

Perspective in the Management of Diabetes Mellitus: Deciphering Beneficial Role of Diet and Nutrients

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Abstract

Diabetes Mellitus (DM) is a global health problem and increasing all over the world at an alarming rate that appears dramatic as to have been characterized as an epidemic. DM is a chronic metabolic and hormonal disorder and is characterized by increase in blood glucose level accompanied by other biochemical disturbances and clinical manifestation. In addition to disorder of carbohydrate metabolism, DM is also associated with abnormality in fat and protein metabolism. Epigenetics in the target cells due to metabolic memory is also linked to etiology and complications in DM. The etiology of DM is multilateral and multifactorial resulting primarily from the nutritional imbalances and finally due to dysregulated gene function. Among the various therapy for treatment and management of DM, drug therapy is the major and popular approached used to contain DM. However, recently diet therapy is also considered an effective way to control the disease. The diet must be acceptable, readily available, must supply with adequate amount of nutrients and be formulated in a way to normalized body weight. The diet should be low in simple carbohydrate, high in complex carbohydrate, low in fat and high in monounsaturated fatty acids, n-3 fatty acids and rich in dietary antioxidants like vitamin-E, vitamin-A and vitamin-C. Essential minerals like Magnesium (Mg) and Chromium (Cr) also have crucial role in carbohydrates and lipids metabolism and thus important for DM. Not only these, recording the role for nutrition in epigenetics in DM and its complications will provide new insights identifying the molecular mechanism of disease and proper management of DM. This review will update the researchers of the field and the concerned individuals about the role of diet and nutrients in the management and treatment of DM. The role of nutritional epigenetics in DM is also highlighted.

Keywords: Diabetes Mellitus; Carbohydrate; Protein; Fats; Vitamins; Essential Minerals; Epigenetics***Corresponding Author:** Kshetrimayum Birla Singh, Department of Zoology, Pachhunga University College, Mizoram University, Aizawl- 796001, Mizoram, India; Tel: +919863385796; E-mail: birla.kshetri@gmail.com**Introduction**

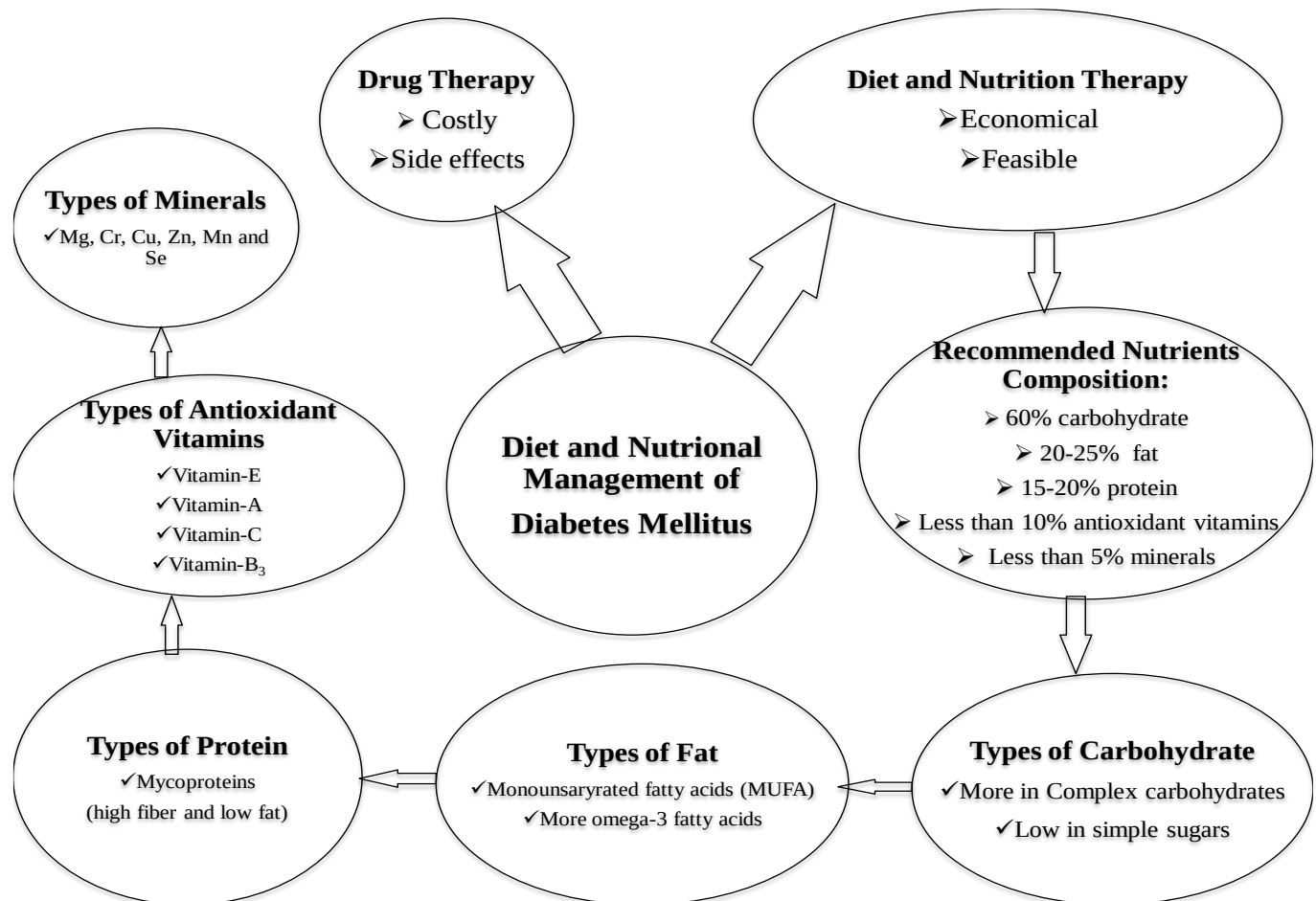
Diabetes Mellitus (DM) is a major worldwide health problem predisposing to markedly increased death from cardiovascular related diseases and associated mortality related to development of nephropathy, neuropathy & retinopathy[1]. There are two main types of DM depending upon its etiology and treatment. Type-1 or Insulin Dependent Diabetes Mellitus (IDDM) involves auto immune or idiopathic etiology and can only be control by insulin therapy. Type-2 DM or Non-Insulin Dependent Diabetes Mellitus (NIDDM) is due to insulin resistance or insulin secretory defects and blood glucose cannot be properly utilized by cells of the body. Out of these two type of DM, type-2 DM is the most common and usually starts at later stage of life [2]. However, in recent decade, the prevalence and incidence of type 2 DM even in the young age population have been dramatically increased in many parts of the world especially in the newly industrialised and developing countries [3]. Due to increasing obesity, sedentariness and dietary habits in both western and developing countries, the prevalence of type- 2 DM is growing at exponential rate [4]. It has been estimated that the number of diabetic patients will be more double within 15 years and the majority of cases of type 2 diabetes in the future will occur in developing countries with India and China having more cases than any other country in the world [5]. There are also reports that dramatic changes in the prevalence or incidence of

type - 2 DM have been observed in communities where there have been major changes in the type of diet consumed, from a traditional indigenous diet to a typical 'Western' diet [6-7]. These changing disease rates are almost certainly explained by changes in several dietary factors as well as by changes in other lifestyle related factors, notably sedentary life style habits. It is also well established that diabetes is caused by either a lack of insulin secretion or by insulin resistance. The resultant disease or metabolic disturbance leads to hyperglycaemia and dyslipidemia in the short term, as well as long term complications such as retinopathy, neuropathy and nephropathy. Besides, persons with DM are 2 to 4 times more likely to develop coronary artery disease or to suffer a stroke. Reducing elevated blood lipids levels has been shown to lower the incidence of acute coronary events in other at-risk populations. One of the most common etiologic factors for DM is metabolic syndrome-X which is the presence of clusters of risk factors like central obesity, insulin resistance, dyslipidemia (high Low Density Lipoprotein cholesterol (LDL-c) and low High Density cholesterol Lipoprotein (HDL-c) level) and low antioxidant vitamins etc [8]. Moreover, DM is influenced by the environmental factors, nutrient uptake, and genetic profile of an individual that together dysregulate gene function. These genetic and non-genetic factors are reported to introduce epigenetic cues that modulate the gene function which is inherited by the offspring [9]. It was recently recognized that epigenetics plays a role in diabetes both in terms of its development and progression as well as its complications. In this regards, methylation of DNA and histones represents an epigenetic mechanism to regulate gene expression [10].

Thus the etiology of DM is multilateral and multifactorial and is link to heredity, age, obesity, diet, sedentary life styles, hypertension and finally aberrant gene functions due to epigenetics. Since last two decades, a number of approaches have been used in order to reduce the incidence rate of the disease and to manage and cure DM. Some of the most popular approaches

are the drug therapy, dietary and nutritional therapies. However, drug therapy is controversial in the sense that it is costly and has number of side effects in the patients. It is a well known fact that DM being a metabolic, endocrine disorder is directly connected to carbohydrate, lipid and protein metabolism. As a result, diet and nutrition therapy forms an integral part of diabetes management which is more natural, economical and feasible. Intake of proper diet can stop the incidences of the disease and even can reduced the severity of the existing cases. Many dietary supplements though are routinely recommended for the patients of DM but the patients start consuming them when the diseases becomes severe and in most of the cases the benefit of such dietary supplements are not as effective as they have been thought of. In this context, it has become essential to have a formulated nutritional supplement that can be included as a part of regular diet so as to prevent the worsening situation diabetic patients. The dietary prescription for people with diabetes was done with an aim to abolish the primary symptoms and long-term macro-vascular and micro-vascular complications. Diet therapies in the DM consist of basically of precaution concerning diet composition, amount of diet, distribution and timing of food intake (Figure-1) [11]. Although dietary modifications is a popular approach for both Type-1 and Type-2 DM management, some subjects with diabetes still continue to be afflicted with numerous life threatening complications. This continued development of diabetic complications even after achieving glucose control indicates a 'metabolic memory' of prior glycemic exposure which recent studies have suggested may be attributed to epigenetic changes in target cells. Thus exploring a role for epigenetics especially nutritional epigenetics in DM and its complications could allow for new insights clarifying the molecular mechanism of disease and proper management of DM. The role of diet and nutrients and mechanism of nutritional epigenetics in DM are also highlighted in this review.

Figure 1: Proposed recommended diet and nutritional management of Diabetes mellitus



Role of Diet and Nutrients

Appropriate food choices are considered necessary for ensuring and maintaining good health. Healthy nutritional habits are established in childhood and adolescence, which are considered the crucial periods in the human's life, because during this the human body is properly programmed and is being built up to maintain a healthy adulthood later on. On contrary, poor nutritional habits established in these periods are responsible for the development of chronic diseases such as obesity, heart disease, osteoporosis and others [12-13]. It is widely accepted that healthy nutrition is the basis for the treatment of type- 2 DM and contributes positively to the maintenance of blood glucose within normal range and minimizes the complications of the disease. Recent literature suggests the Mediterranean diet as the most comprehensive diet choice. It is characterized by olive oil as the main source of fat, and high to moderate consumption of fruit,

herbs, cereals, fish, and legumes in combination with a small portion of meat and wine [14-15]. Diet also plays an important role in the pathogenesis of type-2 DM since development of type-2 DM is directly related to diet. Diet high in simple carbohydrate and fat usually results to type- 2 DM in the later stages of life. Therefore, dietary restriction is an essential factor in management of type -2 diabetic individuals. Dietary restriction includes diet composition, amount, distribution and timing of food intake. For proper management of diabetic individuals, the diet must be designed to supply adequate amount of nutrients namely carbohydrate, fat, protein, vitamins and minerals [16]. The diet of diabetic people should be formulated in a way to normalize body weight. The diet should contain 60% carbohydrate, 20-25% fat and 15-20% proteins. It has been reported that high carbohydrate diet increases the sensitivity of peripheral tissues to both endogenous and exogenous insulin. Such diet improves glucose

tolerance and lowers the level of serum insulin. In addition, the liberalization of carbohydrate might facilitate the reduction of saturated fatty acids and cholesterol in the diabetic diet [17-18]. Simple dietary restriction and increased exercise may help in preventing DM from becoming a major health problem, particularly in identified areas of high prevalence [17]. According to Moser, 1998[20], dietary management is a good approach in diabetics care. Diets that enhance glycemic control are high in dietary fiber, low to moderate in dietary fat and moderate in high biological value proteins. The quantity of such food should be adjusted to maintain optimum body weight. Decreasing caloric intake of type-2 patients results in weight reduction which is beneficial for diabetics [21]. Very low energy diets produced greater improvement in glycemic control than more moderate diets in obese type-2 diabetes, even if weight losses are the same. Diet therapy especially weight loss is a corner stone in the management of obese type-2 diabetic patients. Reduction total saturated fat and limited protein intake with replacement by complex carbohydrate and/or are the recommended diets for type-2 DM. Such precautions improve the metabolic control in diabetic individuals and reduced the risk of chronic complications [22]. Decrease in intake of saturated fat and energy also help in type-2 control. Diet that contains 60% carbohydrate and rich in fibers improves blood sugar and lipid level [23]. In this context dietary manipulation is considered the first line of therapy for diabetic patients. Dietary strategies should aim to normalize blood glucose and lipoprotein levels in order to reduce morbidity and mortality related to derangement of carbohydrate and lipoprotein metabolism in DM. To achieve these goals, quantity and quality of diets must be considered according to each individual and his clinical conditions. Moreover, total energy intake should attain and maintain desirable body weight. Total dietary energy should consist of < 30% of total fat with equal distribution of saturated, monounsaturated and polyunsaturated fatty acids, 10-20% of protein, 50-60% of carbohydrate with restriction of simple carbohydrate. Moreover, cholesterol intake should be reduced less than 300 mg/day [24]. With regard to carbohydrate, it plays a very important role in the development and control of diabetes. Simple sugar is directly responsible for the onset of type-2 diabetes, while complex carbohydrate help in the control of type-2 diabetes. In the management of diabetes, higher carbohydrate diet

allows reduction in the proportion of energy from fat when total energy is controlled and glucose tolerance is improved in diabetics. Thus, a mixture of carbohydrates assists glycemic control [25]. Anderson and Sheiling, 1985 [26], found that the rate of glycogen synthesis and glycogen stimulation in liver, skeletal muscles and jejunal mucosa were greater with high rather than low carbohydrate diets. Glycolysis and activities of key glycolytic enzymes were also higher in several tissues with high carbohydrate diets. DM is basically a disorder of carbohydrate metabolism, but with progression of the disease, protein metabolism is also affected. Gluconeogenesis, a major biochemical process that produces glucose from protein, is accelerated in DM. Therefore, kind and amount of protein may also affect diabetic conditions. It was recommended 15-20% protein in the diet of diabetic individuals [27]. Turnbull and Ward, 1995 [28] studied the effect of mycoprotein on acute glycemia and insulinaemia in normal healthy individuals. Mycoproteins reduced glycemia and insulinemia. They reported that mycoprotein was significant in the dietary treatment of diabetes. Besides carbohydrate, fat is an important constituent of diet. In diabetes, lipogenesis (synthesis of fat) is decreased and lipolysis (decomposition of fat) is increased. Type and amount of fat and fatty acids may have an affect on diabetes complications. The monounsaturated fat diet resulted in lower mean plasma glucose concentration and reduced insulin requirement when compared with high carbohydrate diet. The same diet also lowered 25% plasma triglyceride concentrations, 35% Very-Low-Density Lipoprotein Cholesterol (VLDL) and increased 13% of High-Density Lipoprotein (HDL) cholesterol. Total cholesterol and Low-Density Lipoprotein (LDL) cholesterol concentration did not differ significantly between diets [29]. Axelrod, 1989 [30] observed some apparently beneficial effect of omega-3 fatty acids on platelet function; eicosanoids formation and plasma triglycerides values in diabetes mellitus. High doses (4-10g) daily of these fatty acids affected the patients adversely. Sabina et al. 1992 [31] examined the effects of glyburides for four weeks on glucose, insulin lipid lipoprotein metabolism in 10 men with type-2 DM receiving fasting glucose concentration, basal insulin concentration were unaltered, VLDL- cholesterol concentration decreased and apolipoprotein -B concentration tended higher.

In addition to this, Norris et al. 2007[32] found that dietary intake of omega-3 fatty acids, found in fish, flax seeds, walnuts, soy, canola, and greens, is protective against the development of type 1 diabetes related auto antibodies in children at genetic risk of type 1 diabetes. Omega-3 fatty acids can reduce inflammation, and the lack of omega-3 fatty acids in Western diets may predispose people to inflammation. Yet the same authors later found that omega-3 levels were not associated with later development of type 1 in these children [33]. So, it is possible that omega-3s may be protective against type 1 autoantibody development, but be less significant later in the disease process. An earlier study of the same children found that the dietary intake of expecting mother containing omega-3 fatty acids during pregnancy did not affect the risk of autoimmunity in children [34]. Cod liver oil, however, taken during pregnancy, has been associated with a reduced risk of type 1 diabetes in offspring. Both omega-3 fatty acids and vitamin D are present in this oil, and either or both may play a role [35]. Virtanen et al. 2010 [36], found that the fatty acids associated with milk and ruminant meat fat consumption were associated with an increased risk of type-1 related autoimmunity. Linoleic acid, however, was associated with lower levels of autoimmunity, in children genetically at risk of type 1 diabetes. A group of people with metabolic syndrome were given omega-3 fatty acid supplements or a placebo for six months. Those taking the supplements were found to have lower markers of autoimmunity and inflammation, as well as more weight loss, compared to people who did not take the supplements [37]. Adequate intake of omega-3s during pregnancy may also decrease the risk of obesity in the offspring. It has been reported that, higher levels of omega-6 fatty acids in relation to omega-3s in umbilical cord blood has been associated with higher obesity in children at age 3 [38].

Role of antioxidant vitamins in Diabetes mellitus

Many studies *in vitro* also revealed that dietary antioxidants have been shown to improved insulin sensitivity. Several clinical trials have also demonstrated that the treatment with vitamin-E, vitamin-C or glutathione improves insulin sensitivity in insulin resistance individuals [39]. Studies in patients with type 1 diabetes have revealed an increased level of oxidative stress and reported that vitamin E may help to prevent this[40]. Thus in subjects immunologically identified to be at risk for developing type-1 DM, treatment with antioxidants might

reduced the peroxidation rate, restore body antioxidant capacity and possibly prevent or delay the development of type-I DM. However, little is known concerning the relationship between vitamin E intake and the development of type- 2 diabetes. Two cohort studies conducted in Finland examined the relationship between the blood level of vitamin E and the risk of type- 2 diabetes. One study reported that a low plasma level of this antioxidant vitamin is associated with a 3.9-fold elevated risk of developing the disease [41]. The association was independent of various possible confounding factors. A nested case-control study carried out within a cohort study reported that subjects with a high serum vitamin E level had a 39% lower risk of diabetes compared to those with a low level of vitamin E [42]. However, in contrast to the previous study, this association disappeared when the risk ratio was adjusted for various coronary heart disease risk factors. This suggests that a high level of vitamin E may be merely a marker for a healthy lifestyle. While the relationship between vitamin E and the risk of diabetes should be further investigated, there is insufficient evidence that an increased intake of this nutrient will prevent the disease. Vitamin-E supplementation in diabetic patients results in an improvement of insulin effect and a better glycemic control, by reducing glucose, hemoglobin A_{1c}, by decreasing plasma lipid peroxidation and LDL- oxidation and LDL- oxidizability [43]. In summary, it was showed that an imbalance in the oxidant and antioxidant ratio is already present at the clinical onset of diabetes in children with aldoscents. Diabetes induced oxidative damage increased from childhood to early adulthood [44]. As per Henry, 1996 [45], acute administration of the antioxidants, vitamin -C improved endothelium dependent vasodilatation in patients with type-2 DM. This finding support the hypothesis that oxygen derived free radicals contribute to abnormal vascular reactivity in diabetes, restoring endothelial function has important clinical implications of vascular disease in diabetic patients. Further studies in examining the long term effects of oral antioxidant vitamins supplementation on vascular function and cardiovascular morbidity and mortality will be required before antioxidant vitamin supplementation can be recommended. Beside this, nicotinamide, a component of vitamin B₃ that has been shown to protect against diabetes in animals, and prevent beta cell damage [46]. Even better, one study found that it prevented the development of type 1 diabetes in children with type 1-associated autoantibodies [47]. On the basis of these and

other studies, a large, double-blind, placebo-controlled trial was conducted in Europe, the U.S. and Canada, called the European Nicotinamide Diabetes Intervention Trial (ENDIT). This trial gave nicotinamide to first degree relatives of people with type 1 diabetes who already had developed type 1-associated autoantibodies. Unfortunately, it found no difference in the development of diabetes between the two groups during the 5 year follow-up period. The study gave high doses of the vitamin, up to 3 g/day (30-50 times higher than the RDA) [48]. In another study done at Sweden, double-blind placebo controlled group was given high doses of anti-oxidants (including nicotinamide, vitamin C, vitamin E, Beta-carotene, and selenium) to people after they were already diagnosed with type 1 diabetes and also found that they had no effect in protecting the β - cells against the damage of free radicals [48]. There is no evidence linking the anti-oxidants alpha- or beta-carotene levels and the development of type 1 related autoimmunity in another study as well [49]. Uusitalo et al. 2008 [50] also found that if pregnant women took anti-oxidants and trace minerals (including retinol, beta-carotene, vitamin C, vitamin E, Selenium(Se), Zn or Mn) during pregnancy, there was no effect on the risk of the child's developing type 1-related autoimmunity. Czernichow et al. 2009 [51] found that anti-oxidant supplements were not protective against metabolic syndrome, a group of conditions common in people with type 1 or 2 diabetes. Yet they also found that the people who had the highest levels of some anti-oxidants (betacarotene, vitamin C, and vitamin E) in the beginning of the study, presumably due to a diet rich in plant foods, did have a lower risk of developing metabolic syndrome. While these studies did not find promising results concerning anti-oxidant supplements, they also did not find that these supplements did any harm. Thus, the significant correlation between total antioxidant capacity and clinical characteristics of diabetic patients including their blood levels of glucose and glycated hemoglobin suggest that the measurement of total antioxidant capacity in diabetic patients can be marker of the glycemic control [52].

Role of Essential Elements in Diabetes mellitus

There are reports of pronounced perturbation in mineral metabolism in diabetic population with specific complications and specific difference in the mineral status due to the consequence of the DM [53]. Thus the precise role of antioxidant damage in diabetes, major disturbances of the antioxidant and micronutrient

status in the diabetes status was found[54]. Some minerals particularly the trace minerals are active participants of metabolism and are the essential part of some of the enzymes for their biological activities. As DM is a disease of metabolic abnormality, so minerals as such or as a component of enzymes may be playing a significant role in development and control of DM. Amongst minerals, Mg is considered one of the essential mineral which plays an important role in the pathophysiology of DM. It has been reported that hypomagnesaemia has been associated with DM since 1953. Mg deficiency can exist when serum levels are normal because Mg works mostly in intracellular spaces. Low levels of Mg have been reported in 25% of diabetic outpatients and a higher percentage in hospitalized patients. This has most serious clinical implications because Mg deficiency may intensify or promote any diabetic complications such as atherosclerosis, glycosuria, mineral homeostasis, dyslipidemia, retinopathy, thrombotic tendency, hypertension, decreased insulin release and total seizures [55-56]. According to Hua et al. 1995 [57] there is strong evidence that complication of DM like vascular problems and osteoporosis are associated with Mg deficiency. In a paper, it was reported that seemingly healthy, low Mg levels have been link to insulin resistance, glucose intolerance and high secretion of insulin [58]. High blood pressure or hypertension is one of the disorders associated with syndrome-X while Mg has been shown to lower high blood pressure. In one study, people with high blood pressure, patients who received Mg supplements for four weeks showed a significant reduction in blood pressure[59]. Mg appears to have positive effect decreasing harmful cholesterol and increasing good cholesterol and also prevents blood platelets from sticking together that cause heart attack and stroke[60]. Within last ten years, researchers have discovered that Mg deficiency unleashes free radicals in animals, damage the heart and the inner lining of the blood vessels and thus increasing Mg intake however can protect the heart against damage caused by free radicals [61]. Intracellular Mg deficiency may affect the development of insulin resistance and alter the glucose entry into the cell. Since Mg is required for both utilization of the glucose and insulin signaling, metabolic alterations in cellular Mg which play a role for second messenger for insulin action, contribute to the insulin resistance [62]. In addition to this, Mg is also cofactor of

many enzymes involved in the carbohydrate metabolisms. Studies in adults have shown that lower dietary Mg intake is associated with IR and increased risk for type-2 DB [63]. Mg supplementation in subjects with insulin resistance and type-2 diabetes results in improvement of insulin sensitivity and β -cell response to glucose [64]. Furthermore, large epidemiological studies in adults indicate that lower dietary serum Mg and lower serum Mg are associated with increased risk of the type-2 diabetes [65]. Serum Mg and dietary Mg were inversely associated with insulin resistance (IR), providing the first evidence that the association between Mg deficiency and IR is present during the childhood. This association is not evaluated in previous study that measured serum or intracellular Mg in obese children [66] but agrees with the studies in adults that found that the low serum Mg concentration are associated with hyperinsulinemia, decreased insulin mediated glucose disposal and the metabolic syndrome [67].

Among the trace elements, Cr is also involved in the development and control of DM. Cr is an essential micronutrient that functions in carbohydrate and lipid metabolism primarily via its role in the potentiation of insulin action. Cr functions in maintaining normal glucose tolerance primarily by regulating insulin action. Cr functions by increasing the activity of insulin and therefore reducing the amount of insulin required to control blood sugar and related processes. It is important to keep insulin at low levels to prevent secondary signs of diabetes. For example, arterial plaque formation is an insulin sensitive process and an increase level of insulin often stimulates increased plaque formation leading to atherosclerosis [68]. Insufficient dietary Cr leads to elevated circulating insulin, elevating fasting glucose, impaired glucose tolerance decreased HDL- cholesterol and elevated cholesterol, triglyceride and which is the major contributing factor for the development of cardiovascular diseases.

Other trace minerals may also be playing a role in development or control of diabetes. However, organized work in the area of trace minerals other than Cr and incidence of diabetes has not been done. Cu is involved in normal carbohydrate and lipid metabolism, signs and symptoms of insufficient dietary Cu include anemia, pancreatic atrophy, heart hypertrophy, glucose intolerance of elevated, blood lipids [69]. More data are required to evaluate the role of Cu in diabetes. In addition to role in DM,

demonstration of Mn deficiency syndrome in human is less clear. Low dietary Mn or low levels of Mn in blood or tissue have been associated with several chronic diseases like osteoporosis, epilepsy and DM and some researcher suggests that people with diabetes have significant lower levels of manganese in their body than people without diabetes [70]. Researchers have yet to determine whether this is a cause or effect of the condition. In other words, more organized study is needed to determine whether diabetes causes level of Mn to drop or deficiency in this trace element actually contribute to the development of metabolic disorder. Interestingly, diabetic with higher levels of Mn are better protected from the oxidation of LDL -cholesterol than those with lower level of Mn otherwise contributes to the development of intra arterial plaque, which can lead to the heart attack and strokes[71]. Besides above-mentioned roles, one of the important function of Mn in the DM is through Mn dependent antioxidant enzymes namely Mn-SOD which may protect β cells of pancreas from the onslaught of high concentration of superoxide radicals during oxidative stress. Mn deficiency has also been linked to a reduction in the number of the glucose transporters in adipose tissue [72]. There are some other trace minerals such as Se which may have some physiological effect in diabetes. In study on diabetic patients, type- 1 and 2, with low activities of the SOD and GPX in diabetic patients, it was concluded that the supplementary trace element such as Se, Cu, Zn and Mn the essential component of enzyme structure, may be useful in preventing development of the diabetic complications [52].

Role of Nutrients in Metabolic Memory and Epigenetic Regulation of Diabetes Mellitus

As mentioned before metabolic syndrome is one of the risk factors for DM. The disease is also influenced by the environmental factors, nutrient uptake and genetic profile of an individual that together dysregulate gene function. These genetic and non-genetic factors are reported to introduce epigenetic cues that modulate the gene function which can be inherited to the offspring. Considering the role of nutrients in the epigenetic modulation of the metabolic disorders, nutrigenomics has been distinctly categorized as a branch that deals with modulatory effect of nutrients on metabolic disorders and disease progression by supplementing the individuals with key nutrient-enriched diets which are derived from plant and animal sources[9]. However, the critical issues here is that nutritional components of the diet

regulate the metabolic health of an individual either by controlling the expression of some key genes related to metabolic pathways or by modulating the epigenetic events on such genes. As a matter of concern, epigenetic phenomena seem to be involved in the onset and development of metabolic diseases such as obesity and type-2 diabetes, because they have the ability to change gene expression (Figure 2). Besides genetic predisposition, there are differences in the susceptibility to suffer these diseases that could be explained at least in part by epigenetic differences between individuals. These differences can be inherited or acquired during the lifetime and environmental factors such as diet seem to play a key role in the modulation of the epigenetic marks namely DNA methylation and histone modifications. Fortunately, due to the reversibility of some of these marks, epigenetics is now considered an attractive field of nutritional intervention[73]. As we know, epigenetic modifications regulate critical functions that underlie chromosome metabolism. Understanding the molecular changes to chromatin structure and the functional relationship with altered signaling pathways is now considered to represent an important conceptual challenge to explain diabetes and the phenomenon of metabolic or hyperglycemic memory. Although the specific molecular mechanisms remains unknown whereby hyperglycemic memory leads to the development of diabetic vascular complications, emerging evidence now indicates that critical gene-activating epigenetic changes may confer future cell memories. Chemical modification of the H3 histone tail of lysine 4 and 9 has recently been identified with gene expression conferred by hyperglycemia[74]. In this context, Berezin in 2016 [75], reported that hyperglycaemia, oxidant stress and inflammation are key factors that contribute in type-1 and type 2-DM, even when metabolic control was optimal and/or intensive glycemic control was implemented. It has been suggested that the effect of poor metabolic control or even transient episodes of hyperglycemia in DM associates in particularly with worsening ability of endogenous vasoreparative systems that are mediated epigenetic changes in several cells like progenitor cells, stem cells, mononuclears, immune cells and thereby lead to so called "vascular glycemic memory" or "metabolic memory". Both terms are emphasized the fact that prior glucose control has sustained effects that persist even after return to more usual glycemic control. However, the mechanisms underlying the cellular "metabolic memory" induced by high glucose remain unclear.

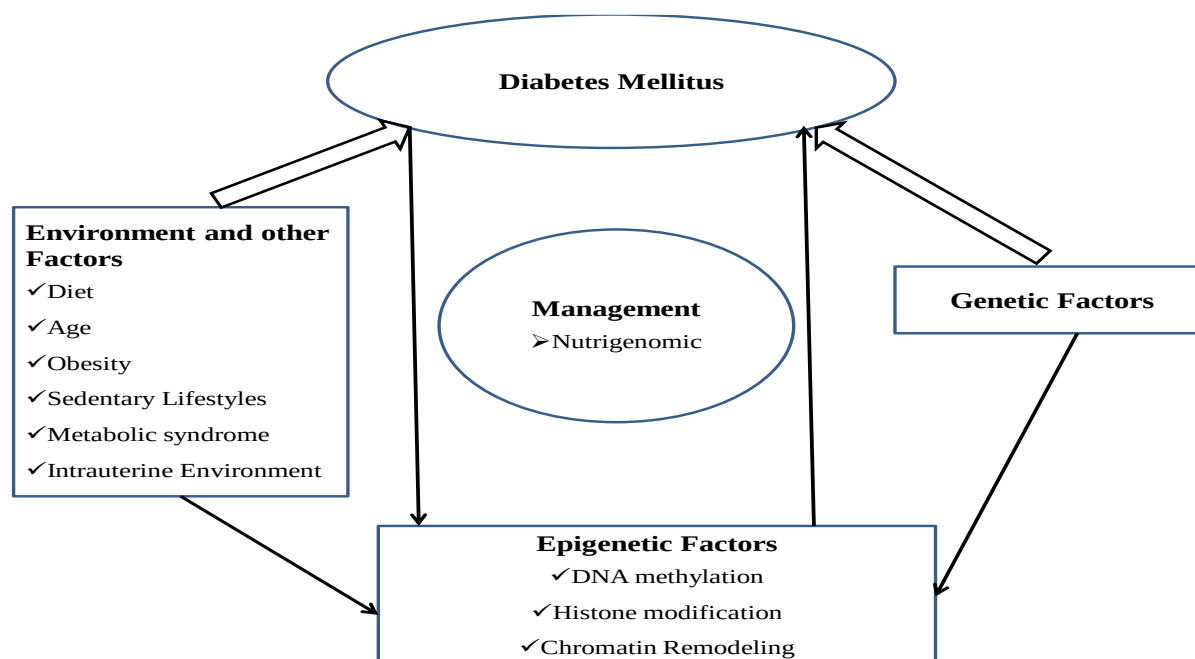
Preliminary work in endothelial cells has shown that transient episodes of hyperglycemia can induce changes in gene expression that are dependent on modifications to histone tails (for example, methylation), and that these changes persist after return to normoglycemia. The persistence of such modifications cannot yet be fully explained, but certain epigenetic changes as well as biochemical mechanisms such as advanced glycation may provide new and interesting clues towards explaining the pathogenesis of this phenomenon. [73, 76]. Further elucidation of the molecular events that enable prior glycemic control to result in endorgan protection in diabetes may lead to the development of new approaches for reducing the burden of diabetic nephropathy. It is evident that metabolic memory, whereby diabetic complications continue to develop and progress in individuals who returned to normal glycemic control after a period of transient hyperglycemia, can have long lasting effect. It was further reported that the transient hyperglycemia causes profound transcriptional changes in vascular endothelial cells mediated by changes in epigenetic modifications specially histone modification. These molecular events represent an integrated response of the epigenome that lead to changes in the expression of genes and proteins that regulate the development and progression of diabetic vascular complications [77]. Further characterization of these glucose-induced epigenetic events and the identification of key enzymes involved will improve more understanding of the pathways implicated in diabetic vascular injury. Thus, the persistence of these key epigenetic determinants in models of glycemic variability and the development of diabetic complications has been associated with these primary findings. As for the role of specific epigenomic changes, it is postulated that further understanding enzymes involved in writing and erasing chemical changes could transform our understanding of the pathways implicated in diabetic vascular injury providing new therapeutic strategies[74]. Here comes the role of nutrients in the regulation of epigenetic mechanism in the DM. As a beneficial effect, nutrients can reverse or change epigenetic phenomena such as DNA methylation and histone modifications, thereby modifying the expression of critical genes associated with physiologic and pathologic processes including embryonic development and aging. It appears that nutrients and bioactive food components can influence epigenetic phenomena either by directly inhibiting enzymes that catalyze DNA methylation or

histone modifications, or by altering the availability of substrates necessary for those enzymatic reactions [78]. In this regard, nutritional epigenetics has been viewed as an attractive tool to prevent DM as well as to delay aging-associated processes. In recent years, epigenetics has become an emerging issue not only in type-2 DM but also in a broad range of diseases such as obesity, inflammation, and neurocognitive disorders. Some bioactive food compounds such as polyphenols, isothiocyanates, vitamins and some minerals may induce beneficial effects because of their ability to modulate epigenetic processes[79]. There is also evidence that both obese and diabetic people have a pattern of epigenetic marks different from non-obese and non-diabetic individuals. The main long-term goals in this field remains in the identification and understanding of the role of epigenetic marks that could be used as early predictors of metabolic risk and the development of diet-related treatments able to delay these epigenetic changes or even reverse them. However, the characterization of all the factors that are able to modify the epigenetic signatures and the determination of their real importance are hindered by the factors like the small and cumulative magnitude of change produced by dietary and environmental factors, great differences among cell types and factors including age and with multiple interactions between them [80].

Although the possibility of developing a treatment or discovering preventative measures of DM is exciting, in the field of nutritional epigenetics our knowledge is still limited. In fact,

the effects of nutrients or bioactive food components on histone methylation or chromatin remodeling complexes are largely unknown. Therefore, in the future, we need to investigate more nutrients or bioactive food compounds to find better ones for our health. Understanding the role of nutrients or bioactive food components in altering epigenetic patterns will aid our ability to find a better way to maintain our health through nutritional modulation that could be more physiologic than any other pharmacotherapies. Further studies are needed to expand the available resources and to better understand the use of nutrients or bioactive food components for maintaining our health and preventing diseases like DM through modifiable epigenetic mechanisms. Further, the regulation of these processes, the magnitude of the changes and the cell types in which they occur, the individuals more predisposed and the more crucial stages of life also remain to be elucidated. However, it seems that during our lifetime, nutrients can modify physiologic and pathologic processes through epigenetic mechanisms that are critical for gene expression. Modulation of these processes through diet or specific nutrients may prevent diseases and maintain a good health. However, it is very hard to delineate the precise effect of nutrients or bioactive food components on each epigenetic modulation and their associations with physiologic and pathologic processes in our body because the nutrients also interact with genes, other nutrients and other lifestyle factors. Furthermore, each epigenetic phenomenon may also interacts with the others and thus adding to the complexity of the system.

Figure 2: Proposed epigenetics mechanisms involved in the development diabetes mellitus and its management



Conclusion, Recommendations and further studies

Though etiology of the DM is multilateral and multifactorial resulting primarily from the nutritional imbalances and if such conditions are not allowed to develop through proper dietary supplementation and manipulation, the increasing prevalence of DM can be checked. Proper formulated amount of carbohydrates, protein, fat and micronutrients in our daily normal diet will be helpful in managing the incidence and increase severity of DM. In order to effectively manage DM, proper education and awareness to diabetic patients about the role of diet and nutrients in DM is vital and important. Regular diet for diabetic patient should be rich in complex carbohydrates, n-3 fatty acids, antioxidant vitamins and essential minerals like Mg, Cr and Mn. Further, even though the knowledge of nutritional epigenetic in DM is still scarce and difficult to delineate the precise effects

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of the diet on each epigenetic modulation, with the advent of high-throughput technologies there is possibility that an altered epigenetic code that is programmed due to improper nutrients can be reverted back by supplementing formulated diet and nutrients containing various plant-derived compounds. More research is highly imperative on the epidemiological, laboratory and clinical aspects of the role of nutrition in the management of DM.

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