first-degree history. We found no evidence of correlation between insulin release and TPN composition or duration. Most of our subjects had a fat mass percentage superior to normal range with regard to values previously reported in healthy children (32). Three of five patients had a percentage $>29\%$.

In conclusion, we report that metabolic conditions associated with long-term TPN can induce a decrease in insulin secretory response to glucose, which was evidenced before any obvious alteration in glucose tolerance in these children. These patients are at high risk of developing an alteration in glucose metabolism and must be closely followed, especially when they are candidates for intestinal transplantation.

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