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WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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Maternal low protein diet and fetal programming of lean type 2 diabetes

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Abstract

Maternal nutrition is found to be the key factor that determines fetal health *in utero* and metabolic health during adulthood. Metabolic diseases have been primarily attributed to impaired maternal nutrition during pregnancy, and impaired nutrition has been an immense issue across the globe. In recent years, type 2 diabetes (T2D) has reached epidemic proportion and is a severe public health problem in many countries. Although plenty of research has already been conducted to tackle T2D which is associated with obesity, little is known regarding the etiology and pathophysiology of lean T2D, a variant of T2D. Recent studies have focused on the effects of epigenetic variation on the contribution of *in utero* origins of lean T2D, although other mechanisms might also contribute to the pathology. Observational studies in humans and experiments in animals strongly suggest an association between maternal low protein diet and lean T2D phenotype. In addition, clear sex-specific disease prevalence was observed in different studies. Consequently, more research is essential for the understanding of the etiology and pathophysiology of lean T2D, which might help to develop better disease prevention and treatment strategies. This review examines the role of protein insufficiency in the maternal diet as the central driver of the developmental programming of lean T2D.

Key Words: Type 2 diabetes; Maternal low protein diet; Fetal programming; Lean diabetes; Developmental origin of health and disease

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Core Tip: This is to review the role of maternal low protein diet and its metabolic impact on the offspring leading to lean type 2 diabetes.

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INTRODUCTION

Type 2 diabetes (T2D) is a metabolic disease, which is rapidly increasing among the human population both in developed as well as in developing countries. Diabetes is divided into four major categories: type1, type2, gestational, and other specific diabetes mellitus[1]. As per the national diabetes statistics reports in 2020, 10.5 % (34.2 million) of the United States population are diagnosed with some form of diabetes and 34.5% (88 million) of adults have pre-diabetes. T2D constitutes 90%-95% of all diabetes cases in the United States[2]. The hallmarks of T2D are insulin resistance and insulin deficiency. In most cases of T2D, the etiology of insulin resistance and insulin deficiency can be traced back to obesity and lifestyle aspects.

Scientists from all over the world have spent a great deal of time and effort to understand the causes and consequences of obesity-induced T2D. However, the number of non-obese/lean T2D cases has also dramatically increased globally and especially in Asia and other developing countries. Recent estimates show that 10%-20% of T2D patients are not obese[3]. Although the etiology is not clearly understood, lean T2D is clustered under the umbrella of T2D for patient care. Interestingly, clues from various studies indicate that lean T2D is often observed in the populations where the fetus is exposed to malnutrition during the intrauterine period or early childhood[3-7]. Adequate birth weight and size of the newborn are often considered as indicators of appropriate fetal growth rate and optimal *in utero* environment[8-10]. In contrast, deprivation of nutrition during fetal development is often marked by low birth weight and it is linked with adult-onset of metabolic diseases such as T2D[11].

Historically, observational studies from the different parts of the world firmly indicate that the individuals exposed to *in utero* malnutrition due to famine were more prone to the hyperglycemic condition in adult life compared to those who are not born during a famine[12]. For instance, the cohort exposed to Dutch famine (1944-45) *in utero* were more prone to glucose intolerance than the non-exposure cohort[13]. Similarly, data associated with the Ukrainian famine of 1932-33 have exhibited a higher incidence of T2D among the people born in the famine-affected region than in the regions where no famine was reported[14]. The link between Australian famines and T2D was studied and analysis showed a positive correlation with three years of famine and an increased number of T2D among those who were born during the famine years[12]. Further, Li *et al*[15] reported that people who were exposed to the Chinese famine in the fetal stage during 1959-1961 were more prone to hyperglycemia and T2D in their adult life, compared to those who were born after this period.

Recent studies indicate that adverse *in utero* nutrition could cause lean T2D later in life among certain ethnic and socio-economical groups, and people with certain lifestyles. Studies from India[16] (up to 26%) and Caribbean islands[17,18] (5%) report the predominance of lean T2D population. A study on American minorities showed that 13% of T2D patients are lean[4,16] with a fivefold higher incidence in Asians[4]. These observations clearly show that not all diabetics are obese and obesity does not necessarily cause T2D[3,16,19]. With > 42 million Americans experiencing food insecurity, it is a major problem even in the United States especially among the economically disadvantaged[20]. WHO estimates that 1.1 million children had ≤ 2 standard deviations for weight for height ratio (an index of protein-energy malnutrition) in the United States[21]. A recent German study shows that 38% of pregnant women did not consume enough protein[22]. With vegetarian and vegan diets gaining popularity worldwide, low protein intake is more prevalent as these diets are often low in protein[23, 24]. Vegetarian mothers consume low protein diet[25,26] and give birth to children with lower birth weights, thus making them susceptible to T2D[26-28].

This atypical diabetic phenotype is known by various names such as Jamaica type diabetes, metabolically obese normal weight (MONW) diabetes, malnutrition-related diabetes mellitus, phasic insulin-dependent diabetes, tropical diabetes, mixed onset type diabetes, J, Z, M or type 3 diabetes, and ketosis resistant growth onset type diabetes[3,17,18,29-33]. This concept of MONW individuals was first proposed in 1981[29] with subsequent validations in animal and human studies[34-37] and the existence of lean T2D has been observed for decades but the etiology and pathophysiology of lean T2D are poorly understood.

The most accepted and validated hypothesis that explains the link between early nutrition and metabolic diseases in adulthood was proposed by David Barker is called, 'thrifty phenotype hypothesis'

[11,38]. This hypothesis explains how impaired *in utero* nutrition availability results in compromised fetal growth and programs subcellular and metabolic effects in the developing fetus. Further, the hypothesis suggests that the metabolic fate of an individual predisposed to T2D is decided at the early developmental stage and thus attempts to explain why a sub-population of individuals born with low birth weight are more prone to lean T2D compared to normal birth weight individuals[11]. Various subsequent studies have confirmed the reproducibility and epidemiological evidence for the 'thrifty phenotype hypothesis'[39].

In addition, studies based on this hypothesis showed the importance of a sufficient amount of protein in the maternal diet for the development of the fetus and the risk of diseases in adulthood[40]. Although overall well-balanced nutrition is essential for a developing fetus and a healthy offspring, the role of protein is vital in the developmental programming paradigm[41]. A low protein diet is well known to cause various programming effects leading to metabolic disorders in adulthood. Low protein or vegetarian diets are consumed due to various reasons such as poverty, famine, lack of availability, cultural, religious, or moral reasons, personal preference, *etc.* Although these are common in the developing world, the recent popularity of vegetarian and vegan diets in the developed world is also an important paradigm to be considered. The emerging popularity of vegetarian and vegan diets among the maternal population might compromise growing fetuses, as the amount and bio-availability of proteins are found to be inadequate from plant sources[23,42]. A low protein diet during gestation is often connected with compromised renal function and impaired glucose metabolism[7]. However, the mechanistic basis and the exact patient phenotype of the maternal low protein associated with lean T2D are not well understood. Therefore, a clear understanding of the epidemiological and clinical features of lean T2D is essential to the prevention or treatment strategies.

PATHOPHYSIOLOGY OF LEAN T2D

T2D is a complex metabolic disease with a spectrum of presentations. It is therefore essential to understand the pathophysiology of the disease to offer appropriate prevention and treatment strategies. The pathophysiology of lean T2D is not well defined, although we and others have considered them as a separate subset of T2D[3,43,44] body mass index (BMI) is widely used as a tool to classify T2D patients. Patients with a BMI greater than 25 are considered to have obese T2D[45]. In contrast, the majority of lean T2D patients have a BMI of less than 25 but they have several metabolic characteristics associated with obesity[3]. Observational studies in humans and experiments in rodents suggested that the various environmental and genetic factors could contribute towards the lean T2D phenotype[3,46]. Poor *in utero* nutrition during fetal development is considered to be the main driver of lean T2D onset[44,46]. We have shown using a novel rat model that the maternal low protein diet is one of the critical causes of the lean T2D phenotype[43].

Although the genetic factors may vary among the different populations, genetic predisposition to fragile beta cells was found to be common in lean T2D patients. The rapid beta-cell apoptosis is the major pathophysiological characteristic of lean T2D compared to elevated insulin resistance in obese T2D[47]. Another interesting aspect that is noticed in this population is the prevalence of truncal obesity. Insulin sensitivity and insulin response are varied among the different ethnic groups (African, Caucasian, and East Asian), and East Asians have more vulnerable beta cells which make them more prone to T2D[48]. Several studies on the South East Asian population have shown that lean T2D patients have central obesity or elevated visceral fat deposits[49]. Even though lean T2D patients have lesser hyperglycemic values, their hemoglobin A1c levels are significantly higher than their obese counterparts[5,44]. Further, the onset of lean T2D is reported at an early age than the obesity-associated T2D[3]. Lean T2D patients showed a significantly lower incidence of hypertension and cardiovascular diseases compared to obese T2D patients but are more susceptible to peripheral neuropathy[3,5]. Apart from environmental and hereditary factors, socioeconomic background is found to be an important aspect of lean T2D prevalence[10,50]. Several studies have reported an inverse relationship between T2D and socioeconomic status[51]. The National Health and Nutrition Examination Survey data indicated this relationship of poverty and higher incidence of T2D among African and Mexican origins in the United States[52]. The Chicago cohort study further showed the prevalence of lean T2D among this minority community[4].

The two crucial characteristic features of developing countries, which make them more vulnerable to lean T2D, are a rapid shift in lifestyle and impaired nutrition. Studies from India have reported the escalating number of lean T2D cases across the country, especially, the urban population of India[53-55]. Similarly, Alemu and the group reported the increased number of lean T2D like cases in the urban population of sub-Saharan Africa[56].

GESTATIONAL LOW PROTEIN PROGRAMMING AND SEX DIFFERENCES IN LEAN T2D

Sex differences in fetal development can be observed as early as the pre-implantation phase[57]. There are major *in utero* differences between the sexes in growth and metabolic parameters leading to a faster fetal growth in males when compared to females. These differences are attributed to the genes expressed by sex-chromosomes and the actions of sex hormones[57-59]. In addition, differences in the incidence of T2D can also be attributed to the differences in the leptin and insulin sensitivity between sexes[59,60]. These metabolic hormones are influenced by the *in utero* nutritional environment[61]. Many studies have found a link between T2D and maternal low protein diet[43,59,62,63]. Further, as the nutritional environment often regulates the epigenetic machinery, any change *in utero* nutritional status may cause permanent alterations in the fetal gene expressions[64].

Our research using a lean T2D rat model indicates a clear sex difference in glucose homeostasis with females developing glucose intolerance earlier in life with faster disease progression than males[43,65]. These animals also showed differential regulation of gluconeogenesis and glycogenolysis as a result of gene expression changes in key genes involved in glucose metabolism[65-68]. Sex difference in hepatic genes associated with glucose homeostasis such as phosphoenolpyruvate carboxykinase (PEPCK) and 11 β -hydroxysteroid dehydrogenase type 1 were observed even in low protein programmed fetuses[69]. Similarly, low protein programmed mice offspring were found to have lower birth weight with more glucose intolerant than the controls[70]. In this study, maternal low protein diet activated the visceral adipose tissue neuropeptide Y-Y2 receptor system in female offspring but not in male offspring, which increased abdominal adiposity and insulin resistance in female offspring[70]. This study indicates the importance of neuropeptide Y-Y2 receptor as a potential sex-specific marker and mediator of metabolic programming[70].

In the last decade, various studies have shown the importance of mitochondrial health and its relationship with glucose homeostasis in low protein programming. Zambrano and group have found maternal low protein diet-induced insulin resistance in male Wistar rats; however, females were responsive to glucose[71]. This study, further, suggested that elevated mitochondrial dysfunction in the pancreatic islets of adult male rats might be the mechanism that leads to insulin resistance[71]. Likewise, male offspring of low protein diet-fed mothers showed higher ROS production and impaired electron transport chain function in the mitochondria of the pancreatic islets when compared to female offspring indicating mitochondrial incompetence in males could predispose them to T2D[72]. Similarly, the sex dependent fetal programming in glucose metabolism was also reported *in utero* low protein programmed piglets. In this study, hepatic gluconeogenesis in newborn male piglets was negatively affected by the maternal low protein diet during pregnancy[73]. Epigenetic changes in the promoter region of the glucose-6-phosphatase gene were sex-specific and resulted in T2D in adult male pigs[73]. In addition, maternal low protein diet diminished liver mtDNA copy number in males and altered the OXPHOS protein expression by the combined binding action of glucocorticoid receptor and methylation of on the hepatic mtDNA promoter, which effect the mtDNA replication and gene expression levels[73, 74].

Studies in humans suggest greater prevalence and impact of lean T2D in males than females. Many studies have indicated that women are physiologically inclined to have better insulin sensitivity than men[75-77]. Estrogen has a protective role in insulin sensitivity and glucose homeostasis by the inhibition of Foxo1 though activation of ER α -PI3K-Akt signaling[78]. Another crucial way estrogen protects women from insulin resistance is through mitochondrial biogenesis, as testosterone reduce mitochondrial proliferation[79]. The male preponderance of lean T2D was evident from the studies conducted in India, where more than 60% of lean T2D patients were men. Although the exact causes of sex differences are not clearly understood, it is suggested that the differences observed in this study may be due to predominant male exposure to oxidative stressors such as smoking and alcoholism[3,80].

Another interesting aspect to consider is the role of folate. Folate is routinely given to pregnant women throughout the world to prevent neural tube defect. Recent studies show that excessive folate can also have negative consequences at least in certain populations, ages and ethnicity/genetic background[81-83]. One study in Indian population shows that it can lead to insulin resistance[7]. The authors primarily attribute this to the deficiency of vitamin B12 which is primarily present in animal protein. Rat studies from our group showed that folate offered some protection in low protein programmed offspring by compensatory hyperinsulinemia but make insulin resistance worse in males [84]. Although the mechanism of this sex dependent folate action in insulin resistance is not known and warrant further research, it is important to note how folate may have sex dependent effects and this may also hold a clue in the sex differences that are observed in the human population.

ANIMAL MODELS

Considering the ethical and technical limitations in conducting impaired maternal nutrition and developmental programming studies in humans, various animal models that mimics several aspects of developmental programming have been developed. Due to the shorter lifetime and availability of

genetic tools, a substantial amount of research is presently focused on developing clinically reliable rodent models of developmental programming.

To achieve a low protein diet model, the majority of studies followed a diet that has around a 50% reduction of total protein in the diet formulation[43,63,85-87]. However, most of the investigations conserved the isocaloric nature of the diet by manipulating macronutrient proportions by various lipid and carbohydrate ratios[88-93]. Although preferred protein, carbohydrate, and lipid ratio are varied among different research groups; a single research group often stick to one specific diet regimen[67,91,94-97]. The other central deviation apparent among the different low protein models is the timing and duration of the maternal diet management. Majority of the studies have started giving low protein diet from the first day of the pregnancy and continued throughout pregnancy or lactation, although some studies initiated the low protein diet before pregnancy or in some cases in a specific period of *in utero* growth[65,86,98-102]. The main aim of these refined diet manipulations is to develop a metabolically compromised adult offspring[103]. Moreover, many studies have succeeded in mirroring low birthweight and catch-up growth pattern, which is considered by many as a hallmark of the developmental origin of metabolic disease[104-108]. Pups from maternal low protein mothers weigh less compared to those from control diet-fed mothers. The differences in birth weight disappeared once the mothers were fed with a normal diet or pups were cross-fostered with control mothers. However, the weight differences were permanent, when the maternal low protein diet was continued throughout the weaning[43,100,109]. In addition, due to the variation in macronutrients ratio and the time regime of the diet, the adult metabolic phenotypes reported by various groups are also varied. Insulin resistance, obesity, cardiovascular diseases, and dyslipidemia are the major clinical disorders observed in these models[104,110-113]. A comprehensive list of different low protein programming animal models used are summarized in Table 1.

PHYSIOLOGICAL EFFECTS AND MECHANISMS

Many animal models based on a low protein diet have been successful in capturing the phenotypic characteristics of fetal programming of adult metabolic diseases. However, the exact mechanism that leads to these metabolic diseases is not well studied. The dominant hypothesis in the field of developmental programming of adult diseases attribute that the fetal epigenome play a central role. This hypothesis postulates that epigenome is reprogrammed as an adaptation in response to a low protein diet, the associated low birth weight, and the catch-up growth. A recent study in Japanese adults indicates that the reduced beta cell mass in low-birth-weight individuals is directly associated with the future development of T2D[114]. Although the epigenome is prone to modification throughout the lifetime, *in utero* developmental period was found to be the most vulnerable time to be dysregulated by stressors[115].

Several studies have reported various key genes that are epigenetically modified as a result of developmental programming. For instance, the transcription factor Hnf4a was found to be epigenetically regulated during gestation, and the maternal diet-induced changes in the expression of this gene can cause T2D in adulthood[116]. Similarly, glucose transporter 4 (GLUT4) expression in skeletal is epigenetically controlled by maternal diet during early development and the impaired gene expression often resulted in peripheral insulin resistance[117]. Even though different biological mechanisms might contribute to fetal programming of lean T2D, many recent studies are indicating epigenetic changes as a potential single important driver of the fetal programming effects[118]. Low protein diet exposure during pregnancy in animals exhibited changes in methylation in promoter regions of genes involved in the glucose homeostasis pathway thereby, affecting the gene expression either directly or indirectly [119]. In recent years, many experimental studies in animals and observational studies in humans show that the epigenetic changes associated with gestational low protein are the main regulatory forces mediating the T2D phenotype[118,120]. Changes in the fetal epigenome often mirror the unique *in utero* environment of the fetus. Epigenetic changes due to gestational low protein arise through the methylation of cytosine in CpG Island present in the promoter region of particular genes, histone protein modification by acetylation, and regulation microRNAs by post-transcriptional modification. The chromatin structure and expression of a specific gene are regulated through DNA methylation in association with histone modifications[121].

A study in pigs found a significant decrease in glucocorticoid receptor binding to the glucose-6-phosphatase (G6PC) promoter which was accompanied by hypomethylation of the G6PC promoter in association with gestational low protein diet[74]. As G6PC is one of the crucial enzymes in glucose homeostasis that catalyzes gluconeogenesis and glycogenolysis, epigenetic changes in the promoter region might contribute to the onset of hyperglycemia[74]. Further, this impaired maternal diet-induced reduction of mtDNA copy number and methylation of mtDNA promoter often leads to changes in OXPHOS gene expression. This may predispose to insulin resistance in adult offspring considering the importance of hepatic mitochondrial OXPHOS activity in glucose homeostasis[73].

Similarly, using maternal low protein programmed rats, Lillycrop *et al*[8] established that the hepatic PPAR α promoter and glucocorticoid receptors were hypomethylated *in utero* and these epigenetic

Table 1 Summary of key animal models used to investigate the maternal low protein associated insulin resistance and glucose intolerance

Animals	Diet regimen	Age of pups	Sex	Observations	Ref.
Sprague-Dawley rats	6% protein, -12 to 43 d	12 wk	Females	Sirt3 dysfunction in skeletal muscle	[138]
Sprague-Dawley rats	10% protein, 2 to 21 d	Newborn	Males	Increased <i>Igf</i> gene expression	[148]
Sprague-Dawley rats	8% protein, 1 to 43 d	17 wk	Males	Lower fasting insulin and HOMA	[85]
Wistar rats	6% protein, 1 to 21 d	11 wk	Females	Insulin resistance and glucose Intolerance	[103]
Wistar rats	6% protein, 1 to 43 d	3 wk	Both	Compromised β -cell structure and function	[163]
Wistar rats	7% protein, 1 to 120 d	16 wk	Females	Higher glucose tolerance and insulin responsiveness	[98]
Wistar rats	8% protein, 1 to 43 d	12 wk	Both	Impaired gluconeogenesis, glucose handling and liver structure	[141]
Wistar rats	8% protein, 1 to 43 d	11 wk	Females	Insulin resistance and glucose Intolerance	[190]
Wistar rats	8% protein, 1 to 21 d	12 wk	Males	Epigenetic regulation of <i>Hnf4a</i> in islets	[116]
Wistar rats	8% protein, 1 to 21 d	12 wk	Both	Altered mitochondrial function in islets	[72]
Wistar rats	8% protein, 1 to 21 d	12 wk	Both	Structural alterations and changes in glucokinase expression in liver	[141]
Wistar rats	8% protein, 1 to 21 d	Fetal Day 21.5	Both	Altered IGF axis and proliferative capacity of liver	[140]
Wistar rats	9% protein, 1 to 20 d	Fetal Day 20	Both	Defective hepatic glucose homeostasis	[69]
Wistar rats	10% protein, 1 to 21 d	4 wk	Both	Impaired hepatic gene expression	[8,122]
Wistar rats	10% protein, 1 to 43 d	15 wk	Both	Modified glucose metabolism and insulin resistance	[71]
C57BL/6J mice	9% protein, 1 to 39 d	8 wk	Both	Impaired glucose metabolism, miR-15b up-regulation	[63]
C57BL/6J mice	8% protein, 1 to 21 d	3 wk	Both	Altered PPAR signaling, insulin resistance and glucose Intolerance	[87]
C57BL/6J mice	8% protein, 1 to 19 d	Newborn	Both	Altered mitochondrial genes expression in liver and skeletal muscle	[89]
Mice	8% protein, 1 to 40 d	21 wk	Both	Increases abdominal adiposity and glucose intolerance	[70]
Pig	6% protein, -18 to 113 d	Newborn	Both	Affected mitochondrial OXPHOS and glucose-6-phosphatase in liver	[73,74]

changes were persistent in adulthood. Further studies demonstrated reduced *Dnmt-1* expression and its role in epigenetic changes of glucocorticoid receptors[73,95,96,122]. Moreover, epigenetic changes in the promoter region of *PEPCK* were found to be the driving force for impaired glucose homeostasis in animals[123,124]. Anandwardhan and colleagues reported a decreased number of (pro) insulin 2 gene transcripts in the pancreas of low protein *in utero* programmed rats, due to the histone modification in the promoter region of the insulin 2 gene[125]. Moreover, these epigenetic changes are potentially engaged in the trans-generational transmission of the induced phenotype[122,124,125].

Recently, Goyal and group demonstrated that the epigenetic modifications by miRNA, small non-coding RNAs consists of 20–22 nucleotides, is one of the molecular mechanisms of maternal low protein-induced T2D[119]. Results from maternal low protein programmed mice found reduced beta-cell mass and insulin levels in the pancreatic islets of the programmed offspring due to the increased expression of miR-15b. As the activities of cyclins are negatively regulated by the presence of miR-15b, the up-regulation of this miRNA may inhibit pancreatic beta-cell proliferation, consequently, stem to T2D phenotype[63]. A microarray study also demonstrated elevated expression of miR-615, miR-124, miR-376b, and decreased expression of miR-708 and miR-879 in maternal low protein programmed mice, which were associated with degenerated metabolic health of the offspring from the weaning age [126].

Apart from the epigenetic changes, maternal malnutrition is the major reason for low birth weight in newborns. Children who are small for gestation age and showed catch-up growth during the early age of development appeared to be more insulin resistant compared with normal-weight children[127]. Moreover, several studies have shown epigenetic changes due to gestational diet-induced fetal programming adult diseases in these offspring[108,128,129].

Even though little is known about the mechanism of programming, the secondary effects of fetal programming and their mechanisms are well studied. For example, various organ systems that play vital roles in the metabolism, and how they are affected by the developmental programming of T2D are well characterized. *In utero* low protein exposure causes long-lasting structural and functional changes in metabolically active organs includes skeletal muscle, liver, pancreas, gonads, and brain.

The *in utero* environment is crucial in the development of skeletal muscles, and the muscles growth is determined by the number, size, and type of muscle fibers formed during fetal development[130,131]. Maternal undernutrition affects the quality and quantity of skeletal muscles and stem cell activity[132-134]. A maternal low protein diet during gestation affects the normal proliferation and differentiation of bone marrow stem cells and satellite cell function[134,135]. Therefore, imperfections of skeletal muscles development during fetal development are often deleterious to normal muscle functions in adulthood [133]. Studies using maternal low protein diet-based animal models have reported lower expression of GLUT4 and mitochondrial dysfunction in skeletal muscles of low protein offspring[66,67,136-138]. As skeletal muscle functions as one of the main sites for peripheral glucose disposal, functional or structural changes of the myofibrils leads to insulin resistance and glucose intolerance[139].

Similarly, low protein-induced developmental programming caused functional and structural changes in the liver[140,141]. The expression of genes associated with oxidative phosphorylation and glucose metabolism were altered in the liver. Further, *in utero* low protein exposed rat fetuses showed the altered structure of the liver with decreased proliferation of hepatocytes[142-146]. These animals also had altered hepatic lipid metabolism and hepatic desaturase activities, which may account for fetal growth retardation and insulin resistance[94,147]. In addition, a maternal low protein diet also induces epigenetic changes in methyltransferase machinery resulting in altered epigenetic regulation in the liver [148]. Although further studies are warranted, it is clear from the existing studies that developmental programming induced by a low protein diet affects hepatic structure and function and this may, in turn, make them susceptible to impaired glucose metabolism[141,145,149].

The ability of the pancreatic β -cell to secrete insulin is dependent on its structural and functional integrity along with the nutritional availability[150]. Consequently, protein deficiency in the maternal diet is a definite contributor to reduced insulin secretion and decreased β -cell proliferation in low protein programmed animals[151]. The reduced islets area and β cell number are mainly due to the downregulation of genes *FoxO1* and *Pdx1* genes, or altered expression of *Reg1* pathway genes[151-155]. Epigenetic regulation of *Hnf4a* expression and expression of microRNAs such as miR-15b, miR-199a-3p, and miR 342, and signaling of mTOR in islets of the progeny also found to be associated with low protein-induced beta-cell dysfunction[62,63,156]. Further, a maternal low protein diet demonstrated greater β -cell apoptosis rates and deviates the equilibrium of islet's apoptosis and replication in the offspring[157-159]. The pancreatic islet cells of these offspring exhibited greater oxidative stress and mitochondrial dysfunction[72,160]. Consequently, lower β -cell reserve, β -cell dysfunction and impaired mitochondrial function in islets may drive towards T2D later in life[62,72,86,155]. With the multiple pathways controlling β -cell functions are modulated by maternal low protein, it is reasonable to hypothesize that the low protein exposure predisposed the offspring to lean T2D[127]. A list of key genes involved in low protein programming is compiled in Figure 1.

A balanced *in utero* nutrition is essential for the normal development of the reproductive system. Epidemiological studies in humans and experimental in studies animals show the low protein/unbalanced diet *in utero* severely impacts the development of reproductive organs, sexual maturation, and reproductive function in the offspring[161-164], resulting in decreased testis weight, reduced Sertoli cell numbers, and late-onset of spermatogenesis in males[164-166]. Moreover, the classical male fertility markers, sperm count, and serum testosterone were also diminished in the offspring of low protein exposed mothers[163,164,167]. Similarly, the low protein programmed female offspring were found to be with compromised follicle development and follicle health[168,169]. The numbers of primordial, primary, and secondary follicles were significantly reduced along with abnormal estrous cycle and redox homeostasis[170-172]. The thyroid hormone production and hypothalamic-pituitary-gonadal axis are also found to be affected by maternal low protein diet[173,174]. The impaired reproductive function of offspring may be due to the altered expression of genes associated with steroidogenesis, folliculogenesis, and steroid hormone receptors in gonads[175-178]. In addition, changes in the hypothalamic-pituitary-gonadal axis to low protein may have adverse effects on the normal development and function of gonads[168,179].

The hypothalamus of the brain plays a critical role in glucose homeostasis by controlling hepatic glucose production and peripheral glucose utilization. Therefore, functional, or structural alteration of hypothalamic neurons may often lead to the onset of T2D[180,181]. The low protein programmed progenies have exhibited structural and functional changes in the neuronal centers, hypothalamic nuclei which regulate metabolism and body weight[102,181]. In addition, maternal low protein can also differentially affect the hypothalamic-pituitary-gonadal axis depending on the timing of the impaired nutrition. Early gestational nutrition impairment has been shown to make the pituitary more sensitive to GnRH, resulting in reduced reproductive function[182]. Further, it also alters hypothalamic-pituitary-adrenal axis function by deregulating corticosterone-inducible enzymes and associated enzyme receptors[183]. Other reports also show that brain sparing may not be as effective during *in utero* low protein exposure leading to compromised brain development in the offspring along with long-lasting deterioration in cognitive and motor functions[184,185].

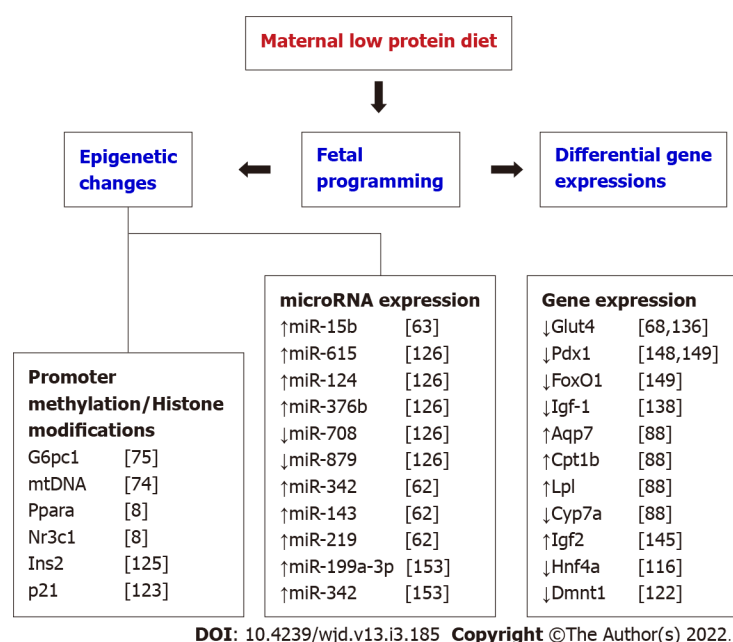


Figure 1 Key gene expression and epigenetic changes observed in different maternal low protein studies.

PREVENTION AND TREATMENT

Insulin resistance and glucose intolerance are the cardinal signs of T2D, and if not prevented, they may lead to severe diabetes complications later in life. Hepatocytes, skeletal muscles, and adipocytes are the major insulin-dependent tissues that participate in the disposal of peripheral glucose. Thus, improving the muscle sensitivity towards insulin and enhancing hepatic glucose homeostasis, along with managing body weight are the central focus of T2D treatment strategies. Among the different drugs that have been prescribed for lean T2D management, metformin is a widely used drug for treating lean T2D along with nutritional and lifestyle modification[186]. Over the past two decades, various randomized control trials conducted in many ethnic groups showed unambiguously that the prevention is feasible by drugs or lifestyle modification[187-190].

Most of the research on treatment or prevention of T2D has been done with obese individuals or animal models, even though 10%-16% of all T2D people have normal BMI. In addition, majority of the studies on the molecular mechanisms of prevention and reversal of T2D were performed in Caucasians. Consequently, it is essential to include other ethnic groups such as Southeast Asian and Chinese populations, which are more prone to diabetes at lower average BMIs or lean T2D compared with white Europeans[191]. Regulating body weight is critical in the management of T2D associated with overweight or obese patients. However, in the case of lean T2D, it seems that leaner patients have severe beta-cell failure than normal-weight patients[4]. Presently, it is not clear that the achievement of lower body weight will help to prevent or reverse the special variants of T2D such as lean T2D[3].

The first trial associated with lifestyle modification and/drug therapy was started in China with a follow-up period of 23 years[192] and many other studies have followed since. Other studies include: the American diabetes prevention program outcome study[193]; the Finnish diabetes prevention study [194]; and the Indian short message service study[195] revealed the influence of lifestyle modification can persist long after the termination of the active phase of the trial. Although lifestyle modifications have been recognized to be very effective, safe, and ideal strategy for prevention, the effectiveness of relative risk reduction through these strategies exhibited some variations among different ethnic populations[192-196]. A study conducted among the impaired insulin tolerant lean Indian population found that lifestyle modification alone prevented the diabetes onset, regardless of relatively low BMI and highly insulin-resistant characteristics of the population[197].

Although the underlying pathophysiology of lean T2D is not completely understood, many studies using the maternal low protein model have shown potential prevention approaches[157]. The most promising approach among them is associated with one-carbon metabolism and the molecules involved in it. Some studies have reported the effectiveness of folic acid supplementation as a preventive treatment against the adverse effects of fetal programming[198-200]. Similarly, Burdge and team reported that the folic acid supplementation reversed the maternal low protein-induced phenotype epigenetically in the offspring when treated during the juvenile-pubertal period[201]. In contrast, our study reported a partial inhibition of gestational low protein-induced glucose intolerance only in female rats, when the maternal low protein diet was supplemented with folic acid from day 4 of the pregnancy until delivery[65]. Similar to our data, Lillycrop and colleagues also reported the inefficiency of folic

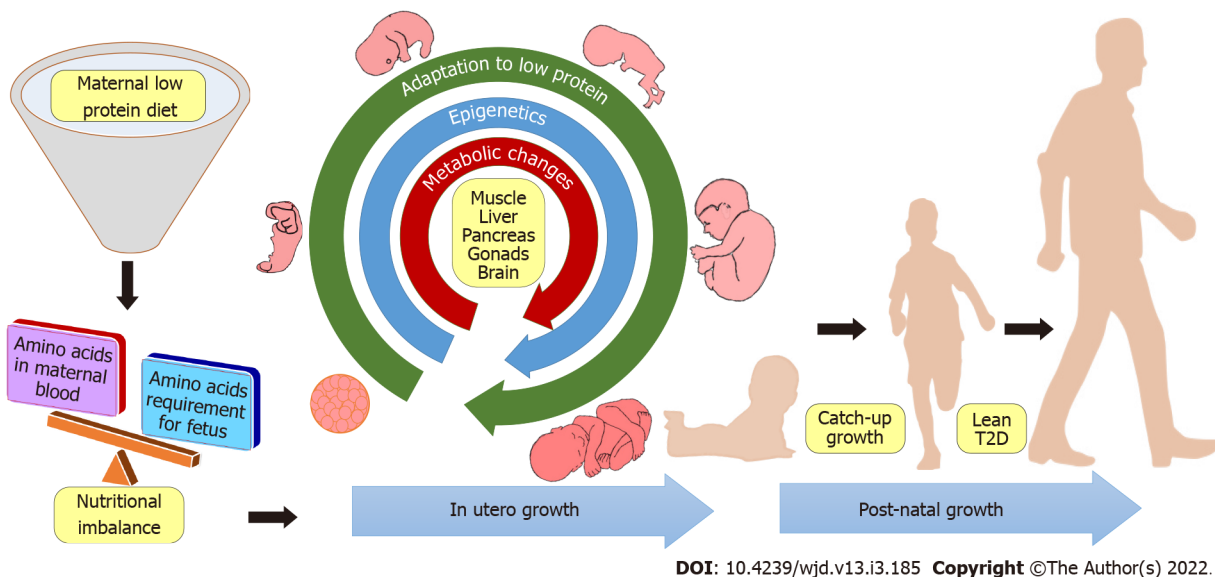


Figure 2 Proposed mechanism of maternal low protein associated lean type 2 diabetes.

acid supplementation for the inhibition of gestational low protein-induced change in gene profile, although they found changes in the expression of genes associated with redox homeostasis[8]. An observational study from Pune, India (Pune Maternal Nutrition Study), noticed that when the mother was vitamin B12 deficient, high amount of folic acid intake was not enough to prevent the insulin resistance in the offspring[7]. However, the high protein to carbohydrate ratio in maternal diet was found to be effective in maintaining glucose homeostasis in the offspring[137]. Thus ensuring sufficient protein in the maternal diet is essential to prevent lean T2D.

CONCLUSION

In summary, lean T2D is a discrete subgroup of T2D with a set of specific clinical profiles. Atypical characteristics of leanness associated with insulin resistance needed to be dissected further for a better understanding of the etiology of the disease. As the progression of T2D may take many years in humans, the assessment and prevention studies with human subjects may also warrant many years. Therefore, the development of a well-defined animal model, which mirrors not only the pathophysiology of lean T2D but also the etiology of the disease, might be the most important step in this area of research. Nevertheless, there is a lack of a single animal model that can constitute all pathophysiological and etiological changes similar to humans. In addition, the severity of lean T2D is different between sexes, due to sex hormones and sex dependent expression of genes. Among different molecular mechanisms involved in the onset of lean T2D, the epigenetic underpinning of metabolism appears to be the most promising lead. Although the mechanism of developmental programming is currently not well characterized. With the current literature, it may be summarized that maternal low protein diet leads to diminished essential amino acids levels in the maternal circulation and consequently to the fetus. In such low protein environment, fetus is acclimatized and revises its growth and metabolic set points. This adaptation is thought to be due to the overall alteration of epigenetic and metabolic attributes of fetal energy homeostasis. Although these adaptations may be beneficial for the fetus, a nutritional mismatch with protein abundance in the adulthood often leads to metabolic derangements leading to diseases such as lean T2D. This concept is summarized in Figure 2. A better understanding of the molecular mechanisms of the disease may pave the way for more effective preventive and treatment strategies.

Obesity associated T2D is a serious public health problem throughout the developing and developed countries whereas nutritional deficiency especially protein deficiency is a major concern in under developed and developing countries. With studies showing a link between maternal protein consumption and T2D in offspring, it is essential to probe further and take action to avert a global crisis. Public health measures to alleviate poverty and access to nutritious and protein rich diet during pregnancy is essential to prevent lean T2D. Scientific understanding of the disease to prevent and treat T2D, along with effective health education and public policies can mitigate this growing global epidemic.

FOOTNOTES

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