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Malnutrition Related Diabetes Mellitus in Indian Population

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ABSTRACT

Malnutrition related diabetes mellitus (MRDM) is rare type of diabetes associated with long term malnutrition and is not uncommon in India. Diabetes mellitus is the most common endocrine disorder of multifactorial aetiology and has been linked to both chronic under nutrition and obesity. Malnutrition is often related to deficient micro and macro nutrients, unhealthy behaviours and low socioeconomic status. Various clinical studies have underlined the relationship between malnutrition and diabetes mellitus. In the present review, we mainly explored malnutrition related diabetes mellitus in Indian population. Maternal under nutrition during pregnancy causes a decrease in the fetal intrauterine development rate known as intrauterine growth retardation (IUGR). Malnutrition majorly causes persistent insulin deficiency, glucose intolerance and insulin resistance and there by increases the risk of diabetes in Indian population. In this study we have also discussed the pathogenesis of MRDM and their management like self- dietary management and evidence based individualized nutritional therapy.

Keywords: Malnutrition related diabetes mellitus (MRDM), under nutrition, obesity, Diabetic risk, intrauterine growth retardation (IUGR), insulin resistance and glucose tolerance.

INTRODUCTION

There has been an exponential increase in prevalence of Diabetes globally and if the current scenario prevails then the cases are expected to double by 2050 with estimated 79.4 million affected individuals in India alone. [2] This could be attributed to the current Indian demographic constituting young population cloaking the prospective effects of genetic, environmental(acquired) and behavioural factors(urban migration, lifestyle changes and rising living standards). Although obesity has been a recognised risk factor for diabetes, malnutrition has shown potential effects in development of insulin dependent diabetes mellitus. WHO recognised malnutrition as distinct entity and had incorporated Malnutrition Related Diabetes Mellitus as a category in classification of diabetes in 1985. [3,8] The present review aims to highlight the impact of malnutrition on diabetes mellitus in Indian population and its relationship with the diabetes mellitus. The literature search strategy involved a retrieval of relevant articles from Google and PubMed database using appropriate search terms.

CLASSIFICATION OF MRDM:

Malnutrition is a nutritional condition which results from the imbalance of energy, protein and nutrients, and poses effects in the form of composition and function of body tissues. [9] MRDM is characterized by insulinopenia, insulin resistance, [10] hyperglycemia and partial failure of the beta-cells in the pancreas. [11] The American Diabetes Association reclassified MRDM into 2 subgroups for research purposes.

2-subgroups of MRDM include:

1. Fibrocalcific or fibrocalculous pancreatic diabetes (FCPD): [6,11] It is characterized socioeconomic background of poverty and malnutrition

and it mostly observed in young adults mainly below the age of 30 years. It is recognized by the clinical evidence of malnutrition, insulin-requirement for control, ketosis-resistance, and radiological evidence of pancreatic calcification and the presence of exocrine pancreatic dysfunction.

2. Protein-deficient pancreatic diabetes (PDPD)/ protein deficient diabetes mellitus (PDDM): PDPD mostly observed in young malnourished individuals in developed countries similar to FCPD but differs from FCPD in absence of clinical and radiological evidence of pancreatic dysfunction and relative to insulin resistance. [12] Having a clinical feature of low BMI, malnutrition and often growth retardation. [12]

PATHOPHYSIOLOGICAL CONSIDERATIONS OF MRDM:

Globally, many factors are involved in the etio-pathology of malnutrition related diabetes mellitus are malnutrition, infection, food habits like increased consumption of cassava, immunological destruction of pancreatic beta cells. But the exact etio-pathogenesis of MRDM remains controversial. [13] MRDM is mostly develops in poor populations. The individuals are mostly less than 40 years of age, are underweight or cachectic and exhibit hair and skin changes and parotid gland enlargement typical of severe malnutrition. [5]

Fibrocalcific or fibrocalculous pancreatic diabetes (FCPD): The radiological evidence of pancreatic calcification or ultrasound signs of ductal dilatation favour pancreatic disease as the cause of the diabetes. [14] Shrunken pancreas shows extensive fibrosis involving the acinar and islet tissues. Exocrine pancreatic and B cell dysfunction is involved in the pathogenesis of FCPD. [5] Genetic susceptibility (undernutrition, deficiency of micronutrients and sulfur containing amino acids, decreased free radical and peroxide removal and environmental agents such as organic nitrides or cytochrome p450 causes pancreatic injury in the form of endocrine B cell damage and acinar and ductal damage manifesting clinically as diabetes, calculi and pain abdomen) plays key role and was demonstrated by restriction fragment length polymorphism (RFLP). [6] Although heavy alcohol consumption is also a major role in the pancreatic damage in older individuals. [5] FCPD develops mainly due to chronic calculous pancreatopathy and hyperparathyroidism. Pancreatic calculi are usually large multiple and intraductal. Marked ductal dilation and fibrosis usually occurs due to inflammatory changes. [12] FCPD is associated with increased risk of pancreatic carcinoma. [12]

Protein-deficient pancreatic diabetes (PDPD)/ protein deficient diabetes mellitus (PDDM): The aetiology of PDPD has remained a subject of debate. Several months and years of survival without treatment after the onset of diabetes, indicates resistance to ketoacidosis. Ketosis resistance(liver fails to reduce glucose production in response to insulin) due to subnormal B cell function further leads to insulin interruption. [5] It shows shrunken fibrotic pancreas without calculi and polymorpho-nuclear and mononuclear inflammatory cell infiltration in addition to extensive fibrosis. [5] Malnutrition with deficiency of micronutrients initiates the functional impairment of the pancreatic B cell. [6]

CHRONIC UNDERNUTRITION AND DIABETES IN INDIAN POPULATION:

Diabetes mellitus was strongly associated with the poverty and malnutrition particularly under nutrition has remained a major health challenge in children in low-income developing countries. [15,16] Previous retrospective study demonstrated the association between chronic under nutrition and diabetes; reported that protein-energy malnutrition (PEM) majorly causes

persistent insulin deficiency, glucose intolerance and insulin resistance. [4] The condition is characterized by the presence of chronic pancreatitis and was first defined in Indonesia in 1959. [4] Clinical studies have demonstrated the mechanisms underlying the feature of malnutrition is impaired insulin secretion, as low circulating insulin levels and inadequate insulinotropic responses to glucose, glucagon, as well as amino acids. [7] Indians typically develop diabetes at younger ages than Europeans and are predicted to reach a harmful threshold of metabolic load earlier, increase in BMI in Indian populations elevate diabetes risk to a greater extent than European populations. [17] Previous determined that Indians have a higher proportion of fat mass in their body weight relative to Europeans. Therefore, we can highlight several ways in which Europeans and Indians differ in their size, shape, and body composition which further increase the risk of diabetes. [18] Beyond this greater ratio of fat mass to lean mass, Indians also have greater metabolic sensitivity to adipose tissue than other ethnic groups. [19] Reduced maternal malnutrition during pregnancy increases the risk of diabetes in offspring. Specifically in Indians, shorter maternal stature and lower BMI are associated with lower birth weight. [20] Previous study noticed that long term influence of maternal micronutrient deficiencies on diabetes risk and is demonstrated by an association between low maternal B12 during pregnancy and insulin resistance in the offspring at 6 years, exacerbated by high folate levels. [21] A recent study in rural areas from Pune has highlighted low intake vitamin B12 and functional folate deficiency as maternal dietary determinants of low birth weight, mediated through their impact on maternal homocysteine levels. [22] Although the risk of diabetes in south Asians may be explained in terms of a reduced metabolic capacity that renders them particularly susceptible to the increased metabolic load associated with the lifestyles that track urbanization, or migration to higher-income settings. [23]

Factors involved in malnutrition are:

Prenatal factors:

Malnutrition and low protein diet:

Various studies described the link between maternal malnutrition, low protein diet, and T2DM. Reductions in total food intake during pregnancy or early postnatal life lead to decreased glucose tolerance and diabetes in the offspring. [15] A study conducted by Orozco-Sol´ıs et al analysed that low protein diet during pregnancy and lactating may cause permanent altered hypothalamic expression of genes in rat offspring; these genes involved in insulin signalling and lipid and glucose metabolism, which may outline the metabolic diseases. [24] Maternal under nutrition during pregnancy causes a decrease in the fetal intrauterine development rate known as intrauterine growth retardation (IUGR). [25] In IUGR, the developing fetus engages different mechanisms include increased sensitivity to insulin for more efficient glucose utilization, increased gluconeogenesis rates in liver, decreased muscle sensitivity to insulin, and abnormal development of the pancreas. [25] Under nutrition during pregnancy affects the methylation and alters the activity of many genes that control hepatic and pancreatic function. [15] Low protein diet during pregnancy may lead to increased oxidative stress, fibrosis, decreased HNF4a expression, defected mitochondriogenesis, and mitochondria dysfunction, and increased cell differentiation instead of proliferation was found in β-cell of adult animal offspring. These may cause β-cell dysfunction and consequently increase the incidence of T2DM in postnatal life. [26]

Over nutrition:

A study done by Maurer and Reimer in brown fat tissue of Wistar rats in 35-day-old offspring has noticed that high protein diet during pregnancy and lactating may cause increased resistin and IL-6 mRNA levels, which are involved in pathogenesis

of insulin resistance. [27] Most of human and animal studies have founded that high fat diet may cause obesity and insulin resistance. [28] A study conducted by Masuyama and Hiramatsu et al noticed that mice offspring exposed to high fat diet during pregnancy developed insulin resistance and hyperlipidemia at 24wks of age, which was associated with altered levels of leptin in adipose tissue. [29]

Postnatal factors:

Malnutrition during postnatal life may lead to decreased glucose tolerance and increases the risk of diabetes in the offspring. [15] Socioeconomic status has significant effect on diabetic risk. Some studies have demonstrated the link between low childhood socioeconomic status and type 2 diabetes. [30] Poor nutrition, unhealthy behaviours, and limited access to material goods and limited socioeconomic opportunities may contribute to altered body composition in later life, which might explain the relationship between childhood socioeconomic position and metabolic disorders in adult. A recent study suggested that Under nutrition during childhood has been found to be associated with an increased type 2 diabetes risk in adulthood. [31]

DIAGNOSIS

Malnutrition related diabetes mellitus was noted to be similar to other clinical syndromes described worldwide such as Tropical Diabetes, J type Diabetes, Z type Diabetes, Type 3 or M Type Diabetes and Phasic insulin dependent diabetes. [37,38] Criteria for identification of malnutrition related diabetes mellitus included the disease onset 10-30 years of age, poor socioeconomic status or history of childhood malnutrition, BMI <18Kg/m2, blood glucose >200mg/dl or 11.1mmol/L, absence of ketosis on insulin withdrawal and insulin requirement of >1.5U/kg/day.

Clinical features of MRDM appear to overlap with features of type 1 and type 2 diabetes mellitus on several occasions. Low BMI and early age of onset might raise suspicion of type 1 diabetes, however, it can be differentiated by decreased levels of islet specific antibodies, lower risk of ketoacidosis on insulin withdrawal and male preponderance in MRDM. Key distinctive feature of MRDM from classic type 2 diabetes is defect in insulin secretion as opposed to resistance to peripheral insulin.

MANAGEMENT OF MALNUTRITION RELATED DIABETES MELLITUS:

According to American Diabetes Association, self-dietary management plays key role in the prevention of diabetes. [1] A study conducted in Indian men with impaired glucose tolerance (IGT) has suggested that healthy lifestyle adjustments comprising a calorie-restricted diet were associated with a decreased incidence of diabetes. [32] Balanced diet and regular physical activity improves insulin sensitivity and beta cell preservation. [32] The major goals of dietary strategies was to restrict fat to > 30% of calorie intake and reduce intake of high-GI carbohydrates such as sugar, flavored beverages and high-calorie snacks. [33] A 12-month prospective study from India reported the success of a dietician-led evidence-based individualized nutritional therapy for macronutrient intake and restricted intake of sugars. Participants with T2DM, randomized to nutritional therapy, achieved significant improvements in HbA1c in all lipid parameters, especially triglyceride levels. [33] Population-based studies from India have documented the association between overconsumption of refined grains that lack dietary fibers and vital micronutrients and saturated fats with insulin resistance and poor glycemic control, whereas intake of fiber-rich foods, fruits and vegetables has shown a negative correlation. [34] study conducted in Indian participants with type 2 diabetes on oral hypoglycemic medications demonstrated the success of a structured diet plan comprising a modified traditional Indian to lower GI and glycemic load (GL) diet. [35] Multivitamin supplementation may be

recommended in deficiencies in vitaminA, C and E, thiamine, pyridoxine, B12 and biotin, which are common patients with diabetes. Particularly treatment with metformin requires B12 and folic acid supplements, as prolonged use of metformin decreases the absorption of these vitamins. **[36]**

DISCUSSION

WHO introduced widely accepted classification of Diabetes mellitus in 1980 which included type 1 and type 2 diabetes. It was later modified in 1985 post study group report and renamed type 1 and type 2 diabetes as Insulin Dependent Diabetes Mellitus and Non-Insulin Dependent Diabetes Mellitus and introduced Malnutrition related diabetes mellitus as a new class. In 1999, International Workshop reviewed characteristic of diabetes in malnourished population. It established the influence of malnourishment exposure leading to diabetes however the evidence provided was insufficient and not convincing, hence MRDM class was deleted from WHO classification. Later in 2006 WHO report, subtype of MRDM which is Fibro calculous Pancreatic Diabetes was classified as disease of exocrine pancreas which may lead to diabetes and it remains till date as per 2019 WHO classification of Diabetes. MRDM is also studied under the term Ketosis resistant diabetes of young (a term coined by Ahuja) and protein deficient pancreatic diabetes.

There is a need for prospective multicenter study in India to elucidate the pathogenetic mechanism of malnutrition related diabetes with consideration to predisposing factors such as insufficient nutrition in intrauterine or early postnatal environment causing genetic predisposition to fragile beta cell mass.

CONCLUSION

The review of various studies established the relationship between malnutrition and diabetes mellitus. Malnutrition during pregnancy or early postnatal life results in decreased glucose tolerance and increases the risk of diabetes in the offspring. Poor nutrition, unhealthy behaviours, and limited socioeconomic opportunities may contribute to altered body composition, which might describe the relationship between childhood socioeconomic position and metabolic disorders in adult. In this review, we concluded the association between malnutrition and diabetes mellitus. Malnutrition majorly causes persistent insulin deficiency, glucose intolerance and insulin resistance and there by increases of risk of diabetes in Indian population.

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