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Neonatal Diabetes mellitus: A review

Prathiksa Pramanik [1], Mohima Das [2], Megha Mahapatra [2] and Shweta Parida [3,*]

[1] *Department of Food and Nutrition, Swami Vivekananda University, Barrackpore, W. B., India.*
[2] *Food and Nutrition, Department of Home Science, University of Calcutta, W. B., India.*
[3] *Department of Food Science and Technology, School of CIST, KISS-Deemed to be University, Bhubaneswar, Odisha, India*

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Abstract

Neonatal diabetes mellitus is regarded as genetic, diversified, and infrequent disorder of babies. This is developed due to mutation of specific gene. ABCC8 and KCNJ11 genes mutation are fundamental cause for the development of this. These genes encrypting the potassium network and are very much involved for seeking the monogenic diabetes like Neonatal diabetes mellitus. Neonate diabetes is classified as transient diabetes mellitus and permanent diabetes mellitus. Transient diabetes mellitus is observed at infancy stage where as Permanent diabetes mellitus is observed at 7 weeks to 26 weeks. With the help of genetic screening, this classified diabetes is discriminated. Transient diabetes is observed during infant stage and furtherly starts in later life. 22 genetic variations are very much interconnected with this type of diabetes. This article will provide a summary of current knowledge on neonatal diabetes mellitus.

Keywords: Dietary Habits; Hyperglycaemia; Insulin; Monogenic Diabetes; Neonatal Diabetes; Gene.

1. Introduction

Among the group of metabolic disorders, Neonatal diabetes mellitus (NDM) is another important wing of it. The aetiology of diabetes mellitus is lots like excessive fat inclusion in the diet, genetical inheritance, age, gender, life style, socioeconomic position, and also depressive disorders (Jana *et al*., 2019). Most importantly, diabetes mellitus is caused of hyperglycaemia therefore excessively both insulin production and function of insulin are observed. Fundamentally, diabetes mellitus is classified as monogenic and polygenic diabetes. Among classified monogenic diabetes, Neonatal diabetes is present predominantly. This type of diabetes is observed in 6 months prior; this may be ephemeral or indefinite (Dahl & Kumar, 2020). NDM is observed firstly at the start of 9th century. However, in case of children, diabetes is not established as insulin dependent or T1DM and ketotic diabetes (Sood *et al*., 2017). Additional 20 genes are caused of NDM. Authors have asserted that, another monogenic diabetes mellitus is Maturity-onset diabetes of the young (MODY). Some genes are very much interrelated along with NDM. Some of genes are KCNJ11, INS, ABCC8, GATA6 (Naylor *et al*., 2011), GATA4, RFX6, PDX1, NEUROD1, GCK, EIF2AK3, FOXP3 (Catli *et al*., 2013) etc. NEUROG3 genes are involved into neonatal hyperglycaemia. HNF1β gene mutations are attached with neonatal polycystic kidney. Furthermore, ABCC8 and KCNJ11 genes are the frequent to cause of NDM. ABCC8 and KCNJ11 genes encrypting for the subunit Kir6.2 and sulfonylurea receptor SUR1 of the ATP enriched potassium medium of the β cell cause to the transitory and tenacious NDM. ABCC8/KCNJ11 variants of diabetes patients have DEND (Developmental delay, epilepsy, neonatal diabetes mellitus) ailment (Bowman et al., 2018; Letourneau & Greeley, 2019). NDM develops in new born children as they do not able to fabricate insulin hormone therefore develop unrestricted glucose levels (Katanic *et al*., 2017).

Authors have highlighted that, mutation in the insulin which is the protein encoding gene in heterozygotes develops familial hyperinsulinemia, that is closely related with to diabetes through autosomal dominant inheritance. Genetic

* Corresponding author: Shweta Parida

inheritance as well as maternal inheritance are very much interlinked with NDM (Barbetti *et al*., 2018). NDM is elaborated as development of chronic hyperglycaemia that begins from first month of life of the neonates (De Franco *et al*., 2015). Globally prevalent NDM from 1:90,000 to 1:160,000 in livelihood (Wirth *et al*., 2018). Furthermore, NDM is also elaborated as tenacious hyperglycaemia at starting months of life and shows a savage inhibition in β cell consequences. NDM infants are very much susceptible for enhancing the insulin opposition (Beltrand *et al*., 2020).

The manifestations of NDM are hyperglycaemia, intrauterine growth restriction (IUGR), fatigueness of muscle, biasness in growth and development, difficulty in cognition, epilepsy, disappointment, and restricted ketoacidosis (Lemelman *et al*., 2018). A survey has shown an outcome that 80% children are very much affected with NDM and have caused of mutation in genes. 22 genes are directly associated with phenotype, inheritance, and another clinical attributes (Khan *et al*., 2015). Genes are involved in NDM which is important for the growing and combining of the β cells of pancreas. The foremost aetiology of NDM is mutation in the 6q24 locus as well as mutation in the ATP dependent potassium channel (K_{ATP}). Noteworthy, K_{ATP} channel is crucial at the time of triggering the β cells of pancreas activate the growing up of insulin concentration that is defined to glycosis (Beltrand *et al*., 2020). The adjustment of K_{ATP} channel in NDM children have served with sulfonylurea (Ozsu *et al*., 2016). Mendelian form of diabetes is also regarded as Paediatric diabetes (Barbetti *et al*., 2018). Genetic mutation of these genes is the fundamental aetiology of NDM promotion.

2. Classification of NDM

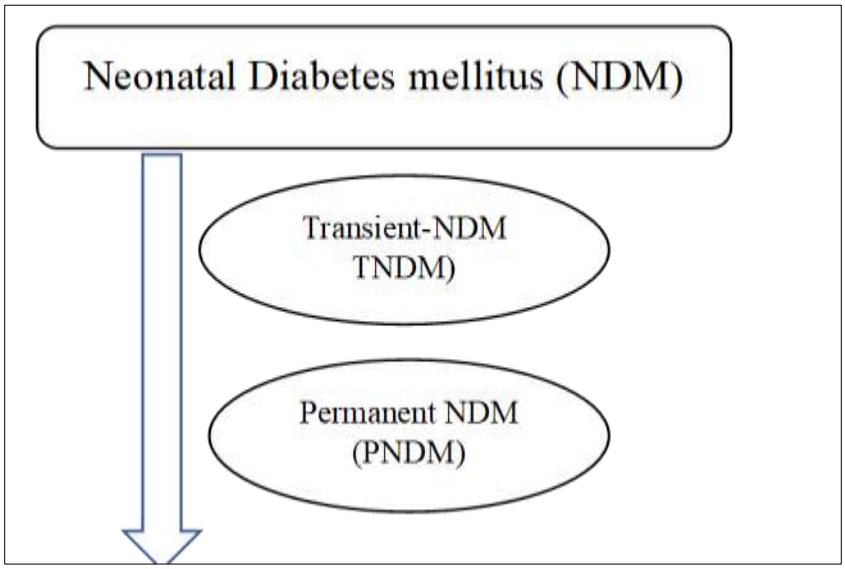

Figure 1 Classification of NDM

2.1. Mechanism of TNDM

TNDM is regarded as miscellaneous syndrome that influence 50-60% of NDM in infantile. TNDM is departed in infancy may be persist in later life that means in stage of adolescence and need prolonged treatment (Müller, 2021). Hyperglycaemia is started in neonate period and solved at the age of 18 months and remove the ketoacidosis and dehydration. Macroglossia and umbilical hernia may be present as symptoms of TNDM. 6q24-TNDM is interjoined along with multilocus imprinting disturbances (MLID) which may be developed hypotonia, congenital heart disease, deafness, epilepsy etc. TNDM begins at first week of life and completes at 3 months averagely however may longer than a year. The pervasiveness of TNDM occurrence span among the proportion of 1:400,000 and 1:500,000 (Priyadarshi *et al*., 2015). This type of diabetes emerges in first few weeks of life but it is transient. The fundamental mechanism of TNDM is dysregulation of pancreatic hormones depending upon the intensity of weakness in β cells (Gunes *et al*., 2021). Other symptom of TNDM is the gradual growth and development of neonates who is prone to hyperglycaemia and dehydration. 70% TNDM are caused of chromosome 6q24 aberration and 25 % are caused of the mutation in the ABCC8 and KCNJ11 genes (Demirbilek *et al*., 2019). TNDM is generally linked with HYMA1 and ZAC1genes because of good linkage along with parental and maternal allele slicing. Moreover, TNDM is the occasional. In case of TNDM children, IUGR is the recurrent and decreased amount of insulin is needed than PNDM children (Novak *et al*., 2020). TNDM neonates, born in amalgamation of malformation with 6q24 and IUGR grows chronic non ketonic hyperglycaemia at early life stage. The ABCC8 and KCNJ11 mutation trigger the genes of K_{ATP} channels (Ozsu *et al*., 2016). TNDM children

have nothing diabetes manifested HLA haplotypes. In case of TNDM, hyperglycaemia occurs where the concentration of glucose is >200 mg/dl.

2.2. Mechanism of PNDM

like TNDM, another monogenic diabetes mellitus is known as PNDM which develop at first 6 months of life (Ma *et al*., 2018) along with hyperglycaemia. PNDM is linked with partially or completely insufficiency of insulin. Babies along with PNDM have difficulties in intrauterine growth limitation, hyperglycaemia, glycosuria osmotic polyurea, chronic dehydration etc. at this PNDM, manifestation of DEND disorder is arrived. At first of 12 months DEND ailments are regarded as PNDM along with epilepsy (Taberner *et al*., 2016). PNDM is very infrequent syndrome. It has prevalence rate in between 1:120,000 to 1:260,000 (Huang *et al*., 2014). Mutation of KCNJ11 genes are most prevalent causes of PNDM expression. ABCC8, INS1 are autosomal recessive genes. GCK and PDX1 are another autosomal recessive gene. GCK, EIF2AK3, FOXP3 which are also interlinked with the pathophysiology of PNDM. INS1 gene mutation is the second aetiology of PNDM after the KCNJ11 and ABCC8 gene mutation. Furthermore, PNDM is severely caused of Wolcott-Rallison disorders. An interconnection is arrived among PNDM and mutation of KCNJ11 and ABCC8 gene by Kir6.2 and SUR1 that decrease the functions of potassium network and inhibit the insulin production (Vedovato *et al*., 2016). In case of PNDM, persistent hyperglycaemia occurs where the concentration of glucose is >150-200 mg/dl.

2.3. Strategy of dietary habit and lifestyle

Mediterranean diet is very much helpful for the improvement of NDM because it consists of plant-based compounds like fruits and vegetable, olive oil, seeds and nuts, low to moderate quantity of lean meat or dairy products along with lesion quantities of red meats and eggs mitigate this disorder. Furthermore, this diet has strong and active correlation with antioxidants like glutathione peroxides and superoxide dismutase which is functioned against ROS (MacLean *et al*., 2017) but western diet has increased level of sugar and calorie enrich foods secrete insulin concentration as well as enhances oxidative stress and insulin resistance so that, western dietary pattern should not follow to mitigate NDM. NDM is generally decreased with the help of plant components enrich diet along with do exercise on regular basis (D'Innocenzo *et al*., 2019). Western diet affects in prevalence of NDM (Bhatti *et al*., 2020). NDM is very much prevalent along with growing of diabetes and dementia. Adequate dietary habits are very much essential for mitigating the NDM complications. Few alterations are helpful for decreases the susceptibility of NDM these are remove the interest in bottle feeding which have high possibility to enormous calorie consumption, decreases the sedentary life style habit, should maintain at least 1-hour physical exercise for 3 to 5 years children and most importantly limited fat consumption less than 30% (Balasundaram & Krishna, 2022).

Dietary habit should be improved for instance ω-3 PUFA, curcumin, flavonoids, minerals like calcium, magnesium, potassium should be included. Reduces calorie dense foods and processed foods or sugary drinks are avoided totally. Decreases excessive body weight, adequate glycaemic index, mitigate hyperglycaemia, dyslipidaemia which is helpful for NDM mitigation (Wahl *et al*., 2019).

3. Conclusion

Neonatal diabetes mellitus is the very much serious issue of diabetes mellitus among infants. It is the caused of disarray in genetic elements and another ecological constituent. Most pronounced genes are ABCC8 and KCNJ11 are involved as a cause of this type of diabetes. Not only these two types of genes but also other type of genes is also advocated for developing Neonatal Diabetes mellitus. Few of genes are related with sulfonylurea. Substantial ratio of potassium network harmful microbes in case of MODY diabetes are observed. This serious issue is prevented with the help of Mediterranean diet but Western diet may not give positive effects to improve this. Apart from the dietary intervention, life style upgradation also gives positive effect to ameliorate this ailment. Furthermore, still a gap is unfilled about what quality along with quantity of diet is needed to prevent this serious issue.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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