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Original Article

Diabetes Mellitus and Vitamin B 12 (Cobalamine)

Memona Ali[1], Samreen Raiz[2]

[1]Tertiary Care Hospital Pakistan .Lahore, [2]Department of Microbiology and Molecular Genetics, University of the Punjab, Lahore, Pakistan.

Abstract

Objectives: Diabetes Mellitus is a disorder of metabolism that associate to the impairment of the metabolism of fats, carbohydrates and proteins that causes defect in the secretion and action of insulin.

Methods: It is supposed that about 285 million people including adults were suffering from this chronic disease and due to the absence of better cure this number rises to 430 million. Two are the main reasons that are responsible for this increase, one is aging people and other is obesity. About 440,000 children were suffering from diabetes in 2007. Before the diagnosis of diabetes, many children were died due to this fatal disease. To overcome from this disease children were treated by the use of insulin injection.

Results: Long term diabetes may results in blindness, neuropathy, renal failure, and risk of foot ulcer, impairment of immune system, periodontal disease and dysfunction of autonomic nerve. Diabetes is also responsible for macro vascular disease.

Conclusion: People with diabetes have more chances of death with other illness (like influenza and pneumonia) as compared to non-diabetic people. Diabetic patients with 60 years old are unable to walk even for a quarter of mile, they are unable to climb stairs and unable to do some other daily routine activities like household works.

Key words: diabetes, vitamin B 12, Pakistan, History, Type 2.

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Corresponding Author: Samreen Riaz**.** **Email:** samreen.mmg@pu.edu.pk

Introduction

Diabetes is a disorder of metabolism that results in increasing the level of glucose in the individuals. Diabetes ranked 7th in the worldwide as it increases day by day. There are various factors that are responsible for the diabetes. Diabetes mellitus cause hyperglycemia and various cardiovascular diseases. If diabetes not controlled it would rise to a maximum level in the future therefore it is important to know the causes of diabetes mellitus. So for analysis, the samples were collected from the Ghurkitrust teaching hospital, I selected this hospital because this hospital is nearest to my house and it is convenient for me to collect the samples and took the background history of the patients and the control individuals.

Diabetes Mellitus results due to the defect in the metabolism of carbohydrates, fats or lipids. Due to this defect the blood sugar level increases and the rise of glucose level results in thirst, hunger and frequent urination. This disorder is becoming prevalent worldwide day by day. Almost in every family, one of the members is definitely suffering from diabetes.

Diabetes is a disorder of the endocrine system that occurs due to the deficiency of the insulin. It is a main cause of mortality through the worldwide. There are many risk factors associated with diabetes one of them is obesity. As obesity is correlated with insulin so it results in severity of diabetes. The regulatory hormones that are involved in maintaining the balance of glucose in body are responsible for diabetes if it does not function properly. In 1995, the rate of diabetes prevalence in adults worldwide was about 4% which will rise to 5.4% by the year 2025.

Diabetes is more prevalent in the developed countries as compared to developing countries. On diabetes prevalence list, Pakistan is ranked 6th and it is also responsible for cardiovascular diseases. The rate of diabetes prevalence is increasing day by day and if it is not controlled now it will become fatal and very difficult to control later. People suffering from diabetes have high glucose level in their blood.

Diabetes occurs due to a variety of causes. Women are suffering from diabetes more as compared to men. This is because of economic, social and cultural trends. The risk of diabetes increases in the women who are poor and do not take care of their health and those who do not exercise regularly and become obese.

Obesity is one the major cause of diabetes due to which many other problems also occur. The growing obesity epidemic in United States has been extensively linked with diabetes. Diabetes can affect both the mother and the unborn child. It can also cause miscarriages. Women who are not suffering from diabetes can have the risk of developing it during pregnancy known as gestational diabetes. Besides genes and obesity, vitamin deficiency is also related to diabetes.

It has been evident that the use of metformin by diabetic patients to lower the serum level results in deficiency of vitamin B12. In the 2nd century AD, Aretaeus of Cappadocia was clearly described the type1 diabetes. The term diabetes was first used by Aretaeus. The sweetness of diabetic urine was first recognized by Charak and Sushrut between 400 and 500 BC, both were the Hindu physicians. The sweetness was recognizable by tasting the urine and by observing that the ants were congreted around the urine. They both observed that this disease was most common in the individuals that are overweight and liked to eat sweet and fatty foods.

The disease was not identified in Europe until Thomas Willis (1621-1675) wrote Diabetes or the Pissing Evil. According to him, this disease was neglected because it was very rare at that time. He described that urine was as sweet as honey or sugar but it did not considered that its sweetness was due to sugar.

The hyperglycemia was first described by MatthewDobson(1735-1784)in 1776. According to him, his patient's (Peter Dickonson) urine and serum tasted as sweet. Moreover the evaporation of urine smells as brown sugar so he concluded that the sugar was existed in the serum of the patient and after that patient's kidney excreted the sugar.

The adjective Mellitus (Latin word meaning honey) was applied by a John Rollo who was a trained surgeon of Edinburgh. He observed that diabetes was treated by the use of animal's diet. In 1815 it was proved by Michel Chevreul (French chemist) that the sugar found in diabetic patient was glucose. A famous Frenchman named as Claude Bernard (1813-1878) clearly explained the metabolism of glucose.[1,2]

Diabetes Mellitus is a disorder of metabolism that associate to the impairment of the metabolism of fats, carbohydrates and proteins that causes defect in the secretion and action of insulin. All type of diabetes is representing an excessive diabetic disorder range. The interaction between genes and the environment results in different type of diabetes. Frequent environmental changes results in increasing the diabetic forms now-a-days. Type 2 diabetes risk is due to the obesity that is main cause of type 2 diabetes.'[2,3]

Diabetes is a disease that increases day by day and become a global problem. In 2010 it is supposed that about 285 million people including adults were suffering from this chronic disease and due to the absence of better cure this number rises to 430 million. Two are the main reasons that are responsible for this increase, one is aging people and other is obesity. About 440,000 children were suffering from diabetes in 2007. Before the diagnosis of diabetes,many children were died due to this fatal disease.

To overcome from this disease children were treated by the use of insulin injection. Long term diabetes may results in blindness, neuropathy, renal failure, and risk of foot ulcer, impairment of immune system, periodontal disease and dysfunction of autonomic nerve. Diabetes is alsoresponsible for macro vascular disease.[4]There are different types of diabetes mellitus. The other name for Type 1 diabetes is juvenile diabetes that results because of beta cells destruction caused by the process of autoimmune and causing the deficiency of insulin.

There are many symptoms of type 1 diabetes such as constipation, fatigue, blurred vision, polydipsia, polyurea, polyphagia and candidiasis. If patient persist this disease for a long time.

Characteristics	**Type 1**	**Type 2**	**Monogenic**
Clinical presentation	Rapid and acute	Variable from low to severe	Incidental in glucokinase
Association	Yes	N0	NO
Age onset	From 6 months till adulthood	Puberty	Post pubertal

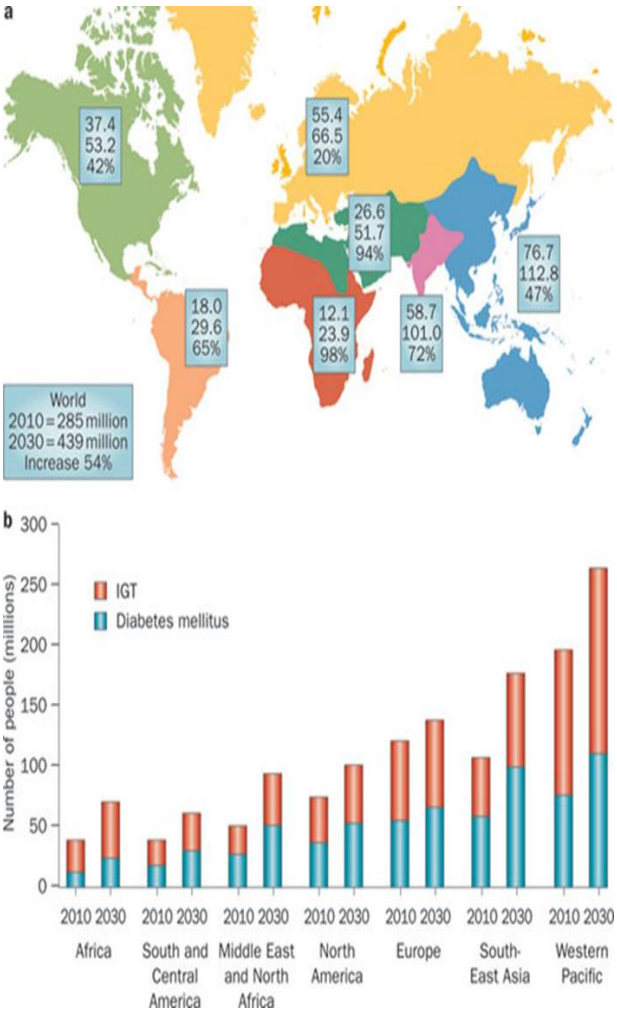

Fig 1: *The Graph showed epidemiology of diabetes.*

then it may lead to disease of macrovascular (heart, artery of coronary and peripheral vascular diseases).[5]

Type 2 diabetes mellitus is prevalent in diabetic patients, it comprises about 80-90 percent. Individuals with this type of diabetes have intra-abdominal obesity that is considered as resistance of insulin. These individuals are often suffering from dyslipidemia and hypertension.

This type of diabetes is due to obesity, increase in age and lack of physical activity. It is prevalent in females, Blacks, Native American and Hispanics.Various Diabetes mellitus types are grouped into "other specific types". This group can includes person with the impairment of insulin action, destruction of beta cell function, exocrine pan crease disease, endocrinopathies, and pancreatic dysfunction.[6]

Table 1: *The characteristics of type 1, type 2 and monogenic diabetes*

Patients suffering from diabetes have severe complications like:In the history of 2004, 68 percent diabetic patients were suffering from heart disease and died due to heart disease.In the history of 2004, 16 percent diabetic patients were suffering from stroke and died.

Death rate of diabetic adult with heart disease was about 2-4 times greater than non-diabetic patients. Diabetic patients have a very high risk for stroke. In the history of 2005-2008, 20 years old adults were suffering from diabetes and about 67 percent had a very high blood pressure.

Diabetes is the cause of blindness and it is common in 20-74 years old people. In the history of 2005-2008, about 4.2 million people had a diabetic retinopathy along with diabetes.Failure of kidney is also due to the diabetes, it was noted that in 2008, 44 percent people were suffering from kidney failure and the treatment of about 48374 people for end stage kidney began to start.In 2008's history, kidney transplant and dialysis of 202,290 patients were done due to serious kidney failure.[7]

About 60-70 percent diabetic patients are suffering from nervous system damage. As a result of this severe damage pain in the feet, impaired sensation, slow food digestion in stomach, carpel tunnel syndrome, other nerve problems and erectile dysfunction occurred.

About 30% of patients with diabetes have feet impaired sensation.Non-traumatic lower limb amputation occurs in about 60 percent of diabetic patients. In the history of 2006, 65,700 diabetic patients reported that suffer from non-traumatic lower limb amputation.In women if the diabetes is not controlled during the first trimester then it can cause serious birth defects and may lead to abortion.

In case of women that have pre-existing diabetes can avoid from the complication of birth defect by optimizing the level of glucose. Extremely large babies result due to uncontrolled diabetes during second and thirst trimester of pregnancy that cause risk of life for both mother and infant.[8]

Uncontrolled diabetes may leads to the death and causes severe events like diabetic ketoacidosis and hyperosmolar coma, these events are life-threatening.People with diabetes have more chances of death with other illness (like influenza and pneumonia) as compared to non-diabetic people.Diabetic patients with 60 years old are unable to walk even for a quarter of mile, they are unable to climb stairs and unable to do some other daily routine activities like household works.

Diabetic patients are more susceptible to depression and due to depression there will be a chance of occurring type 2 diabetes.

The diabetes prevalence in Pakistan is estimated through visiting the all four provinces of Pakistan. The survey informed that from 5433 individuals, 1893 are the males that are suffering from diabetes and 3540 are the females that are also suffering from this risk of life. Actually the purpose of this survey was to check the percentage of individuals of urban and rural areas suffering from diabetes.

This survey informed that in urban areas diabetes is prevalent in 6.0% of men and 3.5% of women and in case of rural areas men are of 6.9 percent and women are of 2.5 percent (Shera *et al.*, 2007). This percentage shows that how much diabetes is prevalent in Pakistan so we have to take a major step to overcome from this life-threatening disease.[8]

Treatment of diabetes includes oral medication, injections of insulin and animal diet. Self-caring plays a key role in diabetes management due to which patients live a happy life. Type 1 diabetic patient use insulin injections for glucose level maintenance. Type 2 diabetes patients can maintain their level of blood glucose by using healthy meal, by losing their weight, and by taking oral medications. Some type 2 diabetic patients use injections of insulin to maintain their blood glucose level.

Diabetic patients must maintain their blood pressure and their cholesterol level in order to overcome from this disaster disease.It is a Vitamin that is soluble in water and plays a very essential role in the synthesis of DNA, neurological functions and optimal haemopoesis.It is named as Cobalamin and performs function in the folate metabolism and also important for the synthesis of Krebs cycle intermediates and succinyl-coA. It has a very complicated structure.

It contains metal ion, cobalt and is important due to its unique feature.Vitamin B12 together with folate are important for the homocysteine metabolism as high level of homocysteine is responsible for cardiovascular diseases. It performs an essential function in the normal maintenance of stomach as its deficiency causes a severe stomach inflammation. In mammals it behaves as a cofactor of L-methylmalonyl-co-enzyme Amutase and

methioninesynthase.[9]

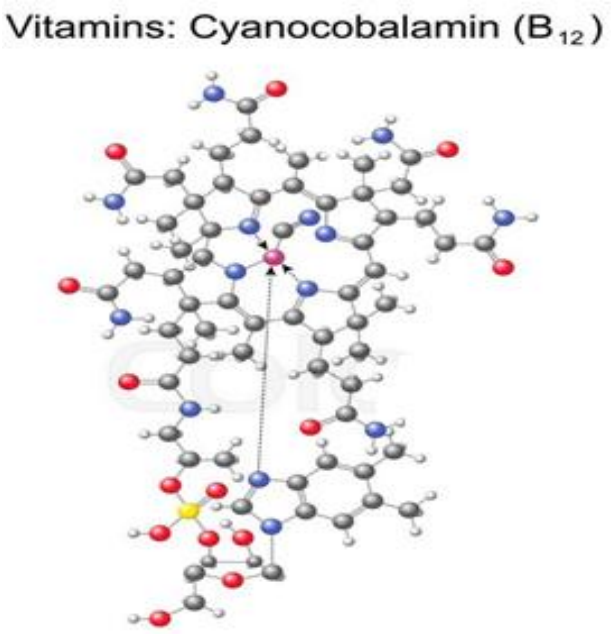

Fig2: *The detailed structure of Cobalamin.*

Methods

- Recruitment of 40 diabetic patients with no other serious ailment between the 40-80 years, and 40 age and sex-matched normal healthy individuals (control) selection from the diabetic clinic Health Centre University of the Punjab, Lahore.
- Consents taken from the recruited patients and normal healthy control for the clinical history and tests for base-line.
- Estimation of the physical and biochemical parameters were done in all the control and diabetic patients at the baseline by standard referred kit protocols.
- Estimation of the Cobalamin levels in the blood samples by HPLC chromatography.
- To compare the results and data of control and diabetic patients by the application of statistical analysis.

Many products of animals have vitamin B12, like poultry, meat and fish. Milk and products of milk are also the source of vitamin B12. Vitamin B12 can only be synthesized by bacteria. Individuals that are not vegetarians, they obtained supplemental vitamin B12. Recent evidence shows that vegetables, fermented beans, edible mushrooms and algae also have a sufficient amount of vitamin B12. Vegetarians' diet is used to fulfill the body requirements and to avoid from the risk of Vitamin B12 deficiency. Fortified foods such as fortified cereals are the best source of vitamin B12.[10]

Fig3:*The sources of b12.*

Methionine synthase is a folate dependent enzyme and for its proper function, Methylcobalamin is needed. This enzyme plays a key role in methionine synthesis and amino acids from homocysteine. In return methionine required for synthesis of S-adenosylmethionine, a methyl donor required for the methylation within proteins, DNA and RNA.

Cobalamin is very important for the proper functioning of folate dependent enzyme "Methionine synthase" as the improper

functioning of this may results in homocysteine accumulation. Accumulation of homocysteine can result in cardiovascular disease. The homocysteine metabolism and Cobalamin is shown in the figure 4. [11]

Table 2: *The properties of Vitamin B12*

Chemical formula	$C_{63}H_{88}CoN_{14}O_{14}P$
Melting point	>300 degree Celsius
Appearance	Dark red solid
Solubility in water	Soluble
Boiling point	>300 degree Celsius
Molar mass	1355.38 g/mol

Cobalamin is needed to perform function of digestive system. It helps in neurotransmitter synthesis and in the protection of a myelin sheath that is present around the neuron. Its supplementation helps in reducing the level of homocysteine.Animal proteins are the principle vitamin B12 sources.

The initiation of metabolism of Cobalamin is the release of animal sources Vitamin, a process which is performed by gastric acid and pepsin action. Due to its release, Cobalamin binds with protein which is R-protein that is the release of salivary glands. In duodenum, basic medium presence and pancreas protease, Cobalamin is released due to R-protein hydrolysis and then this R-protein binds to the factor which is called as intrinsic factor (IF) and it is released through gastric parietal cells.

Results

The Cobalamin-IF complex is capable of resisting the degradation of proteins. This complex binds at specific receptor on the terminal mucosal ileum, which is a site of absorption and absorption of Cobalamin is intimated by calcium.

Following IF degradation, intracellular vitamin is released. This free vitamin B12 then binds with to transcobalamin- II, which is other carrier of protein and then secreted into circulation. This complex (vitamin B12-TC-II) then carried by liver, bones marrow and body cells. Liver is the site of storage that stores upto 90% total body of Cobalamin. .The following figure 6 shows the absorption of Vitamin B12:[12]

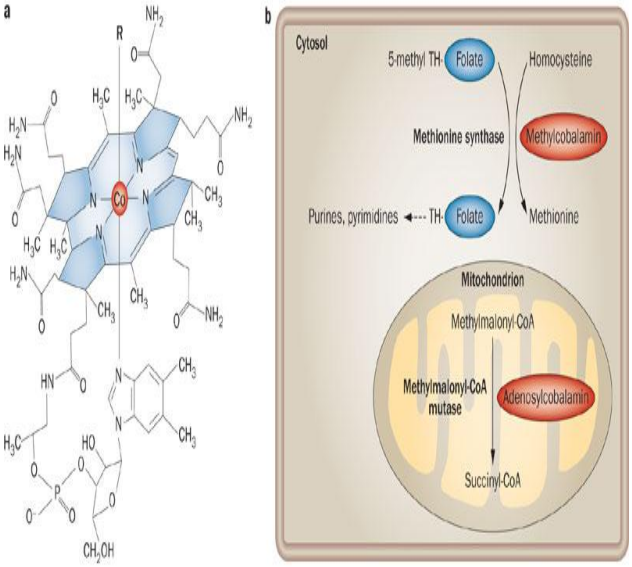

Fig 6: *The transport of B12 from food to body cells.*

The deficiency of Vitamin B12 is very rare in healthy adults because dietary intake of 2.4mcg/day is enough to maintain the status of vitamin B12. Because of impaired intestinal absorption, deficiency of Cobalamin is prevalent in elders.These complications have been linked with the stomach inflammation called as **atrophic gastritis.**People age of over 60 years are thought to be affected 10-30 percent by atrophic gastritis.[13]

This condition has been associated with the infection caused by the bacteria named

ashelicobacterpylori.

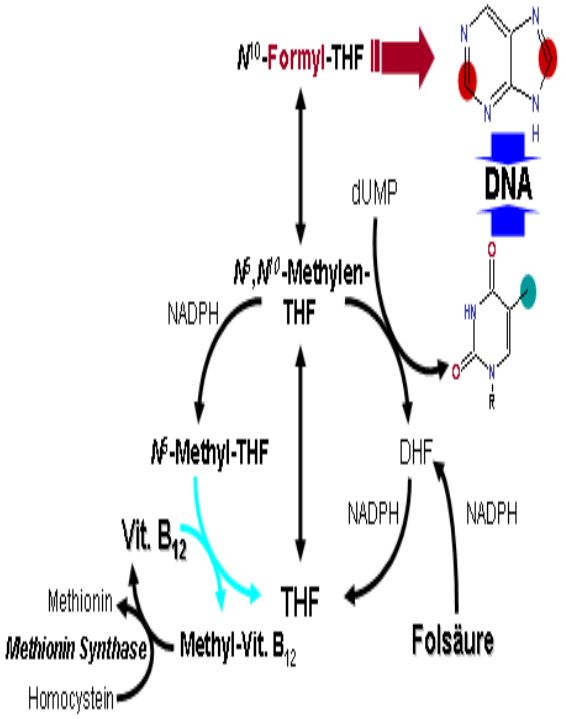

Fig 4: *The role of B12 in folic acid metabolism.*

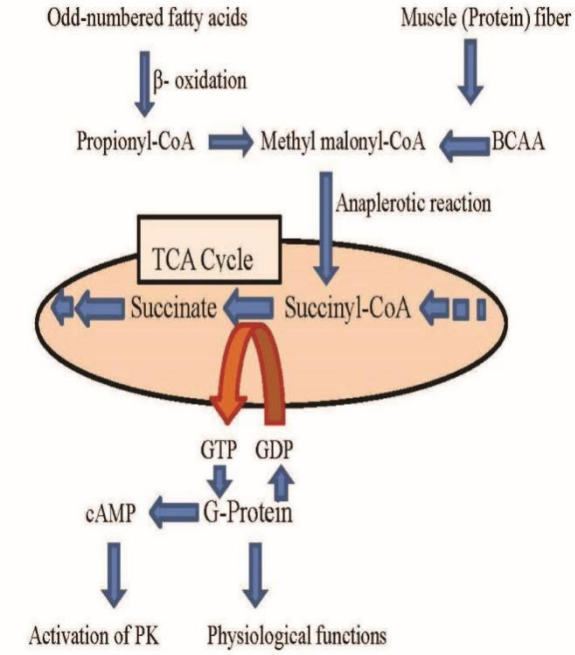

Fig 5: *The metabolism of odd number fatty acid carbons by mutaseenzyme .*

This bacterial infection causes severe stomach inflammation that may lead topeptic ulcer diseaseand in some individuals it causesgastriccancer.Decreased gastric function results in increasing the growth of bacteria in the small intestine. Individual suffering from Helicobacter pylori infection have low level of B12 in their plasma, gastric fluid and serum.[13]

People age of over 60 years are thought to be affected 2 percent by pernicious anemia. Pernicious anemia is a last stage of stomach inflammation called as autoimmune of atrophic gastritis that results in the damage of cells of stomach by autoantibodies. Rapid damage of stomach cells results in lowering the secretion of enzymes and acids that needed for the release of free-bound vitamin B12. Antibodies associate with intrinsic factor thus blocking from the complex formation known as IF-B12 complex thus inhibiting the absorption of Vitamin B12. It is thought that autoimmune response can be initiated by the infection of Helicobacter pylori. It is a condition in which there is an improper protein-bound Cobalamin absorption and food, individuals that are suffering from this kind of condition are able to absorb the free form.

It has been associated with the stomach inflammation that results in the decrease production of acid as this acid is very important for releasing the Cobalamin from food, thus diminishing absorption of Cobalamin.Enzymes and calcium are required for Cobalamin absorption and this enzyme and calcium are provided by pancreas, if there is any insufficiency in pancreas then it causes the deficiency of Vitamin B12. There is a reduced intestinal B12 absorption in Alcoholics.[14]

Type 1 diabetes is a scenario of autoimmune that occurs from beta cells secreting insulin, destruction of pancreas. It is linked with

endocrine conditions that lead to the development of autoimmune polyglandularsyndromes. These patients are more susceptible to pernicious anemia that results from chronic autoimmune gastritis. About 1% of chronic autoimmune gastritis and 2% of pernicious anemia takes place in population.

The wide spread presence is elevated by 3-5 folds in these patients. In research on South India revealed that there is no relation between low B12 levels, age, gender, glycemic control level and diabetes mellitus duration. Celiac disease is more prevalent about 1-16% in these patients rather than normal population that is about 0.3-1%.[14]

any researches have revealed an enhanced number of deficiency of Cobalamin within patients of 2nd type of diabetes Metformin use is described as a prime factor which is associated with deficiency of Cobalamin in patients suffering from diabetes mellitus type 2. Type 2 patients that has taken metformin, revealed the deficiency of Cobalamin that varies from 5.8% - 33%. It has been reported that in India which is a country of high proportion of vegetarians are at high risk of Cobalamin deficiency within the normal population.In the research that is done to know deficiency of Cobalamin and hyperhomocysteinemia within 441 healthy patients was reported within 67% of the participants. These participants have vitamin B12 concentration <150 pmol/L. In this study of multivariate analysis, vegetarian diet was the only factor that was linked with the low levels of Cobalamin.[15]

In older adults due to risk of Cobalaminmalabsorption bound with food, Food and Nutrition Board (FNB) recommended that adults of over 50 years old must take RDA from the fortified food to fulfill their requirements.[16]

All the patients who are suffering from the deficiency of Cobalamin must take therapy associated with parenteral or Oral Cobalamin . To improve deficiency of Cobalamin type 2 diabetes patients, doses of one thousand microgram for a week daily are sufficient. In severe cases, Vitamin B12 oral or parenteral administration of 1000 microgram per day for a week is advised.[17]

Fig 7: *The recommended B12 intake*

Vitamin B12 has not been associated with any side effects due to high dose. Oral dose of 2mg is helpful for the treatment of pernicious anemia without any harm. Only a small amount of absorption of Cobalamin takes place when high doses are given to individual orally which indicate low toxicity.In the past years, the individuals suffering from diabetes has increased very much all over the globe and it has become a

challenge of public health to all nations. Pre-diabetes and diabetes mellitus 2 has been extensively observed in children and adults. Diabetes prevention is a whole of life task and an appropriate treatment and care is required from its origin.The plasma level of homocysteine can be improved by using B12 therapies. It can be taken orally or by injections. Oh and Brown in 2003 observed that intramuscular injections were taken for treating deficiency of vitamin B12. Many other scientists have also reported the treatment of B12 with B12 therapies and it showed great improvement in the level of vitamin B121.[18,19,20]

Discussion

The research was made to check Cobalamin level and different parameters in diabetic patients. Diabetic patients as well as controls were taken and a comparison was made between them by checking the blood urea, S.creatinin, HbA1c and lipid profile. The results revealed a great difference between the control and diabetic patients.

First of all, the physical parameters were measured and recorded that include age, weight, height and BMI. In case of age, after applying the statistical analysis it is cleared that there is no age difference between the control and diabetic male and female categories. The same results are shown for the other three physical parameters such as weight, height and BMI as the p value is greater than 0.05 that shows no significant difference between the control and diabetic categories.[15,16]

As far as biochemical parameters are concerned, there is a significant variation or difference in the both control and diabetic category. In case of glucose estimation results, there is a remarkably increased level of glucose in the male and female diabetic category rather than normal control category.

When we compared the male and female categories it has been showed that this level has a marked increase in male category rather than female category. So this shows that male are more prone to increase the glucose level rather than females. In case of blood urea, there is too much variation in this level in the normal and the diabetic category. And when we compared the results of diabetic male and female category it is shown that diabetic males are showing more increase in urea level rather than diabetic females. In case of S.creatinin, this value is also showed the increase level more in diabetic male rather than diabetic females.

As far as HbA1c level is concerned, it is more in diabetic category rather than control category so it is cleared that the patients suffering from diabetes must suffer from many difficulties as there is rise in many biochemical parameter levels rather than the control category.

The triglyceride level is increased in the diabetic category rather than normal category. After analysis it is cleared that there is a variation in the triglyceride level of diabetic male and female category rather than the normal category. When we correlate the male and female triglyceride level, it is shown that diabetic females have high triglyceride level rather than diabetic male. As far as the level of H.D.L, V.L.D.L and L.D.L is concerned it is cleared that this level is less in normal category rather than the patients suffering from the diabetes.

When we compared this level between the diabetic male and diabetic female it is shown that the diabetic males have high level of these parameters rather than the diabetic females.The cholesterol level is associated with the diabetes. When we

check this parameter we came to know that this level showing the remarkably increase in the patients suffering from diabetes rather than the normal individuals category.

This level is more increased in the diabetic male category rather than the diabetic female category. B12 level is measured by a special technique that is High Performance Liquid Chromatography; there is a fall in quantity in diabetic patients rather than control category. Due to deficiency of Cobalamin level many disorders are associated with it including diabetes. When I compared the male and female patients suffering from diabetes it is shown that female patients from suffering diabetes have low level of Cobalamin that associate with diabetes.

So after concerning with these parameters it is cleared that diabetes is more prevalent in males rather than females so after giving the B12 supplements and the therapies people may overcome from the increase of diabetes level worldwide.

Conflict of Interest: None

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