Chapter

Therapeutic Effect of Folate and Cobalamin in Diabetics

Farah Qudsia and Samreen Riaz

Abstract

Diabetes Mellitus type 2 is a metabolic ailment. It is a condition when insulin is produced by our body but, it is not used properly by us. The number of diabetic patients is increasing in the whole world. The problem of obesity is also very closely related to it, which itself is expanding. The individuals diagnosed with type 2 Diabetes Mellitus have high chance of microvascular problems (like nephropathy, retinopathy and neuropathy). They are also at the verge of facing macrovascular ailments (like cardiovascular comorbidities). This indicates that many antidiabetic agents should be administered in combination, to maintain normal sugar level in blood. The management for the patients suffering from diabetes should be effective and harmless for them. It should also improve the general well-being of the patients. So many remedies have been developed for the management of diabetes. Several of them are being developed. We should enhance insulin sensitivity to let our body use insulin effectively. We also must stop the increasing pancreatic β-cell failure which is a specific characteristic of Diabetes Mellitus type 2. The microvascular complications must also be avoided or revoked. Our direst need is to develop agents which may help us in achieving goals mentioned earlier. Many micronutrients are involved in combating the Diabetes Mellitus and complication associated to the malady. These micronutrients are vitamins. Our main focus in this chapter are Vitamins B9 (Folate) and B12 (Cobalamin). Many researches have shown that the said parameters were decreased in patients suffering from Diabetes Mellitus. The level of these two vitamins should be maintained to the normal level and not toward the border line. The maintained level of these vitamins will help in controlling the main problems in patients suffering from Diabetes Mellitus like neuropathy, anemia and many others. By taking these vitamins along with other preventive measures, Diabetes Mellitus can be controlled and can be less dangerous.

Keywords: diabetes mellitus, cobalamin, folic acid, microvascular complications, micronutrients

1. Introduction

The permanent harm, dysfunction, and failure of multiple human body parts, like eyes, kidneys, heart, nerves and blood vessels could be caused by persistent hyperglycemia [1].

1.1 Preventing the development of diabetes mellitus

The risk of the diabetes raises seven times in older age (55+) than it is in younger age (20 to 34 years old). So, it is really important to gear up to control diabetes in

midlife. Specially minimizing the spread of type 2 Diabetes Mellitus is crucial for individuals and even the societies. The importance of eradication of *type 2 Diabetes Mellitus* is even because of its harmful side effects.

Healthy lifestyle and body-weight control in midlife plays a crucial role in avoiding or postponing manifestation of type 2 Diabetes Mellitus since lifestyle interventions seem more durable concerning their protective potential in this part of life. The different pharmaceutical approaches to eradicate type 2 Diabetes Mellitus are not effective after they root out the disease for the first time. Also, such approaches have so many side effects on the patients going through such techniques. Therefore, for the time being, no drug is licensed for diabetes prevention.

Nonetheless, novel medicaments' attempts for diabetes prevention and supporting healthy aging are under scientific investigation. The diabetes can result in severe hypoglycemia, premature cardiovascular complications, other severe problems and even death. So, every possible step should be taken in order to eradicate this. The lifestyle of the patient should be changed to fight diabetes. All possible pharmaceutical techniques should also be applied to control the ailment. Diabetes prevention has a vital influence in the making of health policy [2].

1.2 Pathophysiology of diabetes

Numerous pathogenic processes are responsible of the growth of diabetes. These range from autoimmune demolition of the pancreatic β-cells with subsequent insulin shortage to anomalies that result in confrontation to insulin action. Lacking insulin action results from insufficient insulin emission and/or reduced tissue responses to insulin at one or more points in the complex paths of hormone action. The basis of the abnormalities in carbohydrate, fat, and protein metabolism in diabetes is deficient action of insulin on target tissues. Weakening of insulin secretion and defects in insulin action frequently coexist in the same patient, and it is mostly uncertain which anomaly, if either alone, is the main reason of the glucose excess in blood [1].

When we take the meal, the glucose levels in blood rise that activates insulin secretion. This results in a rise in biotransformation, transport and storage of insulin in fat tissues and muscles. During fasting, liver provides the glucose in blood that is used by the brain, without any dependence on insulin. Besides storing glucose, insulin also hinders the secretion of glucagon and drops the quantity of serum fatty acids resulting in a downfall in production of glucose in liver [3]. Inadequate insulin or confrontation to insulin in the body results in lessened uptake of glucose by tissues that has intracellular hypoglycemia and extracellular hyperglycemia as its outcome. The glucogenesis is caused by intracellular hypoglycemia and gluconeogenesis that results in breakdown of fats (resulting in diabetic ketoacidosis) and reduces synthesis of gamma globulins and protein (resulting in polyphagia, cachexia and reduced wound healing), while osmotic dieresis and hyperglycemic coma are caused by the extracellular hyperglycemia [4].

1.3 Pathogenesis about type 1 diabetes mellitus

A deficiency of insulin secretion occurs in Insulin dependent Diabetes Mellitus (IDDM). It is because of the autoimmune demolition of pancreatic beta cells that results in metabolic disorders associated with Insulin Dependent Diabetes Mellitus [4]. The last stage of β-cell demolition shows the beginning of clinical ailment resulting in type 1 diabetes mellitus. There the infiltrating lymphocytes, monocytes and a blend of pseudo atrophic islets form along with a few cells emitting glycogen, somatostatin and polypeptide from pancreas. This results in an immunogenic

process whose outcome is the ailment [5–7]. Genetic makeup, autoimmunity and environmental factors are accountable for islets cell demolition [8].

1.4 Pathogenesis about type 2 diabetes mellitus

Many healthy operations are impaired in Non-Insulin dependent diabetes mellitus (NIDDM). This lessens the adjustment of tissue acceptance to insulin which results in reduced insulin influence via insulin confrontation and reduced insulin emission by the beta cells of pancreas [9].

Several genetic imperfections, and some environmental factors like overweightness are important in this type of diabetes. They are accountable for peripheral tissue insulin reluctance and beta cell problems [8].

2. Therapy of diabetes mellitus

As indicated by ongoing appraisals, the human populace overall seems, by all accounts, to be amidst a pestilence of diabetes. Notwithstanding the incredible steps that have been made in the comprehension and the executives of diabetes, the infection and sickness related difficulties are expanding continuously. Along with this, ongoing improvements in comprehension of the pathophysiology of the ailment procedure has unlocked a few new roads to distinguish and create novel treatments to battle the epidemic of diabetes [10]. The cure of diabetes with artificial medications is expensive and odds of reactions are so many. Phytomedicine has been utilized since old occasions in different regions around the globe where access to up-to-date drugs is restricted. Therapeutic plants and phytochemicals assume a significant job in the administration of diabetes mellitus particularly in underdeveloped nations where assets are small. Utmost pervasive amongst phytochemical bunches are the glycosides, alkaloids, polysaccharides and phenolics, for example, terpenoids, steroids and flavonoid. Regardless of impressive advancement in the improvement of artificial medications, the disclosure of phytomedicine as an elective treatment is increasing [11]. Simultaneously, phytochemicals recognized from customary medical plants are exhibiting an energizing open door for the improvement of new kinds of therapeutics. This has quickened the worldwide exertion to saddle and gather those restorative plants that bear significant number of potential phytochemicals appearing advantageous impacts in battling diabetes and diabetes-related entanglements. In this manner, as the malady is advancing continuously, there is a critical need of recognizing native resources occurring in nature so as to get them, and concentrate in detail, their potential on various recently distinguished focuses so as to create them as new treatments [10]. The improvement of type 2 diabetes might be decreased by the admission of cancer prevention agents in the eating routine [12].

2.1 Vitamins and diabetes mellitus type 2

Nutrients are the natural mixes needed by our body which are termed as mandatory ingredients required in definite quantities. They cannot be made in adequate quantity by the human body, and thus, should be gotten from the eating routine. Thirteen distinct kinds of vitamins are found that are ordered by their organic and substance action; every one of them keeps a particular job in human body [13].

Vitamins are termed as either fat-dissolvable or water-solvent. There are thirteen vitamins found in nature. Nine of them could dissolve in water (8 B Vitamins and Vitamin C) whereas, four of them could dissolve in fat (A, D, E, and K). The

water-solvent Vitamins effectively make solution in water and are discharged from the body quickly since they could not be kept for quite a while, aside from nutrient B12 [14]. Whereas, fat-solvent Vitamins are caught up in the digestive system within the existence of lipid and they are bound to be kept in the body. As they are kept for quite a while, they can prompt hypervitaminosis more than the water-dissolvable vitamins; a few nutrients are necessary for the body cell development and improvement (for instance folate and vitamin B12).

Vitamin B6 also play a crucial role in diabetics as it is a cofactor for approximately 150 reactions that regulate the metabolism of glucose, lipids, amino acids, DNA, and neurotransmitters. In addition, it plays the role of antioxidant by counteracting the formation of reactive oxygen species (ROS) and advanced glycation end-products (AGEs). Epidemiological and experimental studies indicated an evident inverse association between vitamin B6 levels and diabetes, as well as a clear protective effect of vitamin B6 on diabetic complications. Interestingly, by exploring the mechanisms that govern the relationship between this vitamin and diabetes, vitamin B6 can be considered both a cause and effect of diabetes [15].

Folate is known as vitamin B9 which has significant functionality in human body. We need folate for the repair, creation and methylation of DNA [16]. In a study in America, it was seen that the **intake of folate in young adulthood was inversely associated with diabetes incidence in midlife amongst Americans. The observed association may be partially explained by mechanisms related to homocysteine level, insulin sensitivity, and systemic inflammation** [17].

Besides, it goes about as a helper in numerous fundamental natural responses. Folic Acid has a significant job in cell division and it is particularly required amid early stages and pregnancy. Our body needs folic acid so as to avoid iron deficiency and create sound RBCs (Red Blood Cells), while Vitamin B12 assumes a significant job in providing basic methyl bunches for protein and DNA amalgamation. Vitamin B12 is bound to the protein in our meal and hydrochloric acid in the stomach discharges B12 from it amid ingestion. Once discharged, vitamin B12 consolidates with an ingredient known as intrinsic factor [18].

The type 2 Diabetes Mellitus is a heterogenous malady which is usually connected to vital chemical reactions, especially starch and fat administration in the living being. Be that as it may, most micronutrients are likewise associated with some route either as a component of the reason or impact of this perpetual pathology. The outcomes and problems of diabetes are the aftereffect of a disparity between free radical development and their control by common cancer prevention agents [19]. Thus, those micronutrients that have an antioxidant function are very important in the development of the disease and its complications, while other non-antioxidant vitamins have also shown a relationship.

Vitamins A, C and E, which have antioxidant properties are discovered diminished in diabetic patients, may be because of an expanded need to limit the extraordinary oxidative pressure created by irregularities in glucose digestion. Then again, retinol binding protein applies a tweaking impact, as it has adipokine capacities. As for the B complex Vitamins, pyridoxine, thiamin and biotin have been discovered diminished though the systems are not obvious, whereas using its supplements has demonstrated some betterment of the metabolic control in individuals suffering from diabetes. The assimilation of folate and Vitamin B12 is critically diminished by the prolonged utilization of metformin, which is the most used medicine in simple diabetes, subsequently these two supplements have been discovered insufficient in the ailment and most presumably should be administered consistently. Whereas, Vitamin D is viewed as a hazard for the improvement of diabetes just as its difficulties, especially those related to heart and blood vessels. Though a few examinations

have discovered a relationship of Vitamin K admission with sugar digestion which require more research. Research on the utilization of multivitamin supplements have indicated uncertain outcomes. The individuals utilizing metformin amid delayed periods may require folate and Vitamin B12 [20].

2.2 Cobalamin or B12 vitamin

Vitamin B12 is a non-protein ingredient in the single-carbon metabolic pathways, engaged with the making of methionine, pyrimidine and purine bases. Its deficiency due to DNA damage or faulty repair is involved in cancer, vascular diseases and some birth defects, while a consequent hyperhomocysteinemia, also related to folic acid deficiency; it has been recognized as a risk for hypertension and atherosclerosis [21].

The water-soluble vitamin is *Vitamin B12*. It is found within many foodstuffs as well as exists in nutritional medicines. It is present with many types as well as has mineral cobalt [22–25], thus compounds having vitamin B12 features may together know as "Cobalamins".

2.2.1 Forms of vitamin B12

These compounds are listed as [26].

- Hydroxocobalamin
- Methyl cobalamin
- 5-deoxyadenosylcobalamin and Adenosyl cobalamin
- Cyanocobalamin

2.2.2 Functions of vitamin B12

- It is essential of the suitable RBCs development, neurological role, and DNA synthesis. Vitamin B12 acts as a cofactor for methionine synthase and L-methyl malonyl-CoA mutase. Methionine synthase activates the alteration of homocysteine to methionine [26, 27]. Methionine is vital for the development of S-adenosylmethionine which is a general methyl donor for roughly 100 different substrates, including RNA, DNA, hormones, lipids and proteins. L-methyl malonyl-CoA mutase transforms L-methyl malonyl-CoA to succinyl-CoA during destruction of propionate [22, 26, 27], which is an important biochemical reaction in metabolism of protein and fat. Succinyl-CoA is also necessary for the making of hemoglobin.

- It is present within the protein of food and may be free through action of gastric protease and HCl during digestion. When artificial vitamin B12 is mixed in prepared meals and nutritional supplements, it is now in free form and, therefore, does not involve this detachment process. Free vitamin B12 joins with intrinsic factor which is a glycoprotein released by the gastric tube's parietal cells. The complex formed as a consequence experiences ingestion inside the distal ileum by the help of receptor-mediated endocytosis [26, 28].

- It can be in particular main component to keep strong nerve cells as well as this assists for making of RNA and DNA hereditary matter of body [28].

- Its mechanism is directly with vitamin B9 as well-known as folic acid or folate, to aid build RBCs and hence keep anemic conditions from building up in the body. Folic acid and Vitamin B12 play role jointly for making S-adenosylmethionine (SAMe), a chemical compound concerned in immunity related functions and person's mood changes.

- Vitamins B12, Vitamin B6 as well as B9 act mutually for the management of status of the homocysteine amino acid. Elevated status for homocysteine is linked by heart disease. Though, scientists do not have confidence that homocysteine can be reason for heart disease otherwise only an indicator which shows the risk of heart attack.

- Vitamin B12 has a key role in the production of energy in the body. It keeps the cells fit. Without it, cells become weak.

- The heart as well as whole cardiovascular system requires B12. It has functions of eliminate hazardous protein known as homocysteine. When homocysteine becomes tolerable so that it stays throughout blood, this devastates arteries results in swelling as well as heart disease.

- Research works explain people having osteoporosis can contain elevated status for homocysteine as well as decreased status for B12 as compared to persons having strong and fit bones [29].

- Nerves contain defensive cover for their protection from pollutants as well as free radicals within blood. Devoid of casing, known as myelin sheaths, bare nerves are injured as well as might expire. Such deceased nerves disturb signals toward and away from brain as well as might take part in function in nerve associated circumstances. Vitamin B12 assists approach by which the body replenishes this defending casing [30].

2.2.3 Sources of vitamin B12

The Vitamin B12 is found within organic foodstuffs, as well as in meat, fish, eggs, poultry, milk products and milk itself. It does not find within plants and its products only in very small quantity, but prepared breakfast cereals may be easily accessible resource for vitamin B12 having elevated availability for vegetarians [26]. Some dietary yeast foodstuffs also have vitamin B12.

Prepared foodstuffs have different formulation and this may be essential understand tags of manufactured goods find out the nutritional ingredients. Various food origins of vitamin B12 are enlisted in the **Table 1** [31].

2.2.4 Metabolism of vitamin B12

The Vitamin B12 is utilized by us in two ways, as methyl cobalamin or 5-deoxyadenosyl cobalamin. Methionine synthase is an enzyme which needs methyl cobalamin as a cofactor. It is usually responsible of the transformation of the amino acid homocysteine to methionine, whereas methionine, is needed for the methylation of DNA. 5-Deoxyadenosyl cobalamin is a helper enzyme needed by those enzymes which transform l-methyl malonyl CoA into succinyl CoA. This transformation is a primary point in the taking out of energy from fats and proteins. Additionally, succinyl CoA is needed for the making of hemoglobin which is the compound that is a carrier of oxygen molecules in red blood cells [32].

Food	Micrograms (mcg) per serving	Percent DV*
Beef	70.7	1,178
Breakfast cereals, fortified with 100% of the DV for vitamin B12, 1 serving	6.0	100
Trout	5.4	90
Salmon	4.8	80
Tuna fish	2.5	42
Cheeseburger, twofold pastry as well as bread roll, 1 sandwich	2.1	35
Milk	1.2	18
Yogurt, fruit	1.1	18
Cheese, Swiss	0.9	15
Egg	0.6	10
Chicken	0.3	5

** Percent Daily Value. A guide to the nutrients in one serving of food*

Table 1.
Different sources of vitamin B12 [31].

3. Vitamin B12 and diabetes

The connection between diabetes and vitamin B12 can be explained as:

3.1 Vitamin B12 deficiency and type 1 diabetes mellitus

Diabetes Type 1 is an automatic immune state which is the outcome from auto immune devastation for insulin releasing from beta cells of pancreas. This can be consistently related to new organ as well as non-organ particular auto immune plus endocrine situations results in growth of autoimmune polyglandular disorders [33].

Pernicious anemia due to chronic autoimmune gastritis can be very much widespread amongst people having type 1 diabetes. Pernicious anemia and Chronic autoimmune gastritis are present within almost 2% as well as up to 1% common people correspondingly. Amongst people having type 1 diabetes, incidence raises 3 to 5 times [34]. vitamin B12 shortage because of pernicious anemia present repeatedly amongst individuals having type 1 diabetes.

Individuals suffering from type 1 diabetes show parietal cell antibodies (PCA) plus auto antibodies to intrinsic factor (AIF) type 1 as well as 2 (De Block *et al*., 1999) in particular people having antibodies of glutamate decarboxylase-65 (GAD-65) as well as HLA-DQA1*0501-B1*0301 haplotype [35]. The PCA hampers release for intrinsic factor leading to pernicious anemia, state that can be 10 times further prevailing amongst people having type 1 DM as well as people do not have DM. Type 1 AIF lead to vitamin B12 deficit inhibiting attachment of vitamin B12 to IF. This inhibits transport toward assimilation spot, terminal ileum. Such auto antibodies can be present within 70% people suffering from pernicious anemia.

Main autoimmune hypothyroidism as well as celiac ailment is common comorbidities between people having type 1 diabetes [36] and directly influence vitamin B12 metabolism. Vitamin B12 shortage between people having autoimmune hypothyroidism is described as existence of gastric parietal cell antibodies as well as intrinsic factor, decreased ingestion by mouth because of thyroid hormone insufficiency as well as flawed assimilation because of bowel wall edema, decreased bowel

motility and increased growth of bacteria [37]. Celiac disease can be greatly widespread autoimmune mediated gastrointestinal state happen within 1–16% people having type 1 diabetes in contrast to 0.3–1% of common people. Intake for wheat gluten as well as further associated proteins is recognized as activator for situation within genetically liable persons. Because of linked enteropathy, people frequently stop to thrive, anemia and chronic diarrhea owing to micronutrient (mainly folate, vitamin B12) malabsorption [38].

3.2 Metformin stimulated vitamin B12 deficiency amongst patients with T2DM

Due to lack for contradictions such as renal as well as hepatic dysfunction, current guiding principles support utilization of metformin like primary line glucose reducing mediator parallel to changes in way of life [39]. Regardless of better glycemic reducing influence, metformin is revealed for reduction of vitamin B12 status. The possibility for having metformin coupled vitamin B12 deficit can be deeply affected of growing age, metformin dosage as well as period of use. The given methods for clarification of metformin induced vitamin B12 shortage amongst people having type 2 diabetes comprise: variations of small bowel motility that induces increased growth of bacteria as well as resulting vitamin B12 deficit, viable reduction and vitamin B12 malabsorption, changes within intrinsic factor status as well as contact to tubulin endocytic receptor. Metformin hamper calcium bound assimilation for complex of vitamin B12-IF at the terminal ileum. Such inhibition consequence could be inverted using calcium medication [40].

4. Folate, folic acid or B9

The term folate includes 150 components of the family of pteroilglutamate, which participate in cell replication by enzymatic activity in purine base synthesis for DNA and are a primary co-factor for transamination in the transformation of amino acids, particularly homocysteine into methionine. Folates are present in animal tissue, leafy vegetables, legumes and nuts and their deficiency has been associated to megaloblastic anemia, neural tube defects, cardiovascular disease, cancer and senile dementia [41].

Implication of folate in pathogenesis of type 2 DM is linked with vitamin B12 shortage and its consequent hyperhomocysteinemia, and although its deficiency is not widespread, supplementation trials have been carried out in diabetic patients [42].

Folates are made up of 4[(2-amino-4-oxo-1,4-dihydropteridin-6-yl) methyl-amino] benzoic acid, pteroic acid which is bonded with multiple or single monomers of L-glutamate. They lie in the family of heterocyclic organic compounds group [43].

There are eight different types of B vitamins. They are collectively called as B complex vitamins. Folate i.e., Vitamin B9 is also one of them. The naturally present folate forms are also based on vitamin B9. Many of the foods contain B vitamins. Many of folates are also taken from foods. They are generally made up of a mix of reduced folates. Reduced folates are any type of pteroyl mono glutamates, or an amalgam of pteroyl glutamates. They have a peculiar degree of pteridine ring reduction. Also, they have a different number of glutamates remains and one-carbon replacements [44]. The seven of total eight B vitamins can dissolve in water and hence cannot be kept by our body. We must constantly get their supply in our daily diet. Folates (vitamin B9) have that property. We can get them from

foods like beans (and other legumes), salmon, citrus fruits, whole grains, leafy vegetables, meat and dairy etc. If we fail to fulfill our need of folate form our daily diet then we can take supplements which contain artificially synthesized folate to fulfill our needs. Folate fortification is also done to increase the folic acid intake by people. A number of commercially sold synthetic forms of folates are even better as compared to the natural ones [45]. They could be easily broken down chemically, especially reduced type of unsubstituted tetra and di-hydro forms are chemically stable. Tetrahydrofolates are usually found as the unsubstituted poly glutamates and tetrahydrofolates, that is, 5-methyl, 5,10-methylene, and 10-formyl etc. [46]. Reduced substituted forms of vitamins are prone to the chemical changes. Oxidative reactions occur in them which results in the activeness loss of vitamins. There are no acknowledged undesired effects of folates. An excess intake of them is not dangerous for human beings. The maximum usage limit of synthetic folates is capped to 1 mg daily. It is advised because excessive administration of folates may cover up the vitamin B12 deficiency [47].

4.1 Roles

Folic acid is considered to be an essential nutrient for our body. Folic Acid derivatives are necessary components for the DNA production. They are also needed for the erythrocyte synthesis. The biosynthesis of some amino acids needs tetrahydrofolates as a crucial ingredient. They are needed in the biosynthesis of precursors of DNA also [48]. Folic acid is necessary for the production of deoxyribose nucleic acid (DNA). They even aid maintenance of the process of methylation [49]. They also participate as helper molecules in some biological reactions. The cell division in our body essentially needs folate. We need it even more during pregnancy and infancy. It is needed in multiple crucial processes like quick cell growth and proliferation. The production of RBCs also needs folate. This acts to keep from anemia [50]. Nucleotide synthesis is the most important function of folate. It is required for the production and repair of DNA. Folates are also responsible of the production of methionine by alteration of Homocysteine in the procedure of re-methylation. Methionine is a useful amino acid which is in turn used to produce other necessary proteins. It may get converted to an important methyl donor i.e., S-adenosylmethionine [51].

4.2 Inadequacy

The deficiency of folate is not common in developed countries. But it is reported in many of the third-world countries. Folate deficiency could be due to multiple reasons. The poor diet and erroneous metabolism of vitamins could be responsible for it [52]. The US government along with that of many other countries has made fortification of food with folate to be mandatory for their nationals. This helps in eradication of NTDs worldwide. Mostly they use floor for the fortification because it is widely used by the public. The routine ingestion of folate is examined by taking the blood samples and measuring the folate levels in them. If the level of folate is low in blood samples then it means the folate is not taken up to required level [51].

We can fulfill our folate requirement by taking folate fortified diet. Artificial folate supplements are also available in the market which can serve the purpose. But the availability of any of the options of folate intake vary in different regions of world. The folate absorption also differs for every supplement used. Dietary Folate Equivalent (DFE) is the amount of folate our body can absorb out of the supplement taken per serving. Every DFE unit is considered to be one micro gram of folates or 0.6 micro grams of artificially made folate [50].

Loss of appetite along with decrease in body weight may occur due to deficiency in folate. The deficiency might be faced when one's need of folate increases or diet is reduced from a certain level. It is reported as a key health issue in some countries. Though it is rare in developed countries which enforce folate fortification of foods. Folate and vitamin B12 deficiency impacts all public of all ages. It is related to many diseases like neural tube defects in infants, diarrhea, anemia and other birth defects etc. [52].

The loss of methyl groups from DNA is termed as DNA hypomethylation. This could be affected by the deficiency of folate. The folate ingestion can fix such problems [53]. The overall methylation and DNA synthesis processes could also be negatively affected by the deficiency of folate in human body. Thymidyl acid, dTMP (Deoxythymidine monophosphate), is used as a monomer in DNA. Its supply in body becomes limited due to increased rate of removal of dUMP (Deoxy uridine Monophosphate) from the molecule of DNA. This is increased due to defective methylation cycle as a result of folate deficiency. DNA repair reactions start due to these problems which in turn declines the required cell division [45].

4.3 Metabolism of folate (vitamin B9)

Folic acid is inactive biochemically, it is transformed by dihydrofolate reductase into methyl tetrahydrofolate and tetrahydro folic acid. These folate congeners are carried by receptor-mediated endocytosis through body cells. There they are required to generate and use format, and synthesize thymidylate nucleic acids and purine, methylate tRNA, keep general erythropoiesis, interconvert amino acids. Utilizing vitamin B12 as a helper enzyme, folate can standardize high homocysteine quantities by re-methylation of homocysteine to methionine via methionine synthetase [16].

Author details

Farah Qudsia* and Samreen Riaz
Department of Microbiology and Molecular Genetics, University of the Punjab, Quaid-e-Azam Campus, Lahore, Pakistan

*Address all correspondence to: farah.qudsiaa@gmail.com

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