

Postnatal growth of infants with neonatal diabetes: Insulin pump (CSII) versus Multiple Daily Injection (MDI) therapy

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Summary. *Background:* Permanent neonatal diabetes mellitus (PNDM) is characterized by the onset of hyperglycemia within the first six months of life. Their diabetes is associated with partial or complete insulin deficiency with variable degree of intrauterine growth retardation. Insulin therapy corrects the hyperglycemia and results in improvement of growth. However, no studies have reported the longitudinal growth of these infants (head circumference, length and weight gain) after starting insulin therapy. *Patients and methods:* We assessed the growth parameters weight (Wt), Length (L) and head circumference (HC) in 9 infants with PNDM, during the first 2 years of their postnatal life. Five infants were on insulin pump therapy (CSII) and 4 were on multiple doses of insulin injection (MDI) therapy. *Results:* On insulin therapy for 20±4 months catch-up growth occurred in the majority of infants. L-SDS increased from -1.45 to -0.65, HC-SDS from -2.3 to -0.51 and Wt-SDS increased from -1.94 to -0.7 at the end of the 20±4 months of age, after starting insulin therapy. Two out of 9 infants had a L-SDS <-2, in 4 Wt-SDS was <-2 and in 1 the HC-SDS was <-2 at 20±4 months of postnatal growth. The level of HbA_{1c} was lower in infants on CSII compared to those on MDI (9.6±1%) compared to those on MDI (10.2±2%). However, growth parameters improved significantly in both groups (CSII and MDI) with no significant difference among them. *Conclusions:* Infants with PNDM with positive anti-GAD and antiTPO were diagnosed later and their intra-uterine and postnatal growth differed compared to those with negative antibodies. The majority of infants with PNDM exhibited significant catch up growth within the first two years of life irrespective of the etiology of diabetes. HbA_{1c} appeared to be better in infants with PNDM on CSII therapy when compared to those on MDI therapy. (www.actabiomedica.it)

Key words: permanent neonatal diabetes mellitus, multiple daily injections, growth parameters, body mass index

Introduction

Diabetes mellitus occurs in about 1 in 400,000 newborn infants in the first few months of life. However, in about half of these babies have a permanent form of diabetes mellitus (PNDM) (1).

Insulin deficiency leads to hyperglycemia, glycosuria with excessive loss of fluids and energy that leads

to dehydration, failure to thrive and ketosis. In some cases, infants with PNDM also have certain neurological problems, including developmental delay and recurrent seizures. This combination of developmental delay, epilepsy, and neonatal diabetes is called DEND syndrome (1-6).

A small number of individuals with permanent neonatal diabetes mellitus have pancreatic aplasia or

hypoplasia. In these cases insulin and other pancreatic hormones as well as the digestive enzymes may be affected. Defective pancreatic enzymes lead to malabsorption with fatty stools and an inability to absorb fat-soluble vitamins (7, 8).

PNDM may be caused by mutations in several genes. In about 90 percent of these cases, the condition results from new mutations in the gene and occurs in people with no history of the disorder in their family. About 30% of individuals with PNDM have mutations in the *KCNJ11* gene. An additional 20% of people with PNDM have mutations in the *ABCC8* gene. These genes provide instructions for making parts (subunits) of the ATP-sensitive potassium (K-ATP) channel. Each K-ATP channel consists of eight subunits, four produced from the *KCNJ11* gene and four from the *ABCC8* gene. Mutations in the *INS* gene, which provides instructions for making insulin, have been identified in about 20% of individuals with PNDM. Mutations in the *INS* gene are believed to disrupt the cleavage of the proinsulin chain or the binding of the A and B chains to form insulin, leading to impaired blood sugar control. In addition, PNDM can also be caused by mutations in other genes, some of which have not been identified (9-14).

Insulin therapy is crucial in PNDM to obtain satisfactory weight gain and growth in these infants. A variety of methods for providing insulin such as: intravenous infusion, short-acting and long-acting subcutaneous injections, or continuous subcutaneous insulin infusion (CSII) can be used. Some authors recommended subcutaneous injection of ultralente insulin, rather than lente or isophane (NPH) insulin to avoid hypoglycemia during treatment. However, there is currently no license for its use in this age group. Insulin glargine treatment is suggested, because of its flat pharmacokinetic profile which might prove useful in this condition.

In some centers in Europe, the use of CSII in all cases of neonatal diabetes mellitus is proposed, stating that during the neonatal period, CSII therapy is safe, more physiological, more accurate and easier to manage than insulin injections (15-19).

Infants with PNDM have higher risk for defective growth because for many reasons. They lack the intrauterine anabolic effect of insulin and born small

for gestational age. In addition, difficult control of their hyperglycemia may adversely affect their weight gain and linear growth. The presence of other congenital abnormalities like pancreatic aplasia or epilepsy may also compromise normal growth. However, there is scarce information about longitudinal growth of infants with PNDM (4, 18). No study assessed the growth of these infants after insulin treatment using multiple daily Injections versus CSII therapy.

The present study aimed to evaluate the growth parameters in relation to diabetes control in all children with PNDM diagnosed at Hamad General Corporation (HMC) of Doha, (Qatar).

Patients and methods

Children diagnosed with PNDM within the first 6 months of life, attending to the Diabetes Clinic of Hamad General Hospital of Doha (Qatar) between January 2006 and January 2016 were enrolled in the study. The study protocol was approved by the ethical committee of Hamad Medical Centre.

The longitudinal growth data [weight (wt), length (L) and head circumference (HC)] at the time of the diagnosis and after 12 and 24 months were recorded. Their diabetes control, monitored by the level of HbA_{1c} every 3-4 months, was also recorded. Their insulin requirement and the mode of insulin delivery (pens versus pump) were evaluated. Exclusion criteria included infants diagnosed with Type 1 DM after 6 months of life and those with other congenital abnormalities or systemic disorders. Growth data were correlated to birth size, mid-parental height-SDS and average HbA_{1c} concentration. The growth data published by the WHO were used as reference for our infant's growth.

Patient anthropometric data are presented as means±SD and were compared to the appropriate population (WHO) growth standards of the same age and sex. Correlations between anthropometric and clinical variables were assessed using linear regression equations. A p value of <0.05 was considered to be statistically significant (20).

Results

At the age of diagnosis (2.7 ± 1.9 months), our infants with PNDM (5 males and 4 females) had persistent hyperglycemia which continued for more than 6 months and required early insulin therapy.

They were born from a consanguineous marriage. None had clinical or immunological evidence of congenital viral infection.

Five infants were treated with insulin pump (CSII) and 4 with MDI, using Detemir and Humalogue insulin.

At presentation, all infants with PNDM had low or absent circulating C-peptide (0.45 ± 0.53 ng/ml; normal range: 0.9–4 ng/ml) and low insulin levels (1.54 ± 1.7 μ U/ml; normal values: 14.6 ± 7.2 - mean 8 μ U/ml) during the episodes of hyperglycemia. Their mean HbA_{1c} concentration was 8.82 ± 0.96 % (normal values: 5.3 ± 0.24 %, range 4.8–6.0%). One infant had a low free thyroxine level and a high thyroid-stimulating Hormone (TSH) value. All patients were negative for anti-tissue transglutaminase. During the observational period of study, none of them had exocrine pancreatic deficiency or developmental delay.

In 4 out of 6 infants with negative anti-GAD antibodies, genetic testing did not document mutations in the *ABCC8* and *KCNJ11* genes encoding respectively the SUR1 and Kir6.2 subunits of the voltage-dependant potassium channel.

At diagnosis, the 9 infants with PNDM had compromised growth (Wt-SDS: -1.9 ± 1.5 , L-SDS: -1.46 ± 1.2 , and HC-SDS: -2.3 ± 0.89). On insulin therapy, for 20 ± 4 months, catch-up growth occurred in most infants. At the end of the second year of life, Wt-SDS increased from -1.94 to -0.7 , L-SDS increased from -1.46 to -0.65 , and HC-SDS from -2.3 to -0.51 . Two out of 9 had L-SDS < -2 and 4 had Wt-SDS < -2 , and 1 infant had HC-SDS < -2 at 20 ± 4 months of postnatal growth. (Figures 1 and 2). The HC-SDS was the most affected growth parameter at diagnosis (HC-SDS = -2.2) with a catch-up of 1.7 SD in the first 20 months of insulin therapy. WT-SDS was also markedly affected at diagnosis (Wt-SDS = -1.95) with significant improvement of 1.22 SD on insulin therapy. Length SDS improved 0.79 SD during the 20 months of insulin therapy (Table 1, Figures 1 and 2).

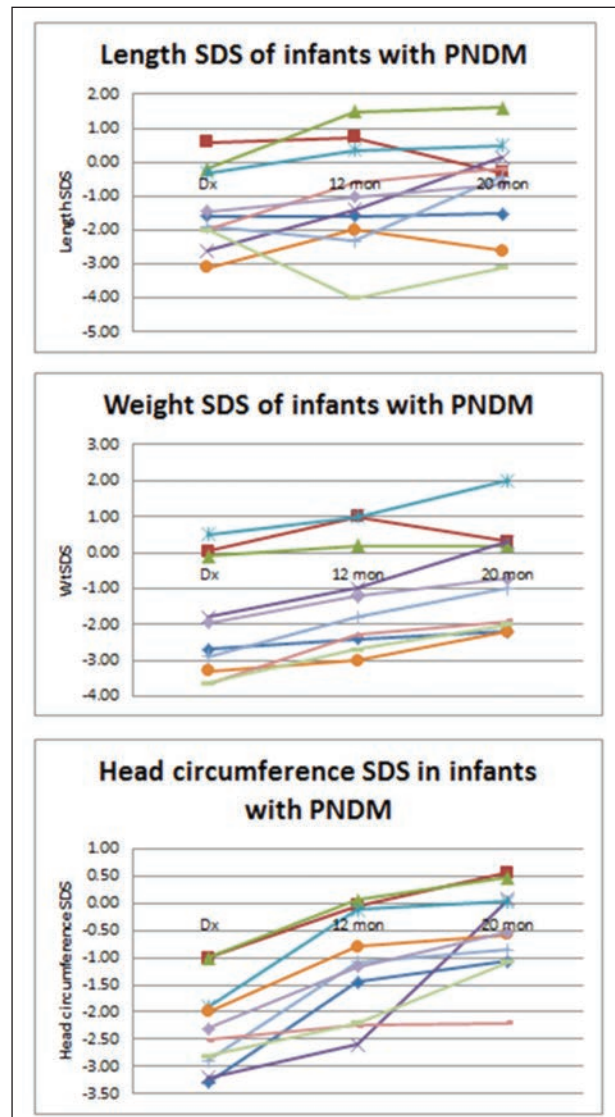


Figure 1. Growth parameters in infants with neonatal diabetes mellitus (PNDM) on insulin therapy

All infants with positive antibodies were diagnosed between 2 and 6 months of age. The diagnosis of PNDM was later in infants anti-GAD negative. The birth size (L, Wt and HC) of infants with PNDM, positive anti-GAD and anti-TPO antibodies (n=4) was markedly better than those without antibodies. Both groups had improved growth during insulin therapy (Table 2, Figure 3).

The average HbA_{1c} of infants on insulin pump (CSII) therapy (n = 5) was significantly lower than

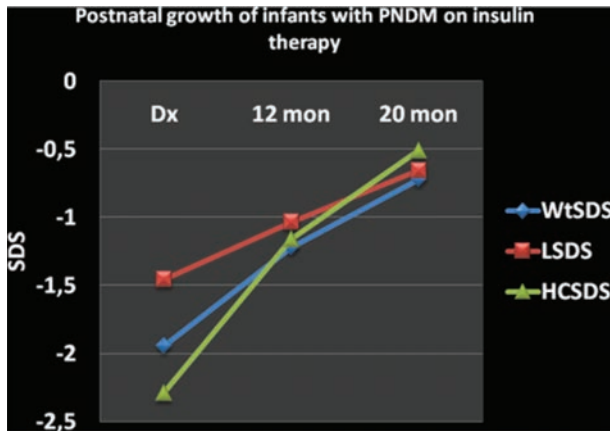


Figure 2. Growth parameters in infants with permanent neonatal diabetes mellitus (PNDM) on insulin therapy (mean values)

Table 1. Postnatal growth parameters in infants with permanent neonatal diabetes mellitus (PNDM)

Postnatal Growth	At diagnosis	At 12 months	At 20±4 months
Wt-SDS	-1.9456	-1.2211	-0.7222
L-SDS	-1.4556	-1.0367	-0.6567
HC-SDS	-2.2889	-1.1611	-0.5111
Growth MDI vs Pump			
L-SDS (Pump)	-1.28	-1.01	-0.80
L-SDS (MDI)	-1.68	-1.07	-1.07
Wt-SDS (Pump)	-1.95	-1.12	-0.62
Wt-SDS (MDI)	-1.94	-1.12	-0.95
HC-SDS (Pump)	-2.22	-1.11	-0.72
HC-SDS (MDI)	-2.38	-1.22	-0.25

Legend: Weight (Wt), Length (L) and head circumference (HC). MDI: multiple doses of insulin injection

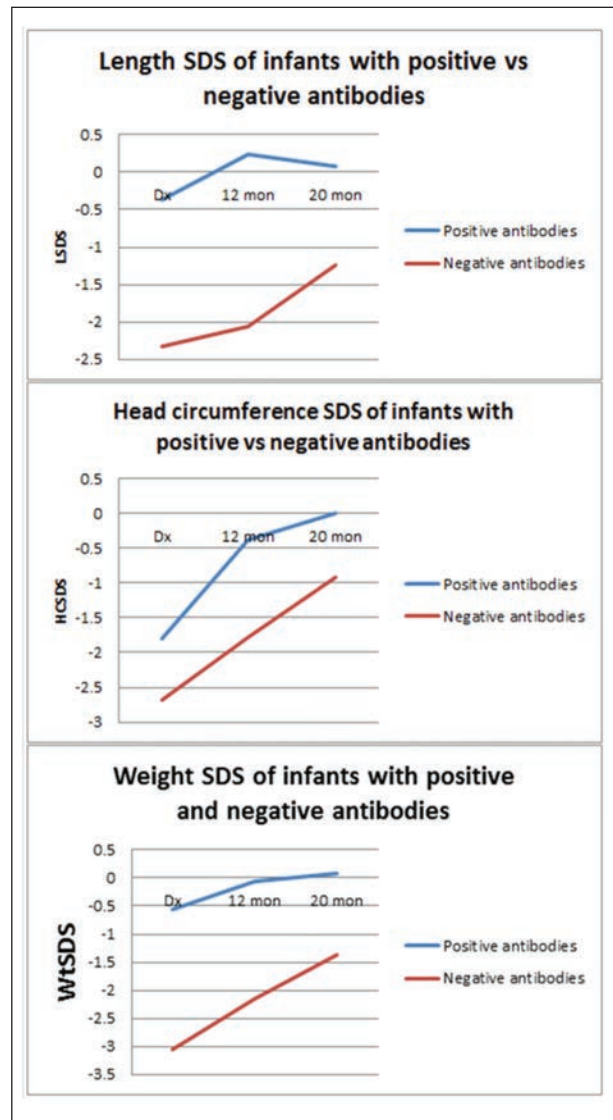


Figure 3. Growth parameters in infants with permanent neonatal diabetes mellitus (PNDM) with positive versus negative antibodies

Table 2. Postnatal growth in infants with permanent neonatal diabetes mellitus (PNDM), positive and negative antibodies

	At diagnosis (Dx)	At 12 months	At 20±4 months
Wt-SDS			
Positive antibodies	-0.5625	-0.05	0.075
Negative antibodies	-3.05	-2.16	-1.36
L-SDS			
Positive antibodies	-0.375	0.2425	0.075
Negative antibodies	-2.32	-2.06	-1.242
HC-SDS			
Positive antibodies	-1.8	-0.385	0.005
Negative antibodies	-2.68	-1.782	-0.924

Legend: Weight (Wt), Length (L) and head circumference (HC)

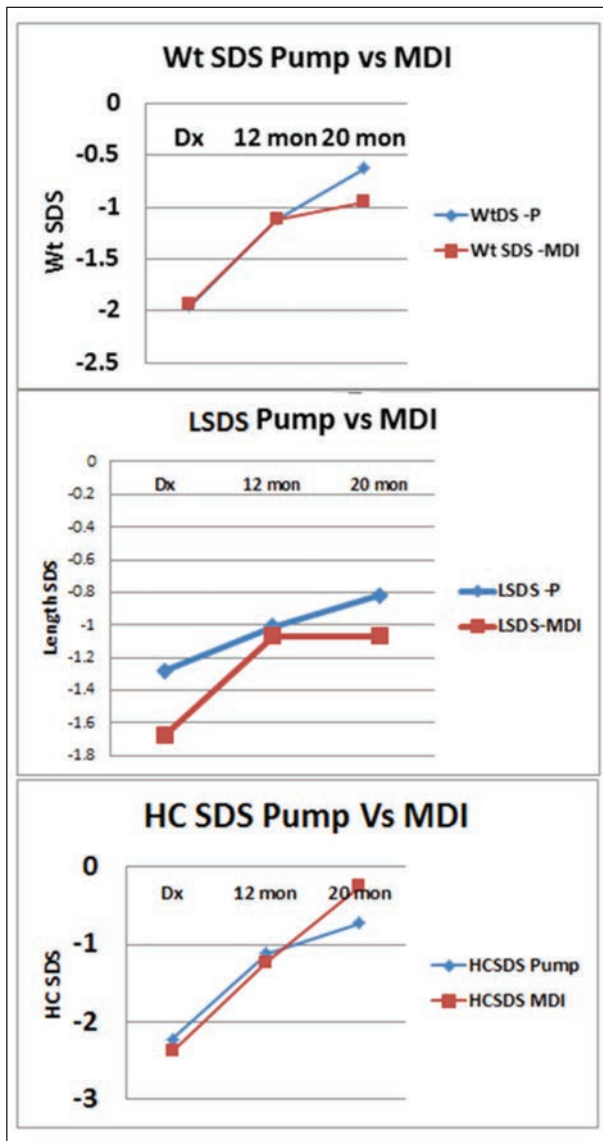


Figure 4. Growth in infants with neonatal diabetes mellitus (PNDM) on insulin pump versus multiple doses of insulin injection (MDI). Legend: Weight (Wt), Length (L) and head circumference (HC).

those on MDI ($n = 4$) ($9.6 \pm 1\%$ versus $10.2 \pm 2\%$, respectively). The mean Wt-SDS and L-SDS of infants on pump therapy were higher than those on MDI. However, the differences did not achieve a statistical significance ($p = 0.09$ and 0.15 , respectively), probably due to the small number of patients (Figure 4).

HbA_{1c} at 20 months of age was correlated significantly with L-SDS and HC-SDS ($r: -0.55$ and -0.43 , respectively; $p < 0.01$).

Discussion

Permeant neonatal diabetes mellitus (PNDM) is defined as persistent hyperglycemia (plasma glucose concentration >150 - 200 mg/dL) in infants younger than age six months. Neonatal diabetes mellitus (NDM) is an infrequent cause of hyperglycemia in the newborn period. Typically, infants are of low birth weight and develop hyperglycemia requiring exogenous insulin within the first 6 weeks. Intrauterine growth retardation, failure to thrive, fever, dehydration, hyperglycemia, acidosis with or without ketonuria are the clinical features of the disease.

In-utero growth retardation is due to loss or defective insulin secretion by the fetal pancreas that negative affect fetal growth and metabolism especially during the last half of gestation. All our patients with PNDM, with negative anti-GAD antibodies reported here had intrauterine growth retardation and had low levels of insulin and C-peptide (21, 22).

Our PNDM patients with negative antibodies presented with growth retardation at birth, as well as in other studies, denoting impaired intrauterine growth. Insulin-like growth factor 1 (IGF-1) axis is the major hormonal mediator of growth in utero, and levels of IGF-1 are often very low after preterm birth (23, 24). Umbilical cord IGF-1 concentrations reflect fetal IGF-1 levels at birth and correlate with birth weight. Cord serum IGF-1 concentrations are lower following intrauterine growth restriction. Infants with NDM have low concentration of IGF-1 that improves on insulin therapy (25-29).

In the majority of our infants with PNDM, the correction of insulin deficiency state lead to significant catch up growth in all growth parameters (Wt, L, and HC). In the newborn infant, hepatic IGF-1 generation is controlled by nutrition and insulin and not dependent on growth hormone secretion. The acid labile subunit levels are reduced, and this means that much of the circulating IGF-1 is in binary complexes. Insulin through IGF-1 plays an important role in regulating IGF-1 bioactivity. Finally there is evidence, that in the newborn infant IGF-1 signaling through the IGF1 receptor may have a role in maintaining pancreatic β -cell function. We can assume that insulin therapy increased linear growth in our patients with

PNDM through its effect on IGF-1 secretion and indirectly through improving nutrition (4, 5, 29).

As a result of the scarcity of PNDM case reports, no universal clinical guidelines exist for PNDM. Though genetic etiologies of many cases of PNDM have been identified, there has been no consensus on its management. Various modalities reported as effective include oral sulfonylureas, intravenous regular insulin, continuous subcutaneous insulin infusion pump therapy, neutral protamine Hagedorn (NPH) insulin, and subcutaneous insulin glargine (30-32).

The treatment of neonatal hyperglycemia must be based on the diagnosis and suspected etiology of the condition in each case. If severe hyperglycemia persists, exogenous insulin administration may be warranted. Guidelines about when to use insulin treatment and how to provide this form of therapy remain highly controversial and vary widely among clinicians and institutions. The treatment is complex because: 1) dietary compromises the caloric provision; 2) there is a lack of a pharmacokinetic profile for subcutaneously administered insulin in neonates; 3) the use of small insulin doses are highly error-prone; 4) there are limited data for dilution of commercially available insulin formulations; and 5) there is a lack of subcutaneous fat deposits in a small gestational age (SGA) neonate for the subcutaneous insulin administration (33-36). Furthermore, hypoglycemia is a potentially severe problem if insulin is administered through a single IV line.

Insulin Detemir is a long-acting basal insulin analogue manufactured by recombinant DNA technique. The prolonged action of insulin Detemir is the result of reversible binding of the fatty acid residue to serum albumin, which slows release of active insulin monomers into systemic circulation following subcutaneous injection. From a pharmacokinetic perspective, the duration of action of insulin Detemir is dose-dependent, ranging from 5.7 to 23.2 hours, with onset of action at approximately 1 to 3 hours and with peak effect occurring between 3- and 10-hours post-administration. Lack of subcutaneous fat and /or hypoalbuminemia could have profound effects on the pharmacokinetics of insulin Detemir. No studies have evaluated the efficacy in terms of release pattern or stability of diluted long-acting insulin products. However, our 4 infants with PNDM had fairly good response to Detemir

(basal) twice daily and lispro insulin (at prandial time) (37, 38).

Continuous subcutaneous insulin infusion (CSII) in our 5 cases of PNDM proved effective with lower HbA_{1c} concentration compared to MDI therapy. CSII can control blood glucose with few hypoglycemic events, which are particularly frequent and dangerous at this age. Infants tolerated the subcutaneous infusion lines well and we did not observe any side effect. In addition, postnatal linear growth appeared better compared to MDI (L-SDS and Wt-SDS). Therefore, our result support the safety and benefit of CSII reported in other studies in treating this group of infants (39,40).

In summary:

Infants with positive anti-GAD antibodies were diagnosed between 2 and 6 months of age. The diagnosis of PNDM was later in anti-GAD negative infants. Infants with PNDM who had positive anti-GAD and anti-TPO were diagnosed later than those negative for antibodies and they had also a different growth pattern. Insulin therapy using CSII appears to be better than MDI in treating PNDM infants because of achieving lower HbA_{1c} levels.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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