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Ushasee Garai
M.Sc., Department of Food and Nutrition, JD Birla Institute, Jadavpur University, West Bengal, India

Saptarshi Mukherjee
Makaut, Maulana Abul Kalam Azad University of Technology, Nadia, West Bengal, India

Poulami Chakraborty
M.Sc., Department of Food and Nutrition, JD Birla Institute, Jadavpur University, West Bengal, India

Souvik Tewari
Assistant Professor, Department of Food and Nutrition, Swami Vivekananda University, Barrackpore, West Bengal, India

Correspondence
Souvik Tewari
Assistant Professor, Department of Food and Nutrition, Swami Vivekananda University, Barrackpore, West Bengal, India

Neonatal Diabetes Mellitus: Unravelling the clinical, genetic, and nutritional dimensions for enhanced management

Ushasee Garai, Saptarshi Mukherjee, Poulami Chakraborty and Souvik Tewari

Abstract
Neonatal Diabetes Mellitus (NDM) stands as a rare and intricate form of diabetes, presenting unique challenges in its clinical, genetic, and nutritional dimensions. With a prevalence of approximately 1 in 350,000 live births, NDM remains a seldom-encountered clinical entity. The genetic intricacies of NDM are notably characterised by autosomal dominant inheritance, where a single mutated allele of specific genes, such as KCNJ11, ABCC8, or INS, can be transmitted from one generation to the next, thus perpetuating the condition. Furthermore, the interplay of environmental factors, including gestational diabetes mellitus (GDM), can modulate the genetic landscape of NDM through DNA methylation and the differential expression of NDM-related genes. Recent studies have unveiled a pivotal role of gut microbiota, specifically, the abundance of certain bacteria like *P. Copri* and *E. Cloacae*, in influencing gene expression and, consequently, the epigenetic modulation of NDM risk. At the molecular level, NDM pathogenesis involves multiple mechanisms, including defective insulin regulation due to mutations in genes such as GLUT-2, SUR1, and Kir6.2, and disruptions in proinsulin processing. On the clinical front, managing NDM requires a multifaceted approach. Pharmacological therapy primarily involves the use of sulfonylureas like glibenclamide, which target the defective KATP channels in pancreatic beta cells, facilitating insulin release. Non-pharmacological strategies encompass gene therapy, nutritional therapy, Nutraceuticals, and nutrigenomics, offering a comprehensive management framework for this complex and rare condition, aiming to enhance the quality of life for affected individuals.

Keywords: Autosomal Dominant Inheritance, DNA methylation, Gene mutation, Gestational Diabetes Mellitus (GDM), Pathogenesis, Non-pharmacological, Pharmacological therapy

1. Introduction
Neonatal Diabetes Mellitus (NDM) is a rare and autosomal dominant heterogeneous monogenic form of diabetes characterised by hyperglycemia within the first six months of life (Bizzarri *et al.*, 2023) [10]. It poses unique challenges in diagnosis, management, and long-term care. Neonatal Diabetes Mellitus (NDM) is a rare form of diabetes that presents in the first six months of life. It is distinct from Type 1 Diabetes Mellitus (T1DM) in terms of its onset, underlying causes, and treatment (Rabbone & Iafusco, 2023) [39].

1.1. Prevalence
Neonatal Diabetes Mellitus or NDM is extremely rare, with an estimated prevalence of about 1 in 20,000–350,000 live births (Delvecchio *et al.*, 2023) [15]. It accounts for a very small fraction of diabetes cases and is often under-diagnosed. NDM can be categorised into two main genetic groups, as transient and permanent. Transient NDM is often caused by a specific genetic mutation that impairs insulin secretion during the neonatal period but usually resolves with age. Permanent NDM, on the other hand, results from mutations that cause lifelong insulin deficiency (De Franco & Johnson, 2013) [14]. Monogenic forms of NDM are linked to specific gene mutations, such as those affecting the KCNJ11, ABCC8, and INS genes (Bizzarri *et al.*, 2023) [10].

1.2. Onset and Symptoms
Neonatal Diabetes Mellitus typically presents within the first few months of life, hence the term 'neonatal'. Infants with NDM often display symptoms such as excessive thirst, frequent urination, dehydration, poor weight gain, and sometimes even ketoacidosis.

(Dahl & Kumar, 2020) [13]. This early onset makes it different from T1DM, which usually develops in childhood or adolescence. On the other hand, Type 1 Diabetes Mellitus usually emerges in childhood or adolescence, although it can occur at any age (Dahl & Kumar, 2020) [13]. It is characterised by an autoimmune attack on the insulin-producing beta cells in the pancreas. Common symptoms include increased thirst, frequent urination, unexplained weight loss, and fatigue (Beltrand *et al.*, 2020) [9].

1.3. Underlined causes & risk factors

Neonatal Diabetes Mellitus or NDM is primarily caused by genetic mutations that disrupt the normal function of the pancreatic beta cells, leading to a deficiency of insulin production. These genetic mutations can be sporadic or inherited (Pino *et al.*, 2023) [38].

1.3.1. Genetic Inheritance: NDM can be inherited in an autosomal dominant or autosomal recessive manner. In cases of autosomal dominant NDM, a single copy of the mutated gene from one parent is sufficient to cause the condition. In autosomal recessive NDM, both parents must carry a copy of the mutated gene. Therefore, the genetic makeup of both parents can influence the risk of passing on the NDM-associated gene mutations to their children (Khan, 2021) [30].

1.3.2. Sporadic Mutations: In some cases, NDM can result from *de novo* (new) mutations that occur in the egg, sperm, or during early foetal development (Stanik *et al.*, 2014) [40]. These mutations are not directly related to parental genetics or nutritional factors. Sporadic mutations can lead to NDM even in families with no prior history of the condition (Auble & Dey, 2023) [6].

1.3.3. Epigenetics: Epigenetic modifications, which can be influenced by parental nutrition and environmental factors, can potentially impact the expression of genes associated with NDM. While epigenetic changes do not alter the underlying genetic mutations causing NDM, they can influence how those genes are expressed and may contribute to the severity or course of the condition in an individual (Pino *et al.*, 2023) [38].

1.3.4. Maternal Nutrition during Pregnancy and Gestational Diabetes Mellitus (GDM): While neonatal diabetes itself is not caused by maternal nutrition during pregnancy, it is important to note that a pregnant woman's diet and nutritional status can influence her own health and the health of her developing foetus. Proper maternal nutrition is essential for the overall well-being of both the mother and the child, including the development of vital organs, which may indirectly affect the health of the pancreas and other systems. Neonatal Diabetes Mellitus (NDM) is a monogenic disorder with a genetic aetiology, characterised by infants carrying autosomal recessive or dominant mutations in genes linked to various subtypes, including Transient Neonatal Diabetes (TNDM), Permanent Neonatal Diabetes (PNDM), and associated syndromic forms (De Franco & Johnson, 2013) [14]. Furthermore, the interplay of epigenetic factors is emerging as a significant contributor to NDM susceptibility. Notably, prior investigations have suggested that epigenetic modifications, particularly DNA methylation patterns in the cord blood of newborns exposed to Gestational Diabetes Mellitus (GDM), exhibit alterations that potentially influence the expression of genes associated with glucose metabolism. NDM is an intricately regulated condition influenced by a network of genetic determinants (Bukhari *et al.*, 2022) [11]. Research has pinpointed seven genes that exhibit noteworthy changes in expression patterns in response to exposure to GDM. Among these genes, four demonstrate up regulated expression (TRIB1, POU2F1, PON1, and TXNIP), while three exhibit down regulated expression (PGC1α, MEST, and NRF2) in the context of NDM. Furthermore, emerging studies have begun to explore the potential role of the gut microbiota, which might be transmitted from mother to new-born, in the context of NDM. Nevertheless, the precise nature of gut microbiota dysbiosis in NDM remains largely uncharted territory. It is worth noting that GDM has been associated with alterations in the gut microbiota composition of new-borns, thereby highlighting a potential link between dietary factors, gut microbiota imbalances, and NDM. In particular, diet and dysbiosis in gut microbiota in the context of GDM could serve as predictive biomarkers for NDM (Bukhari *et al.*, 2022) [11].

Furthermore, Short-Chain Fatty Acids (SCFAs) are gaining recognition as epigenome modifiers capable of mitigating intestinal inflammation and influencing the expression of genes relevant to NDM. Maternal dietary patterns during GDM have been associated with distinct alterations in gene expression patterns in the context of NDM (Alsharairi *et al.*, 2023) [3]. The intricate interplay between complex carbohydrate or low-fat diets and gut microbiota-derived SCFAs, such as those derived from Bifid bacterium and Roseburia, is implicated in the modulation of specific genes, including down regulation of TRIB1 and up regulation of PGC1α (Sugino *et al.*, 2022) [41]. Conversely, a high-fat diet has been found to augment the abundance of certain gut bacteria, including *P. copri* and *E. cloacae*, potentially inducing genetic alterations within the neonate's gut microbiota (Jeong, 2022) [27], with significant implications for NDM. Notably, NRF2 and PDX1 genes exhibit down regulation, whereas the TXNIP gene shows up regulation in response to a high-fat diet. Increased levels of Bacteroides, *E. faecalis*, and Alistipes in reaction to a high-fat diet may exert a protective influence against NDM, leading to the up regulation of NRF2 and PGC1α genes while down regulating TRIB1. These bacterial strains exhibit the capacity to produce SCFAs, although additional studies are warranted to corroborate their specific role in mitigating NDM. Despite these findings, the precise epigenetic mechanisms by which bacteria such as Bacteroidetes *P. Copri* and *E. Cloacae* may influence gene expression in the context of NDM necessitate further in-depth investigation. Furthermore, comprehensive studies are warranted to elucidate the mechanisms underlying the pro- and anti-inflammatory effects of commensal and pathogenic bacteria on the susceptibility to NDM-associated genes in response to maternal dietary patterns during GDM (Alsharairi *et al.*, 2023; Longmore, 2019) [3, 33].

2. Clinical Presentation of NDM

The clinical presentation of Neonatal Diabetes Mellitus (NDM) comprises two subtypes: transient neonatal diabetes mellitus (TNDM) and permanent neonatal diabetes mellitus (PNDM), with the former typically resolving in early childhood and the latter persisting throughout life (De Franco & Johnson, 2013) [14]. Clinical features include hyperglycemia, failure to thrive, dehydration, and the potential for diabetic ketoacidosis (DKA). NDM, a rare early-onset form of diabetes, is rooted in genetic mutations affecting pancreatic beta cell function and insulin production. Symptoms range from asymptomatic hyperglycemia to severe DKA. NDM patients may exhibit stunted growth due to prenatal intrauterine growth restriction, alongside poor postnatal growth and behavioural changes. The likelihood of DKA increases with age, and certain genetic mutations are linked to a higher risk of DKA (Dahl & Kumar, 2020) [13]. Additionally, NDM may present extra-pancreatic findings, such as polycystic kidney disease, neurologic abnormalities, immune dysregulation, and more, offering diagnostic clues and guiding personalised management (Docherty *et al.*, 2013) [16].

3. Molecular Pathophysiology

Recent advancements in genetic research have identified multiple genetic mutations associated with NDM. These mutations affect critical genes involved in pancreatic beta-cell function, such as KCNJ11, ABCC8, and INS (Hattersley & Patel, 2017) [23]. Understanding the molecular basis of NDM is essential for targeted therapeutic interventions (Barbetti *et al.*, 2023) [7]. Abnormal β cell function constitutes a prevalent underlying factor in the genesis of neonatal diabetes, particularly when pancreas morphology remains within the normal range. The most frequent genetic origins of neonatal diabetes with these characteristics are abnormalities of the 6q24 locus and mutations within genes coding for the ATP-dependent potassium channel. Aberrations of the 6q24 locus, encompassing paternal uniparental disomy of 6q24 (pUPD6), partial paternal 6q24 duplication, and relaxation of the maternal 6q24 imprinted locus, have been recognized as seminal genetic causes (Docherty *et al.*, 2013) [16]. This genomic region contains a CpG island with differential methylation dependent on parental origin (non-methylation on the paternal allele and methylation on the maternal allele). This methylation abnormality leads to the over-expression of imprinted genes located within 6q24, with PLAGL1 or ZAC (pleomorphic adenoma gene-like 1) and HYMAI (Hydatidiform mole-associated and imprinted transcript) emerging as prime candidate genes. PLAGL-1 encodes a transcription factor implicated in cell cycle regulation, apoptosis, and the induction of human pituitary adenylate cyclase-activating polypeptide receptor 1 (PACAP1), a potent stimulator of insulin secretion. While the role of HYMAI remains enigmatic, it is speculated to play a part in the pathology. The precise aetiology of diabetes in these cases remains elusive but may be attributed to a developmental β cell defect, although remission does occur, underscoring potential abnormalities in β cell function. Importantly, 6q24 abnormalities are chiefly associated with 'transient' neonatal diabetes. The ZFP57 gene, found at 6p22.1, participates in maintaining DNA methylation during early embryogenesis. Homozygous mutations leading to a lack of functional protein are associated with extensive DNA hypo methylation, including hypo methylation of the 6q24 locus, although not all 6q24 methylation abnormalities are attributed to mutations in this gene (Docherty *et al.*, 2013) [16]. Mutations affecting the ABCC8 and KCNJ11 genes, encoding the ATP-dependent potassium channel, are instrumental in neonatal diabetes with normal pancreas morphology. These mutations result in the persistent opening of the KATP channel, rendering it incapable of responding to glucose levels and thus impeding insulin release (Abacı *et al.*, 2010; Rabbone & Iafusco, 2023; Pino *et al.*, 2023) [1, 39, 38].

Mutations of the insulin gene (INS) comprise the third most frequent genetic aetiology of neonatal diabetes. Heterozygous mutations predominantly impact preproinsulin's structure, following an autosomal dominant inheritance pattern. These mutations culminate in endoplasmic reticulum stress and β cell death, although recent evidence suggests that beta-cell growth and development are also affected. In some cases, mutations lead to protein expression alterations, typically in a recessive manner, particularly in consanguineous families. These mutations influence insulin promoter function directly or through factors enhancing its activity. Mutations involving the glucokinase gene, which regulates the first step of glucose metabolism in β cells, can lead to neonatal diabetes. Nonsense mutations cause complete deficiency of glucokinase-mediated glycolysis in the homozygous state, although this is a relatively infrequent cause of neonatal diabetes (Yahaya & Anyebe, 2020) [43]. Nevertheless, it underscores the importance of screening fasting blood glucose concentrations in both parents, especially when there is a history of gestational diabetes. Neonatal diabetes with abnormal pancreas morphology can be attributed to mutations in various genes involved in early pancreatic development. The severity of pancreatic damage can result in exocrine pancreas deficiency, and associated congenital malformations may be observed. Notably, the RFX-6 gene, implicated in the differentiation of beta cells during pancreas embryonic development, has been linked to both developmental and functional pancreatic disorders in neonatal diabetes, typically following an autosomal recessive transmission pattern. Autoimmune neonatal diabetes mellitus, though rare before six months of age, is often associated with specific causes. The IPEX syndrome, related to mutations in the FOXP3 gene, can result in early autoimmunity against pancreatic beta cells and necessitates a combination of immunosuppressant treatment and bone marrow transplant (Yahaya & Anyebe, 2020) [43]. This intervention does not eliminate diabetes (Barbetti *et al.*, 2023) [7]. Neonatal diabetes is more common in individuals with Down syndrome (DS), with trisomy 21 being a significant risk factor for early-onset diabetes. Furthermore, mutations such as activating STAT3 mutations can induce neonatal diabetes with concomitant beta-cell autoimmunity, expanding the spectrum of causative factors in this condition (Stanik *et al.*, 2014) [40].

Table 1: Different monogenic genes of neonatal diabetes (NDM) with associated features and treatments

SL No.	Gene	Transient vs. Permanent	Inheritance	Features	Treatment
1.	KCNJ11	Either	Spontaneous (80%), AD (20%)	Low birth weight, developmental delay, seizures (DEND syndrome), may have other neurologic features	Insulin Sulfonylurea
2.	ABCC8	Either	Spontaneous, AD	Low birth weight	Insulin Sulfonylurea
3.	6q24	Transient	Spontaneous, AD for paternal duplications	Low birth weight, possible IUGR; Diagnosed earlier than channel mutations (closer to birth); relapsed cases may respond to SU	Insulin
4.	INS	Either	Spontaneous (80%), AD (20%) AR (Rare--T or P)	Low birth weight	Insulin
5.	GATA6	Permanent	Spontaneous, AD	Pancreatic hypoplasia or agenesis; exocrine insufficiency; cardiac defect	Insulin
6.	EIF2AK3	Permanent	Spontaneous, AR	Wolcott-Rallison syndrome; skeletal dysplasia (1-2 years old) episodic acute liver failure; exocrine pancreatic insufficiency	Insulin
7.	GCK	Permanent	Spontaneous, AR (neonatal diabetes), AD (GCK-MODY)	Low birth weight	Insulin
8.	PTF1A	Permanent	Spontaneous, AR	Neurologic abnormalities, exocrine insufficiency, kidney involvement	Insulin
9.	FOXP3	Permanent	X-linked	Autoimmune thyroid disease; exfoliative dermatitis; enteropathy (IPEX syndrome)	Insulin
10.	ZFP57	Transient	Spontaneous, maternal Hypomethylation Imprinting	Variable phenotype Low birth weight, macroglossia, developmental delay	Insulin
11.	GLIS3	Permanent	Spontaneous, AR	Hypothyroidism, kidney cysts, glaucoma, hepatic fibrosis	Insulin
12.	PDX1	Permanent	Spontaneous, AR (neonatal diabetes), AD (PDX1-MODY)	Pancreatic hypoplasia or agenesis; exocrine insufficiency	Insulin
13.	SLC2A2	Either	Spontaneous, AR	Fanconi-Bickel syndrome (hepatomegaly, RTA)	Insulin
14.	SLC19A2	Permanent	Spontaneous, AR	Neurologic deficit (stroke, seizure) Visual disturbance; cardiac abnormality	Insulin Thiamine (rarely)
15.	GATA4	Permanent	Spontaneous, AR	Pancreatic hypoplasia or agenesis; exocrine insufficiency; cardiac defect	Insulin
16.	NEUROD1	Permanent	Spontaneous, AR	Neurological abnormalities (later), learning difficulties, sensor neural deafness	Insulin
17.	NEUROG3	Permanent	Spontaneous, AR	Diarrhoea (due to lack of enter endocrine cells)	Insulin
18.	NKX2-2	Permanent		Neurological abnormalities (later), very low birth weight	Insulin
19.	RFX6	Permanent	Spontaneous, AR	Low birth weight, intestinal atresia, gallbladder hypoplasia; diarrhoea	Insulin
20.	IER3IP1	Permanent	Spontaneous, AR	Microcephaly; infantile epileptic encephalopathy	Insulin
21.	MNX1	Permanent	Spontaneous, AR	Neurological abnormalities (later)	Insulin
22.	HNF1B	Transient	Spontaneous, AD	Pancreatic atrophy, abnormal kidney and genitalia development	Insulin

Source: Lemelman *et al.*, 2018 [32]

4. Management Strategies

The management of NDM involves maintaining glycemic control through insulin therapy. The choice of insulin regimen, dosage, and frequency should be individualised based on genetic and clinical factors. Continuous glucose monitoring (CGM) and insulin pumps may offer advantages in optimising glycemic control in neonates and infants (Lemelman *et al.*, 2018) [32].

4.1. Pharmacological treatment

The treatment of neonatal diabetes mellitus (NDM) is a complex and individualised process, primarily focused on addressing the underlying insulin deficiency caused by genetic mutations. In most cases, the mainstay of treatment is exogenous insulin administration, which aims to compensate for the impaired insulin production observed in NDM patients (Lemelman *et al.*, 2018) [32]. This therapy utilises regular and long-acting insulin analogy, which are carefully dosed to match the specific needs of each patient. The goal is to maintain blood glucose levels within a predetermined target range. To achieve this, continuous glucose monitoring or frequent blood glucose measurements are crucial for closely tracking the patient's response to insulin therapy. This monitoring helps healthcare providers make necessary adjustments to the insulin regimen, ensuring optimal glycemic control while preventing episodes of hypoglycemia (Ioacara *et al.*, 2018) [26]. In specific instances where genetic testing identifies certain mutations, sulfonylurea medications like glibenclamide may be considered as an alternative to insulin therapy. These

medications work by stimulating insulin release through their interaction with potassium channels on the cell membranes of beta cells. This strategy is effective for individuals with NDM caused by particular genetic mutations that retain some residual insulin-producing capacity. Genetic testing plays a pivotal role in determining whether sulfonylurea treatment is a suitable option for a given patient. Beyond insulin and sulfonylureas, emerging therapies offer additional avenues for NDM management. GLP-1 receptor agonists and SGLT-2 inhibitors are being investigated for their potential benefits in regulating blood glucose levels in NDM patients. These medications work through different mechanisms, with GLP-1 receptor agonists promoting insulin secretion and reducing glucagon release, and SGLT-2 inhibitors blocking glucose reabsorption by the kidneys, leading to increased glucose excretion in the urine. To ensure comprehensive and effective NDM care, a multidisciplinary approach is essential. This typically involves a team of healthcare professionals, including paediatric endocrinologists, geneticists, diabetes educators, and nutritionists. Their collaboration is critical in providing individualised care, guiding treatment decisions based on genetic test results, and adjusting therapies as necessary to optimise long-term outcomes for these young patients (Beltrand *et al.*, 2020; Iafusco *et al.*, 2023; Ashcroft *et al.*, 2017) [9, 39, 5].

4.2. Nutritional Management in NDM

Nutritional management is integral in NDM care. Breastfeeding or formula feeding should be carefully monitored to ensure appropriate caloric intake. Infants diagnosed with diabetes mellitus necessitate a meticulous and individualised approach to nutritional management, paralleling the dietary requirements of their nondiabetic counterparts (Kataria *et al.*, 2014) [29]. Central to this management is the provision of regular, well-balanced meals designed to meet the unique metabolic needs of these infants. Encouragingly, breastfeeding is considered an optimal choice for nourishment, aligned with established paediatric nutritional recommendations. To gauge the adequacy of breast milk intake, a commonly employed method involves weighing the infant both before and after each feeding session. Notably, breast milk contains an estimated 6 to 7 grams of carbohydrates per 100 millilitres, a crucial aspect for carbohydrate estimation. In neonates with diabetes, insulin requirements exhibit a nuanced relationship with the frequency of breastfeeding episodes. A regimen characterised by elevated basal insulin infusion, coupled with modest mealtime boluses (typically around 0.05 units per 12 grams of carbohydrates), is particularly effective when infants partake in more than six breastfeeding sessions per day (Karges *et al.*, 2012; Lora *et al.*, 2023) [28, 34].

Crucially, families caring for infants with diabetes mellitus are integral participants in this multifaceted process and should be empowered with a comprehensive understanding of the intricate interplay between nutrition and glucose control. This educational process encompasses vital concepts such as carbohydrate counting and the essential role of pre-meal blood glucose assessments, which serve as the foundation for accurate mealtime insulin dosing. The practice of offering frequent, smaller meals throughout the day, strategically matched with the duration of action of administered insulin, has been recognized as advantageous in achieving superior glycemic control. In cases where continuous subcutaneous insulin infusion (CSII) is adopted, the administration of the insulin bolus can be thoughtfully deferred until after the meal, aligning with the postprandial rise in blood glucose levels. Alternatively, an extended-release insulin bolus delivered during the meal itself may offer advantages by ensuring optimal glycemic control, thereby mitigating the risk of postprandial hyperglycemic or hypoglycemic episodes (Manerkar *et al.*, 2020) [35].

Emotional distress and caregiver anxiety may manifest when an infant refuses food, adding an additional layer of complexity to diabetes management. Caregivers should be equipped with effective strategies to address this situation, including the substitution of milk as a suitable alternative. Furthermore, to mitigate the risk of nocturnal hypoglycemia in infants, the incorporation of slowly absorbed complex carbohydrates, such as corn starch, into the bedtime regimen is a viable strategy. These meticulously tailored nutritional measures underscore the paramount importance of proactive and individualised dietary management in neonates with diabetes mellitus. By focusing on achieving metabolic equilibrium and minimising the associated risks, healthcare providers and caregivers can optimise the health and well-being of these vulnerable infants (Suzuki & Koga, 2014) [42].

In contrast with some research vital information regarding the maternal gluten intake has given insightful considerations. The gluten exerts multifaceted effects on the body, commencing within the intestinal milieu, where it impacts the composition of the microbiota, has the potential to induce enteropathy in Type 1 Diabetes Mellitus (T1DM), and elevates intestinal permeability. Encouragingly, these effects appear ameliorated by the adoption of a Gluten-Free (GF) diet. In the realm of animal studies, gluten has been observed to traverse the intestinal barrier alongside other molecules, including lipopolysaccharides (LPS), accumulating in diverse tissues such as islets and adipose tissue. Particularly concerning is its influence on animal beta cells, where gluten peptides have been identified as inducers of insulin secretion. Intriguingly, this effect is synergistically potentiated by palmitate, suggesting that gluten peptides might contribute to beta cell stress, dysfunction, loss, and autoimmunity, thereby potentially contributing to both Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM) (Haupt-Jorgensen *et al.*, 2018) [24]. Furthermore, gluten peptides may also play a role in the development of leptin and insulin resistance in the context of obesity and T2DM. Primarily based on animal research, it has been revealed that a GF diet can mitigate the innate and adaptive immune responses, leading to a reduction in overall inflammation. In the case of T1DM, the timing of gluten introduction in children is likely a pivotal factor, and the efficacy of gluten exclusion during pregnancy, coupled with early postnatal gluten introduction, warrants investigation as a prospective prevention strategy via intervention studies. Notably, animal studies even suggest that a GF diet during pregnancy may reduce the risk of Celiac Disease (CD) and result in morphological changes in the pancreas, including an increased number of islets.

Postnatally, a GF diet remains an intriguing therapeutic avenue for the prevention and management of T1DM, although further human intervention studies are imperative (Haupt-Jorgensen *et al.*, 2018) [24]. The concept of inducing mucosal tolerance to gluten represents another potential strategy for diminishing the risk of T1DM, necessitating extensive exploration. Conversely, concerning T2DM, the evidence regarding the alleviating effects of a GF diet is less conclusive, especially in light of the limited human studies conducted to date. However, animal studies do report improvements in both obesity and T2DM in response to a GF diet. It is important to note that GF diets are typically low in dietary fibres and other components with potential antidiabetic properties, making it necessary to undertake long-term investigations on the specific effects of gluten on obesity and T2DM (Pedrini *et al.*, 2020; Moreno-Castilla *et al.*, 2016) [37, 36].

Here are key components of nutritional management for NDM patients (Annan *et al.*, 2022; Yamamoto *et al.*, 2018; Dominguez-Riscart *et al.*, 2022) [4, 44, 17]:

- **Individualised Meal Plans:** Nutritional management should be highly individualised, taking into account the specific genetic mutation causing NDM and the patient's age, growth, and metabolic needs. Meal plans should be tailored to the patient's unique requirements.
- **Carbohydrate Monitoring:** Monitoring carbohydrate intake is essential for managing blood sugar levels. NDM patients may have varying degrees of insulin deficiency, and carbohydrate intake should be adjusted accordingly. Carbohydrates should be distributed evenly throughout the day to avoid large fluctuations in blood sugar.
- **Glycemic Control:** Monitoring and maintaining blood glucose levels within a target range are crucial. Frequent blood glucose monitoring may be necessary to adjust insulin therapy or other treatments as needed.
- **Insulin Therapy:** Many NDM patients require insulin therapy to manage their blood sugar. The type of insulin, dosage, and administration schedule should be determined by a healthcare provider based on the patient's specific needs.
- **Meal Timing:** Consistency in meal timing is important to help regulate blood sugar levels. Regularly scheduled meals and snacks can aid in preventing hypoglycemia or hyperglycemia.
- **Balanced Diet:** Encourage a balanced diet that includes a variety of food groups. Incorporate whole grains, lean proteins, healthy fats, and a rich assortment of fruits and vegetables. A dietitian can help design a well-balanced meal plan.
- **Fibre Intake:** Dietary fibre can help stabilise blood sugar levels. It is important to include fibre-rich foods in the Mediterranean diet, such as whole grains, legumes, and vegetables.
- **Hydration:** Adequate hydration is essential for overall health. Water is the best choice for hydration, and sugary beverages should be limited.
- **Monitoring for Hypoglycemia:** Given the potential for hypoglycemia (low blood sugar) in NDM patients, it's crucial to educate caregivers and patients about recognizing and treating low blood sugar episodes with appropriate carbohydrate sources.
- **Limiting Sugary and Processed Foods:** Foods high in added sugars and processed carbohydrates should be limited, as they can lead to rapid blood sugar spikes.
- **Portion Control:** Monitoring portion sizes can help control calorie intake and blood sugar levels. This is especially important for NDM patients who may be at risk of obesity.
- **Regular Follow-Up:** Patients with NDM should have regular follow-up appointments with a healthcare team, including a paediatric endocrinologist and a registered dietitian. These appointments can help adjust the meal plan and treatment strategies as needed.
- **Nutritional Education:** It is essential to provide patients and their families with education on proper nutrition, carbohydrate counting, and the management of NDM. This empowers them to make informed dietary choices.
- **Psychosocial Support:** Managing a chronic condition like NDM can be emotionally challenging. Providing psychosocial support, including counselling and peer support, can help patients and their families cope with the condition and its impact on daily life.

The nutritional management of Neonatal Diabetes Mellitus patients should be highly individualised, emphasising blood sugar control through proper meal planning, carbohydrate monitoring, and a balanced diet. Working closely with a healthcare team, including a registered dietitian and a paediatric endocrinologist, is essential to ensure the best outcomes for individuals with NDM (Manerkar *et al.*, 2020; Yamamoto *et al.*, 2018) [35, 44].

4.3. Nutrigenomics in NDM

Nutrigenetics is an emerging field that investigates the interplay between an individual's genetic makeup and their response to dietary constituents. In the context of Neonatal Diabetes Mellitus (NDM), understanding the nutrigenetic aspects can help tailor dietary recommendations to optimise glycemic control and overall health (Franzago *et al.*, 2019) [19]. Nutrigenomics delves into how dietary components, such as anthocyanins, low molecular weight polysaccharides, antioxidants, and vitamins, can influence gene expression and genetic factors associated with various health conditions, including monogenic forms of NDM (Chua-Lim *et al.*, 2023) [12]. While genetic mutations are the primary drivers of NDM, ongoing research explores the potential role of dietary factors in modulating gene expression and cellular mechanisms. Specific dietary components like anthocyanin (Bartel *et al.*, 2023) [8], low molecular weight polysaccharides, antioxidants, and vitamins may impact gene mechanisms involved in NDM by reducing oxidative stress, inflammation, and modulating immune responses, thereby potentially improving outcomes in individuals with NDM (Felisbino *et al.*, 2021) [18].

Table 2: Several bioactive compounds of foods that possessed the capacity to effect on Gene associated with diabetes (T2DM) to alter the specific expressions

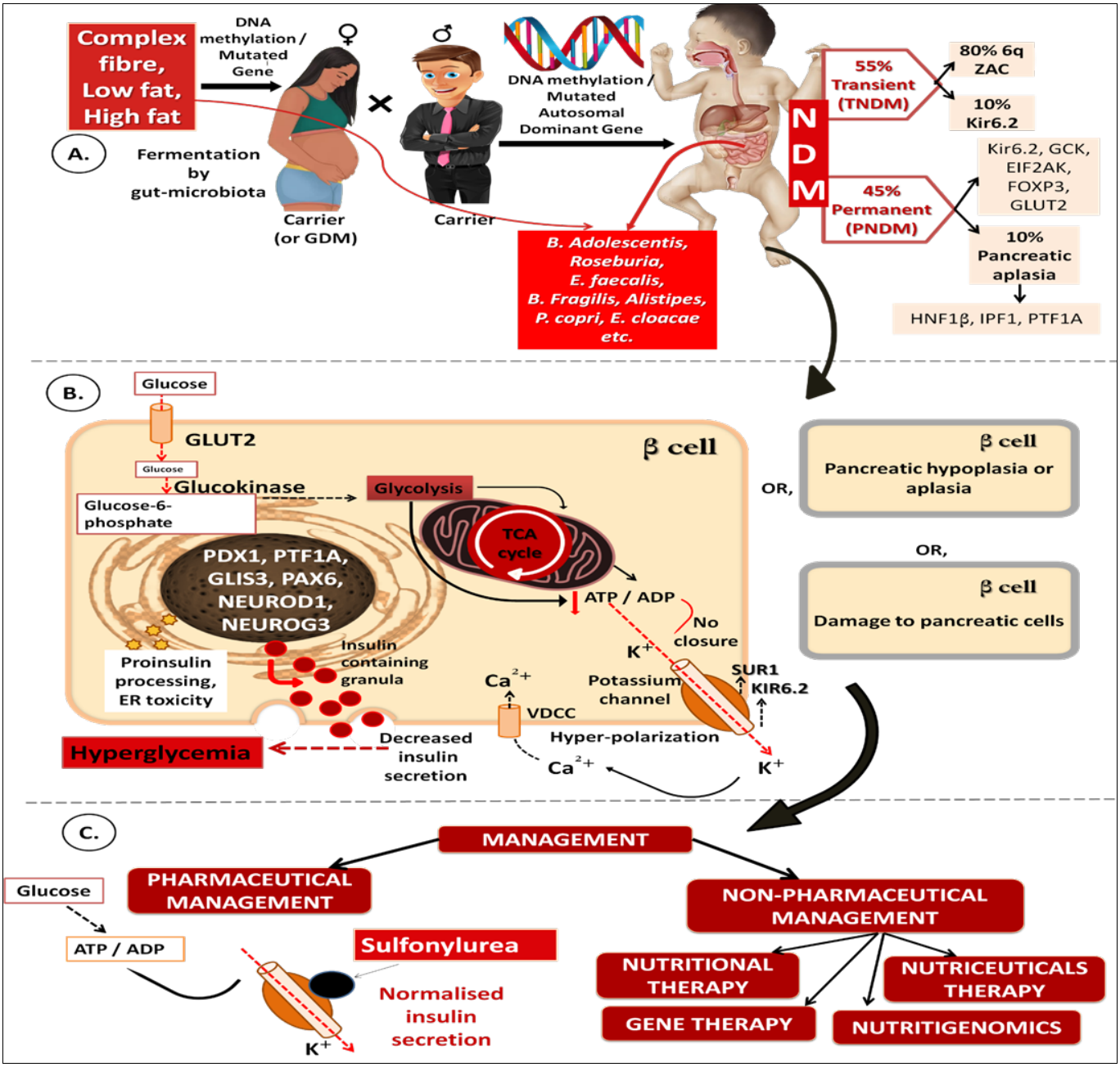
SL. No.	Genes associated with T2DM	Potential bioactive compounds of foods to alter the expression of gene
1.	**AGER gene** Encoded protein: Advanced glycosylation end-product specific receptor Function: Specific recipient of advanced glycation end products.	Curcumin potentially possesses antioxidant and anti-inflammatory characteristics, and it can mitigate oxidative stress induced by AGEs by suppressing the expression of the AGER gene in both mouse liver cells and cardiac tissue. Furthermore, it demonstrates the capacity to interact with transcription factors like NFκB, thereby diminishing gene transcription.
2.	**ENPP1 gene** Encoded protein: Ectonucleotide pyrophosphatase /phosphodiesterase 1 Function: Transmembrane glycoprotein with effect on insulin signalling and glucose metabolism.	No articles are available concerning the influence of foods or bioactive compounds on the modulation or control of the ENPP1 gene. Nevertheless, it has been noted that zinc deficiency can hinder the functions of certain ectoenzymes, including ENPP1.
3.	**ESR1 gene** Encoded protein: Oestrogen Receptor 1 Function: It encodes a transcription factor that responds to the action	In a CACO-2 cell study, it was observed that high concentrations of folic acid induced methylation in the ESR1 gene. Zebu larine reduced the methylation of this gene, while genistein resulted in hyper methylation of the ESR1 gene promoter. Resveratrol promoted an increase in ESR1 gene expression, and EGCG induced hyper methylation of ESR1, causing a non-significant decrease in its expression.
4.	**FFAR1 gene** Encoded protein: Free fatty acid receptor 1 Function: Metabolic regulation of insulin secretion and hepatic glucose uptake in vitro.	Studies on human cells have indicated that the anthocyanins found in purple corn possess the potential to activate the FFAR1 gene, a recognized marker whose activation holds promise in addressing type 2 diabetes and its associated complications. Another article further underscores that certain polyphenols, including anthocyanin, have the capacity to trigger the FFAR1 gene in pancreatic beta cells, thus suggesting their role in the prevention and treatment of diabetes.
5.	**FTO gene** Encoded protein: Alpha-ketoglutarate dependent dioxygenase Function: It forms a nuclear protein involved in insulin signalling, ROS production, and adipose tissue development.	Research conducted in both humans and animals has revealed a connection between the Mediterranean diet and the FTO gene, which is linked to the onset of type 2 diabetes. While there is some indication that the diet may offset the genetic predisposition associated with the FTO gene, the mechanism behind this remains insufficiently elucidated.
6.	**G6PC gene** Encoded protein: Glucose-6-phosphatase catalytic subunit Function: Liver glucose production during fasting or T2DM.	The consumption of EGCG is additionally associated with the regulation of gluconeogenesis through the inhibition of glucose-6-phosphatase gene expression. Administration of saffron stigma extract reduced the expression of the G6PC gene in diabetic rats. Investigations involving quercetin revealed that this compound activated AMPK, leading to the down regulation of the gene and a subsequent reduction in hepatic glucose production, as AMPK exerts negative control over G6PC.
7.	**HNF4A gene** Encoded protein: Hepatocyte nuclear factor 4 alpha Function: Regulator of hepatic gluconeogenesis and insulin secretion.	Luteolin, a flavone naturally occurring in chamomile, peppers, and celery tea, exerts a lipid-lowering impact through epigenetic mechanisms in mouse cells. This effect is achieved by suppressing the HNF4A gene and is associated with histone H3 acetylation.
8.	**IGF2BP2 gene** Encoded protein: Insulin-like growth factor 2 mRNA-binding protein 2 Function: Regulator of cellular metabolism.	Reduced protein intake in the diet was associated with elevated IGF2BP2 levels. However, there is no reported research on the impact of polyphenols or the Mediterranean diet on alterations in the expression of this gene.
9.	**IRS1 gene** Encoded protein: Insulin receptor substrate 1 Function: Insulin signalling. .	At low concentrations, EGCG does not exhibit IRS-1 gene activation but does function as an inhibitor of gluconeogenesis in isolated hepatocytes. Conversely, polyphenol-rich green tea elevates IRS1 gene expression in rat muscle. Additionally, the polyphenol-rich ethyl acetate fraction obtained from Molineria latifolia enhances insulin sensitivity in experimental diabetic rats by activating IRS1/AKT and modifying the phosphorylation of serine and tyrosine residues in related genes.
10.	**NFE2 gene** Encoded protein: Nuclear factor, Erythroid 2 Function: Regulator of the expression of antioxidant proteins.	Research with humans and animals indicates that EGCG and curcumin consumption is linked to enhanced NFE2 levels. These compounds reduce gene methylation, acting as epigenetic agents that activate the gene. Both EGCG in green tea and curcumin inhibit DNA methyltransferase and regulate histone modifications.
11.	**NFE2L2/NRF2 gene** Encoded protein: Nuclear factor erythroid 2 like 2. Function: Regulator of the expression of antioxidant proteins.	Curcumin reduces oxidative stress in different tissues through epigenetic demethylation, activating the NFE2L2/NRF2 gene and offering potential for diabetes prevention and treatment.
12.	**NFKB1, NFKB2 gene** Encoded protein: Nuclear factor kappa B subunit 1, Nuclear factor kappa B subunit 2 Function: Transcription factor involved in anti-inflammatory pathways.	Flavonoids such as fisetin, apigenin, quercetin, chrysin, isoliquiritigenin, rutin, genistein, and others exhibit anti-inflammatory, antioxidant, and anti-apoptotic characteristics. These bioactive compounds are capable of inhibiting NF-κB, primarily by diminishing protein phosphorylation. As a result, they can enhance vascularization in individuals with diabetes and reduce the risk of hypertension, effects that have been previously observed in various tissues of both humans and animals.
13.	**PARP1 gene** Encoded protein: Poly(ADP-Ribose) polymerase 1	Curcumin demonstrates the potential to protect pancreatic islet cells from streptozotocin exposure. This compound has the capacity to reduce the generation of reactive oxygen species (ROS), inhibit the activation of the poly ADP-ribose polymerase-1 enzyme (encoded

	Function: DNA damage signalling.	by the PARP1 gene), and prevent the depletion of ROS levels in free radical scavenging enzymes. In HUVECs cells, flavonoids such as rutin, quercetin, and flavone were found to inhibit PARP activation and ameliorate diabetes-related complications. These compounds are capable of interacting with transcription factors and modulating gene expression.
14.	**PCK1, PCK2 gene** Encoded protein: Phosphoenolpyruvate carboxykinase 1 Function: The PCK1 gene carries the code for the formation of an enzyme called phosphoenolpyruvate caboxycin (PEPCK). This enzyme is a limiter of gluconeogenesis, that is, it regulates the speed of this process.	The polyphenol-rich Juniperus procera plant demonstrated the capability to lower the expression of the PEPCK gene in liver and kidney cells of diabetic rats. This indicates its potential as a treatment for hyperglycemia, offering both anti-inflammatory and hypoglycemic benefits.
15.	**PI3KR1 gene** Encoded protein: Phosphoinositide-3-kinase regulatory subunit 1 Function: It forms a protein involved in insulin signalling, cancer, and cytokines or involved in the immune system, and also in adipocyte maturation.	There are few scientific articles related to nutrigenomics and the PI3KR1 gene.
16.	**PRKAA2 gene** Encoded protein: 5'-AMP-activated protein kinase catalytic subunit alpha-2 Function: It encodes the protein kinase that is activated by AMP molecules. The general function of this protein is to turn on important metabolic pathways for energy production and turn off the pathways that spend a lot of ATP, controlling the body's need for energy according to the situation.	Rat studies demonstrate that quercetin, found in foods like red onions, broccoli, and apples, possesses anti-inflammatory, antioxidant, and anti-apoptotic properties. It enhances glucose uptake in skeletal muscle by stimulating GLUT4 translocation through AMPK activation. Additionally, in the liver, it activates AMPK and reduces hepatic glucose production by suppressing glucose-6-phosphatase.
17.	**SIRT1 gene** Encoded protein: NAD-dependent protein deacetylase sirtuin-1 Function: It encodes the protein called Sirtuin 1 that belongs to the family of proteins that interact with the genetic material causing deacetylation of histone, that is, it is able to inactivate genes by an epigenetic mechanism.	Resveratrol is a potent SIRT gene activator used to treat diabetes by normalising blood sugar levels, enhancing insulin sensitivity, reducing liver glucose production, and regulating mitochondrial and lipid metabolism. However, its effects can vary with concentration, and high doses may harm human muscle cells and inhibit mitochondrial respiration.
18.	**SLC2A1, SLC2A4 genes** Encoded protein: Solute carrier family 2, facilitated glucose transporter member 1, and solute carrier family 2 member 4 Function: They encode glucose transporters (GLUT 1 and GLUT 4).	Several polyphenols, including catechins, flavonoids, phenolic acids, and others, have been associated with the enhancement of glucose transporter expression in both animal and human cells.
19.	**TCF7L2 gene** Encoded protein: Transcription factor 7-like 2 Function: Wnt signalling (β cell proliferation and secretion of the insulin).	The gene is actively expressed in adipose tissue and has already been linked to diabetes risk through SNPs. In a randomised clinical trial involving individuals at high cardiovascular risk, it was observed that adhering to a Mediterranean diet can mitigate the negative impact of the rs7903146 (TT) polymorphism. This dietary approach also led to reductions in fasting blood glucose and lipid levels, as well as a preventive effect against stroke.

Source: Felisbino *et al.*, 2021 [18]

4.4. Nutraceuticals in NDM

Nutraceuticals are bioactive compounds found in food that may have therapeutic effects. In the context of Neonatal Diabetes Mellitus (NDM), a rare early-onset diabetes condition often linked to genetic mutations affecting insulin production, certain nutraceuticals like resveratrol, curcumin, alpha-lipoic acid, and camel milk exhibit promise in enhancing insulin sensitivity and reducing oxidative stress (Ghannadias & Lomer, 2022) [20]. Camel milk, in particular, is known for its unique nutraceutical and antidiabetic properties. Studies have shown that camel milk contains insulin-like proteins and other bioactive components that may aid in improving glycemic control (Alavi *et al.*, 2017) [2]. However, further research is required to establish the full extent of its efficacy and safety in neonatal populations. While nutraceuticals are not a substitute for established medical treatments, they offer potential as supplementary elements in the comprehensive care of NDM patients. Noteworthy considerations for incorporating nutraceuticals into NDM management include vitamin and mineral supplementation, omega-3 fatty acids for their anti-inflammatory properties, antioxidants like vitamins C and E to counteract oxidative stress, probiotics to support gastrointestinal health, chromium for improved insulin sensitivity, alpha-lipoic acid for its antioxidant and insulin-sensitising properties, cinnamon extract for glycemic control, bitter melon extract for potential glycemic regulation, and American ginseng for blood glucose control (Gupta *et al.*, 2021) [22].



A. Genetic and environmental causes of NDM in the next generation: Neonatal diabetes mellitus (NDM) can be inherited dominantly due to mutations in genes like KCNJ11, ABCC8, or INS. Such mutations disrupt insulin production, resulting in high blood glucose levels from birth. If a parent carries the mutated gene, there's a 50% chance of passing it on. DNA methylation also plays a role in NDM among neonates exposed to gestational diabetes mellitus (GDM). Specific bacteria-derived short-chain fatty acids (SCFAs) act as epigenetic modifiers, reducing NDM risk by influencing gene expression. B. Defective insulin regulation in NDM patients at cellular level: Genetic defects in beta cells impact insulin release. GLUT-2 deficiency reduces glucose uptake, glucokinase deficiency impairs glucose phosphorylation, and mutations in SUR1 and Kir6.2 open KATP channels, blocking insulin release. INS gene mutations disrupt proinsulin processing, leading to beta-cell toxicity, while transcription factor gene mutations affect pancreas and endocrine cell development. C. Management of NDM through pharmaceutical and non-pharmaceutical therapy: Sulfonylureas like glibenclamide bind to SUR1 subunits, leading to KATP channel closure, membrane depolarization, calcium influx, and insulin release. Non-pharmaceutical approaches include nutritional therapy, gene therapy, nutraceuticals, and nutrigenomics, complementing pharmaceutical treatments to manage NDM comprehensively.

Fig 1: Diagramatic representation of the genetic and associated causes of NDM and its molecular pathogenesis with the management processes

5. Conclusion

Neonatal Diabetes Mellitus or NDM is a rare and challenging condition that demands a multidisciplinary approach to diagnosis and management. Advances in genetics have shed light on the molecular underpinnings of NDM, leading to more targeted therapies. Food and nutrition play crucial roles in NDM management, and the emerging fields of nutrigenomics and Nutraceuticals hold promise for improving outcomes in NDM patients along with pharmacological therapy. Fig 1 represents the inheritance, epigenetics and environmental factors associated with the onset of Neonatal Diabetes Mellitus (NDM) along with the pathophysiology of the disease at cellular level and different types of treatment strategies that possess effective management of the affected individuals.

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