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Review

# Neonatal Diabetes Mellitus

**Adil Umut Zübarioğlu, Ali Bülbül, Hasan Sinan Uslu**

**Department of Neonatology, Health Sciences University Istanbul Sisli Hamidiye Etfal Health Practice and Research Center, Istanbul, Turkey**

**Abstract**

Neonatal diabetes is a rare cause of hyperglycemia in the neonatal period. It is caused by mutations in genes that encode proteins playing critical roles in normal functions of pancreatic beta cells. Neonatal diabetes is divided into temporary and permanent subtypes. Treatment is based on the correction of fluid-electrolyte disturbances and hyperglycemia. Patients respond to insulin or sulfonylurea treatment according to the mutation type. Close glucose monitoring and education of caregivers about diabetes are vital.

**Keywords:** Insulin therapy; neonatal diabetes mellitus; sulfonylurea.

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Neonatal diabetes mellitus (NDM) is a rare cause of hyperglycemia in the neonatal period, and its incidence is 1 in approximately 500.000 live births.[1] NDM is defined as a hyperglycemic condition requiring insulin therapy that emerges within the first months of life and persists for more than two weeks.

NDM is caused by mutations encoding proteins that play critical roles in the normal functioning pancreatic beta cells.[2, 3] The course of the disease demonstrates variations dependent on the affected genes and proteins, and the disease is divided into temporary and permanent subtypes. In approximately half of the cases, lifelong treatment is required to maintain blood glucose levels under control (permanent NDM, PNDM). In the remaining patients, diabetic state terminates within a few weeks and months later (temporary NDM, TNDM). In some patients with TND, diabetes may manifest again at any point in their lifetime, especially during the adolescence. In a study including 57 neonates diagnosed as neonatal diabetes, 18 of patients detected as temporary type and 26 of patients detected as permanent type. Remaning 13 patients manifested recurrence of diabetes at 7-20 ages which were diagnosed as temporary neonatal diabetes in newborn period.[4]

NDM is a genetically heterogenous disease, and at least 20 diverse, responsible genes have been demonstrated so far. Most cases of neonatal DM caused by a single gene mutation result in impaired insulin secretion.[5] Etiopathogenesis of insulin deficiency occurs via three alternative mechanisms, which consist of impairment in the development or function of beta cells or beta cell destruction (Table 1). Most of the genes responsible from temporary DM have been determined and three genetic anomalies are responsible for the development of TNDM[6] The responsible gene mutations have not been detected in 40% cases of PNDM.[7]

## Temporary Neonatal Diabetes Mellitus (TNDM)

TNDM is described as diabetes mellitus that has an onset within the first weeks of life, and gets resolved by ≤18

**Address for correspondence:** Adil Umut Zübarioğlu, MD. Department of Neonatology, Health Sciences University Istanbul Sisli Hamidiye Etfal Health Practice and Research Center, Istanbul, Turkey
**Phone:** +90 505 787 75 33 **E-mail:** uzubari@hotmail.com

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**Table 1.** Monogenic subtypes of neonatal diabetes mellitus

| Gene | Locus | Hereditary | Other clinical features |
|---|---|---|---|
| ***Abnormal pancreatic development*** | | | |
| PLAGL1 | 6q24 | variable | TNDM±macroglossia±umbilical hernia |
| ZFP57 | 6p22.1 | OR | TNDM (multiple hypomethylation syndrome) ± macroglossia ± umbilical defects ± congenital heart disease |
| PDX1 | 13q12.1 | OR | PNDM+pancreatic agenesis (steatorrhea) |
| PTF1A | 10p12.3 | OR | PNDM + pancreatic agenesis (steatorrhea) + cerebellar hypoplasia/aplasia + central respiratory dysfunction |
| HNF1B | 17cen-q21.3 | OD | TNDM + pancreatic hypoplasia and renal cysts |
| RFX6 | 6q22.1 | OR | PNDM + intestinal atresia+gallbladder agenesis |
| GATA6 | 18q11.1-q11.2 | OD | PNDM + congenital cardiac defects + biliary anomalies |
| GLIS3 | 9p24.3-p23 | OR | PNDM + congenital hypothyroidism + glaucoma + hepatic fibrosis + renal cysts |
| NEUROG3 | 10q21.3 | OR | PNDM + enteric anendocrinosis, malabsorptive diarrhea |
| NEUROD1 | 2q32 | OR | PNDM + cerebellar hypoplasia + visual impairment + deafness |
| PAX6 | 11p13 | OR | PNDM + microphthalmia + cerebral malformation |
| ***Abnormal B-cell function*** | | | |
| KCNJ11 | 11p15.1 | Spontaneous, OD | PNDM/TNDM ± DEND |
| ABCC8 | 11p15.1 | Spontaneous, OD,OR | TNDM/PNDM ± DEND |
| INS | 11p15.1 | OR | Isolated PNDM or TNDM |
| GCK | 7p15-p13 | OR | Isolated PNDM |
| SLC2A2(GLUT2) | 3q26.1-q26.3 | OR | Fanconi-Bickel syndrome PNDM + hypergalactosemia, hepatic dysfunction |
| SLC19A2 | 1q23.3 | OR | Roger's Syndrome PNDM ± Thiamine-responsive megaloblastic anemia, sensorineural deafness |
| ***B-cell destruction*** | | | |
| INS | 11p15.1 | Spontaneous, OD | Isolated PNDM |
| EIF2AK3 | 2p12 | OR | Wolcott–Rallison syndrome PNDM + skeletal dysplasia + recurrent hepatic dysfunction |
| IER3IP1 | 18q12 | OR | PNDM + microcephaly + lissencephaly + epileptic encephalopathy |
| FOX3P | Xp11.23-p13.3 | X-related, OR | IPEX syndrome (autoimmune enteropathy, eczema, autoimmune hypothyroidism, increased IgE) |
| WFS1 | 4p16.1 | OR | PNDM + optic atrophy + diabetes insipidus + deafness |

*TNDM: temporary neonatal diabetes mellitus ** PNDM: permanent neonatal diabetes mellitus.

months of age. However, in some patients it may manifest again, especially around the time of adolescence. The clinical onset of TNDM is characterized by hyperglycemia, glucosuria, dehydration, weight loss, and metabolic acidosis with or without ketonemia. Lower plasma insulin levels are detected both at baseline and after glucose-loading test. Median age at diagnosis is 6 days (1–81 days). Most affected babies are born as low-birth weight neonates.[8] This condition originates from fetal insulin deficiency. In France, in a study performed with 29 babies with diagnosis of TND Mequal gender distribution was detected and intrauterine growth retardation was noted in 74% cases.[9, 10]

In approximately 70% cases paternal uniparental disomy of chromosome 6q24, paternally derived unbalanced duplication or methylation defect of maternal allele are found.[11-17] These anomalies result in the excess production of ZAC/PLAGL1 (a transcriptional regulator of type 1 receptor of pituitary adenylate cyclase-activating polypeptide, which is an important regulator of insulin secretion), which induces TNDM.

In general, patients with the 6q24 anomaly are born with moderate growth retardation (median birth weight 1930 g); they develop clinical symptoms of severe nonketotic hyperglycemia within the first week of their lives.[14, 18] Despite the initial presentation with severe symptoms, diabetes resolves up to median 12 weeks in most of the patients. However, during remission period, temporary hyperglycemis episodes may be seen with the intervening diseases.[19] Di-

abetes recurrence is observed in approximately one-fourth of the babies followed up with the diagnosis of TNDM. Recurrence frequently develops during adolescence, and it is rarely seen before the age of 4 years.

Genetic counseling provided for the families of the TNDM patients with 6q24 mutation varies with the underlying mechanism of diabetes. Uniparental disomy of the sixth chromosome is generally sporadic, and its recurrence in the sibling to be born or future generations has a lower possibility. In cases of unbalanced paternal duplication on 6q24 region, male individuals will transmit the disease and its mutation to their children in 50% of the cases. Methylation defects are generally sporadic among females.

Activating mutations in KCNJ11 and ABCC8 genes affect KIR6.2 and SUR1 subunits of KATP channels, and may induce TNDM in 25% cases. TNDM patients having these mutations demonstrate a mild intrauterine growth retardation and are usually diagnosed after a longer duration, which indicates that a milder prenatal insulin deficiency is present. In addition, diabetes may remits and recur later in this group of patients.[6] Although these mutations may cause either TNDM or PNDM, KCNJ11 mutations more frequently cause permanent NDM whereas ABCC8 mutations more frequently cause temporary NDM.

**Permanent Neonatal Diabetes Mellitus (PNDM)**

This form of neonatal diabetes generally onsets relatively later, generally within the first 3 months of life, and affected neonates require lifelong insulin therapy.[20] Many genetic mutations including 6p parental imprinting are responsible from the development of permanent NDM. With activation of these mutations, the number of open ATP-sensitive potassium channels increases. As a result, pancreatic beta cells hyperpolarize, preventing insulin secretion, resulting in the development of diabetes. ATP-sensitive potassium channel consists of a small subunit of KIR6.2 and four regulator SUR1 subunits surrounding a central pore. Single gene mutations are etiological agents of many cases of TNDM.

Activating heterogenous mutations in KCNJ11, which encode KIR6.2 subunits, are responsible from approximately half of the cases.[21-23] These cases are diagnosed within the first 2 months of age. These patients are born as low-birth weight babies according to their gestational age, and they catch up with their postnatal growth rate only with insulin treatment.[24] Because KATP channels and KIR 6.2 subunits are found in skeletal muscle and neurons, abnormalities as severe growth retardation, epilepsy, muscle weakness, and dysmorphism are detected in some patients; these symptoms are cumulatively referred to as DEND syndrome (developmental retardation, epilepsy, NDM).[25, 26] In patients having this mutation, oral sulfonylurea treatment isfound to be more effective in achieving glycemic control compared with subcutaneous insulin injections. In a study including 49 cases, sulfonylurea treatment initiation allowed for termination of insulin administration in 44 cases, and glycosylated hemoglobin levels decreased from 8.1% down to 6.4%.[27]

Activating mutations in ABCC8 gene that encodes type 1 subunit of sulfonylurea receptor (SUR1) may induce both TNDM and PNDM. In a study including 73 cases with NDM in which molecular analyses were performed to detect mutations, activating mutations in ABCC8 gene were found in nine cases. TNDM was observed in seven cases whereas PNDM was observed in two. In all of these cases, glycemic control was achieved with oral sulfonylureas.[28] Neurological disorders may also seen in patients with ABCC8 mutations at a lesser frequency and generally with milder severity (delay in speech and dyspraxia).[28, 29]

A significant clinical difference does not exist regarding severity of intrauterine growth restriction and median age of onset (4-8 weeks) in these two subtypes of diabetes related to single gen mutation.[6, 7]

More than 90% patients having activating mutations in their KATP channel genes may have improved glycemic control and lower risk of hypoglycemia by switching from insulin to high dose sulfonylurea treatment.[27, 30, 31]

PNDM may rarely manifest because of mutations in GATA6, RfX6, IPF-1, EIF2AK3, GCK, FOXP3, PTF1A, GLIS3, and INS genes.[7, 32-48] In some cases, presence of these mutations causes pancreatic hypoplasia, agenesis, or beta cell agenesis. For example, mutation in EIF2AK3 gene induces Wolcott–Rallison syndrome, which manifests itself with permanent diabetes mellitus, exocrine pancreatic failure, and multiple epiphyseal dysplasia.[38, 39] The patients with recessive INS mutation have lower birth weight and are diagnosed at an earlier age(within the first week of their lives). Approximately 60% of these cases are children of consanguineous couples, and they benefit from insulin therapy.[49] FOX3P mutations demonstrate an X-related inheritance, and causes IPEX syndrome in affected infants, which is characterized by autoimmune endocrinopathy, enteropathy, and eczema.

It should not be forgotten that pancreatic agenesis or hypoplasia may also cause PNDM in rare cases. Molecular genetic analysis of four children with pancreatic development deficiency born to consanguineous couples did not detect a specific gene defect.[50] In these cases, clinical manifestations of diabetes start from birth, and severe developmental delay is found because of severe insulin deficiency in fetal life. Hyperglycemia develops rapidly after birth,

and blood glucose levels reach very high levels. In these cases, insulin treatment is required on an emergency basis. Mostly, the patients have concomitant diseases as congenital heart disease, and most of these patients die because of the presence of anomalies incompatible with survival.

In 50-75% of permanent NDM patients, a mutation is detected in KATP channels or proinsulin (INS) gene. Most of these mutations manifest as heterozygous and de novo mutations, and family history of these patients are unremarkable. However, some ABCC8 and INS mutations, and some other more rarely seen mutations, are homozygous mutations that require recessive hereditary transmission. Consanguineous marriages also increase the risk of development of these recessive subtypes. In children having KATP channel mutations born to consanguineous couples, conversion from insulin treatment to sulfonylurea treatment has a significantly lower likelihood.

### Treatment

Treatment is based on correction of fluid and electrolyte disorders and hypoglycemia. The first step of treatment of hyperglycemia seen in NDM is to decrease glucose intake of the newborn. These interventions are initiated when blood glucose levels rise above180-200 mg/dl. If the baby is receiving intravenous fluids, glucose infusion rate should be decreased in a stepwise manner. Blood glucose levels usually get controlled by decreasing the infusion rate to 4–6 mg/kg/min. If parenteral nutrition fluid also contains amino acids and lipid emulsion, blood glucose levels may be maintained despite decreasing glucose intake because babies may produce glucose through gluconeogenesis from glycerol and amino acids to maintain normoglycemia. Decreasing the glucose infusion rate provides a short-term solution, and by restricting the calorie intake limits growth rate. Both growth and more balanced glucose tolerance may be maintained with enteral nutrition. Insulin treatment is indicated in hyperglycemic babies despite decrease in glucose infusion rate. Insulin treatment ameliorates glucose tolerance, provides higher calorie intake, and improves growth. Definitive indications for insulin treatment are not determined; however, general approach tends to favor initiation of insulin infusion in babies with permanent hyperglycemia (>200–250 mg/dl) despite reduction of glucose infusion rate down to 4 mg/kg/min and who can not gain weight because of decrease in calorie intake.

In babies with de novo diabetes, initiation of insulin therapy at an early stage of the disease is a necessity to prevent acute metabolic decompensation and ensure weight gain.[51] These babies mostly respond good to insulin treatment. Insulin dose should be adjusted based on plasma glucose concentration, glucosuria, or both. Because of an increased risk of hypoglycemia, careful and frequent monitoring of plasma glucose carries utmost importance.

### Insulin treatment

Insulin treatment may be administered as multiple injections daily or continuous subcutaneous infusions.[52] During neonatal period, usually crystallized insulin is preferred. Because only small doses of insulin should be used, crystallized insulin should be diluted with physiological saline to obtain a concentration of 0.1 U/ml. The prepared solution should be changed at every 24 h.

The first step in the continuous treatment of hyperglycemia is to deliver a bolus infusion of crystallized insulin at a dose of 0.01–0.05 U/kg/h for 15 min in addition to intravenous fluid therapy. Blood glucose level measurements are performed at every 30–60 min, and if hyperglycemia persists, then this regimen is repeated at every 4–6 h. If hyperglycemia persists despite three bolus infusions, continuous infusion is started at a dose of 0.01–0.05 U/kg/h and with small increments; a maximum infusion rate of 0.1 U/kg/h may be attained. The targeted blood sugar level is 150–200 mg/dl, and values <150 mg/dl increase the risk of hypoglycemia.

In babies receiving parenteral nutrition or continuous enteral nutrition, delivery of a total daily dose of insulin as a continuous basal infusion is sufficient.[52] At the start of breastfeeding or bottle feeding, it is appropriate to administer basal insulin as 30%, and meal time insulin doses as 70% of total dose. Daily total insulin requirement varies between 0.29 U/kg and 1.4 U/kg/d.[52] In situations where extremely small doses of insulin (≤0.02 U/h or bolus ≤0.2 U) are required, administration of diluted insulin using continuous subcutaneous infusions should be the treatment alternative because it decreases the risk of hypoglycemia.[52, 53] Continuous infusion of insulin via subcutaneous route using an insulin pump provides administration of low doses of basal insulin and variable meal time insulin release similar to physiological insulin release, so allows flexible amount of food intake. The safety and effectiveness of insulin pumps have been demonstrated even in very small children.[55, 56] It is accepted as the first-line treatment alternative for this group of patients.

### Sulfonylurea treatment

In most patients having activating mutations of KCNJ11 or ABCC8, replacement of pre-existing insulin treatment by sulfonylurea treatment results in better metabolic control.[27, 30] Initial sulfonylurea doses of the patients having KCNJ11 mutation are generally higher than that in cases with ABCC8 mutation.[27, 30, 56] Also, patients with neuro-

logical symptoms may require higher doses. Independent from mutation type, the requirement for sulfonylurea doses tends to decrease over time. In the treatment, different types of sulfonylureas have been used (glibenclamide, glipizide, gliclazide) and during long-term follow-up, similar rates of permanent effectiveness and safety have been observed.[27, 30, 31] The detected side effects were temporary diarrhea during replacement period[57] and dental discoloration in the long term.[58]

### Additional treatments

In patients with pancreatic agenesis, pancreatic enzymes should be given in addition to insulin therapy.

### Glucose monitoring

Frequent glucose monitoring is very important for optimal insulin therapy, and it provides the opportunity for detecting attacks of hyperglycemia and hypoglycemia and to make appropriate interventions. Blood glucose levels should be checked by family members or caregivers at least 4–6 times a day. Glucose monitoring should be more frequent in babies whose glycemic control is not achieved and de novo diagnosed ones especially.[59] Nowadays, glycemic variations may closely follow up with continuous glucose monitoring (CGM) by using subcutaneous sensors. Use of CGM in combination with continuous subcutaneous insulin infusion is becoming an increasingly important treatment modality.[60] CGM has advantages of decreasing the frequency of hypoglycemic episodes, alleviating anxiety levels of the families, and revealing undetectable hypoglycemia, especially in small children. However, restricted body surface area of small babies limits its permanent use in the ones who had insulin pump without enough additional subcutaneous area. Also the high financial burden of this application is its disadvantage.

### Method of feeding

Breast feeding is recommended in babies with NDM, similar to the recommendations for other babies.[62] The amount of breast milk received at each breastfeeding may be calculated by weighing the babies before and after each breastfeeding, and each 100 ml breast milk contains 6–7 g carbohydrates.[63] Insulin requirement in neonates is related to the frequency of breastfeeding.[53] A bolus insulin dose may be administered after breastfeeding in babies receiving subcutaneous insulin infusion.[64]

### Diabetes training

One of the main components of diabetes treatment is to make the families competent in managing diabetes through continuous diabetes training. The patients especially in their neonatal and infancy period are completely dependent on their caregivers for insulin injections, appropriate nutrition, monitoring glycemic levels, and other treatments. In this age group, poor glycemic control is caused by the inadequacy of verbal interaction, variations in fasting and appetite, variability of activity, frequent infections, and the fear of hypoglycemia/hyperglycemia.[65] Hence, prevention, detection, and management of dysglycemia is extremely important in this age group.

### Future treatments

To optimize insulin replacement, development of an artificial pancreas that provides insulin release cycle into blood by continuous monitoring of glucose levels is an important field of research in diabetes. Various studies have demonstrated that sensor- sensitive pump treatment improves metabolic control and decreases hyperglycemia risk.[60, 66] However, continuous use of the sensor is important for its effectiveness.[67] Glycemic control provided and hypoglycemia risk decreased in older pediatric groups and adults by continuous glucose monitoring, continuous subcutaneous insulin infusion and computerized algoritms with new technologies.[68, 69] However, these technologies have not been approved for pediatric age groups.

## Conclusion

The diagnosis of NDM in the neonatal period is extremely complex condition both for attendant clinicians and patient's family. Determination of the genetic subtype by molecular diagnosis predicts prognosis, and risk of potential development of nonpancreatic characteristics, and also reveals the risk of development of diabetes in future siblings and generations. The most important impact of genetic subtyping is that it enables switching from administration of insulin injections to sulfonylureas, which provides better glycemic control in patients with $K_{ATP}$ channel mutations. Up to now, 20 distinct gene mutations have been found to be responsible for NDM, and animal experiments are currently ongoing to detect new responsible genes. New genes to be identified using molecular studies will better clarify treatment, management, and prognosis of the disease.

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