"PREVALENCE OF VITAMIN B12 DEFICIENCY AND CLINICAL NEUROPATHY WITH METFORMIN USE IN TYPE II DIABETES MELLITUS PATIENTS"

By

REG NO. BG0116004

Dissertation

Submitted to the
KLE Academy of Higher Education and Research,
Belagavi, Karnataka
In partial fulfillment
of the requirements for the degree of

M. D.

in

GENERAL MEDICINE

DEPARTMENT OF MEDICINE,

JAWAHARLAL NEHRU MEDICAL COLLEGE,

BELAGAVI, KARNATAKA

APRIL – 2019

KLE Academy of Higher Education and Research, Belagavi, Karnataka

ENDORSEMENT

This is to certify that the dissertation entitled **"PREVALENCE OF VITAMIN B12 DEFICIENCY AND CLINICAL NEUROPATHY WITH METFORMIN USE IN TYPE 2 DIABETES MELLITUS PATIENTS"** is a bonafide research work done by **REG NO. BG0116004.**

Dr. REKHA S. PATIL MD

Professor and Head,

Department of Medicine,

J. N. Medical College,

Nehru Nagar, Belagavi – 10

Date:
Place: Belagavi

Dr. N.S. MAHANTSHETTI MD

Principal,

J. N. Medical College,

Nehru Nagar, Belagavi – 10

Date:
Place: Belagavi

LIST OF ABBREVIATIONS USED

ADA	:	American Diabetic Association
AMPK	:	AMP Activiated Protein Kinase
AMP	:	Adenosine Mono Phosphate
ADP	:	Adenosine Di Phosphate
ATP	:	Adenosine Tri Phosphate
Cbl	:	Cobalamine
DM	:	Diabetes Mellitus
DNA	:	Deoxyribonucleic acid
EASD	:	European Association for the Study of Diabetes
FDA	:	Food and Drug Administration
HbA1c	:	Glycosylated Hemoglobin
IF	:	Intrinsic Factor
MATE	:	Multidrug and toxin extrusion
MMA	:	Methyl malonyl Acid
mTOR	:	Mammalian Target of Rapamycin

OCT	:	Organic cation transporter
OHA	:	Oral Hypoglycemic Agent
PMAT	:	Plasma Membrane Monoamine Transporter
PPI	:	Proton Pump Inhibitor
RDA	:	Recommended Dietary Allowance
RNA	:	Ribonucleic Acid
RSSDI	:	Research Society for the Study of Diabetes in India
SAM	:	S-adenosylmethionine
VLDL	:	Very Low Density Lipoprotein

ABSTRACT

BACKGROUND AND OBJECTIVES: Metformin is considered a cornerstone in the treatment of diabetes and is the most frequently prescribed first line therapy for individuals with type 2 diabetes. Various studies have reported that an average of 10-30 % of patients taking metformin for longer duration and at higher dosage have shown vitamin B12 deficiency. In order to study the prevalence of Vitamin B12 deficiency and peripheral neuropathy in patients with Type 2 Diabetes Mellitus treated with Metformin, attending outpatient department of our hospital, the present study was undertaken.

METHODS: 100 consecutive patients aged >18 years attending the outpatient of department of medicine, Jawaharlal Nehru medical college and hospital from January 2017-18, were included according to the inclusion and exclusion criteria. Relevant clinical, biochemical data was recorded. It was a cross sectional study of diabetic patients who were on Metformin. These patients were subjected to estimation of Serum Vitamin B12 levels and monofilament testing. The data obtained was analyzed & findings were correlated and tabulated to make a diagnosis of peripheral neuropathy.

RESULTS: 35% of Diabetic patients who were on Metformin for a long duration of time had Vitamin B12 deficiency which was statistically significant and clinically correlated with peripheral neuropathy.

CONCLUSION: There is higher prevalence of Vitamin B12 deficiency and clinical neuropathy with metformin use in Type 2 Diabetes Mellitus patients.

CONTENTS

LIST OF TABLES

LIST OF GRAPHS

INTRODUCTION

Diabetes mellitus is a metabolic disease involving carbohydrate, lipid, and protein metabolism. It is characterized by persistent hyperglycemia which results either due to defective insulin secretion, or resistance to its action or both. Diabetes mellitus has been known since many centuries, with descriptions been found in ancient Egyptian, Indian and Chinese medical literature, as well as, in the works of ancient Greek and Arab physicians. In the 2nd century AD Aretaeus of Cappadocia, a physician of the Greco-Roman antiquity, coined the term diabetes, which arises from the Greek verb διαβαινω (diabaino) which means I pass through, describing diabetes, the condition that the fluid runs through. In 17th century Thomas Willis, an English anatomist and physician, added the term mellitus to the disease, to describe the extremely sweet taste of the urine. 10 centuries before ,in the 7^{th} century ,Diabetes was also described by the Indian physician Sushruta mentioning the sweet urine of the disease and calling the disease "Madhumeha" because of honey like urine , but his work was unknown to the western world . In 1921, Frederick Banting and Charles Best extended Minkowski's and Mering's experiment. They isolated insulin from pancreatic islets and administrated to patients suffering from type 1 diabetes, saving thus the lives of millions and inaugurating a new era in diabetes treatment.[1]

Historical Background of Biguanides

French lilac, or goat's rue (Galega officinalis), was used as a folk remedy for diabetes in Southern and Eastern Europe during medieval times.7 In the early 20th century, the antihyperglycemic moiety in this plant, guanidine, was isolated. Frank et al.8 synthesized a guanidine compound called Synthalin in Germany and used it to treat diabetes during the 1920s.3 Homologs of guanidine (e.g., Synthalin) were used

for a short period but were hepatotoxic, and the use of these compounds all but ended with the discovery and proliferation of insulin. However, in later years, there was a resurgence in interest in the biguanides. In the 1960s and 1970s, phenformin was widely studied in the United States, while metformin was studied in France and buformin was studied in Germany. Although phenformin and buformin were used clinically, their relationship to lactic acidosis led to their withdrawal from the market in most countries.

Metformin was introduced in 1959 as an ant hyperglycemic agent but was not approved in the United States until the 1990s. Today, metformin is the only clinically significant biguanide and is the most widely used ant hyperglycemic agent in the world. Its primary mechanism of action is its ability to reduce hepatic glucose production, but it also reduces glucose via a mild increase in insulin-stimulated glucose uptake.7 This medication is generally well tolerated and is typically associated with a significant reduction in A1C levels (~ 1.5%).7

Metformin, a biguanide, is one of the commonly used oral hypoglycaemic agent[2]. It has been used for more than 50 years and was approved by the US Food and Drug Administration (FDA) in 1994[3]. Metformin is the preferred drug among type 2 diabetes patients, particularly those who are overweight & obese and having normal kidney function. Currently, many clinical practice guidelines for patients with type 2 diabetes, including the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD), and RSSDI guidelines, recommend that metformin treatment should begin at the time of diagnosis of diabetes with lifestyle modification in the absence of contraindications.

Metformin is the cornerstone medication in the management of type 2 diabetes mellitus (T2DM) with estimates that it is routinely prescribed to 120 million patients with diabetes around the world (38). Accumulating evidence from both observational and interventional studies has revealed the association between long-term use of metformin and vitamin B12 deficiency. It may be surprising knowing that the first article describing metformin associated vitamin B12 malabsorption was published in 1971 (39). While there is almost a current consensus on the medication's potential to lower vitamin B12 levels, four decades have not been sufficient to clarify other significant aspects of the topic.

It is a known fact that age and duration of diabetes can affect the vitamin B12 status of a patient. Vitamin B12 deficiency is assessed by estimating the Vitamin B12 levels (4) Low vitamin B12 level is said to occur in diabetics due to metformin therapy also. Many cross sectional studies showed chronic metformin therapy reduced vitamin B12 levels. Often the initial clinical signs are subtle in low vitamin B12. Vitamin B12 deficiency can present with anemia, peripheral neuropathy, and altered cognition. Most of the time vitamin B 12 deficiency was not thought in such clinical situation. There is no universal recommendation to supplement vitamin B12, especially in high risk populations. Studying the biochemical profile to detect vitamin B12 deficiency in these populations will provide useful data to support the need for supplementation.

OBJECTIVES

To compare the prevalence of Vitamin B12 deficiency and peripheral neuropathy in patients with Type 2 Diabetes Mellitus treated with Metformin

REVIEW OF LITERATURE

Metformin was first discovered by Sterne in the year of 1957 and was named Glucophage. It came to market in 1958 first in the United Kingdom. The drug discovered based on the herb Galego officinal is, which was used in the ancient days for reduction of blood sugar based on the component name galegine. This principle agent was first applied clinically by Muller in the year of 1927. Significant glucose lowering effect was noted in all group of patients studied. Further refining studies on this compound was done by Leclerc and they did well in increasing the safety level and making it compatible for clinical use. Later in 1957, various studies carried out in France used Metformin and showed significant decrease in blood sugar levels. In the same period, Phenformin was introduced from America, but due to increased documented cases of lactic acidosis, it was withdrawn from the market.

During 1970, Stowers and Smith established the relation between treatment with metformin and reduced vitamin B12, and estimated prevalence was stated around 30%. The prevalence varies between different studies, the ranges of incidence in such population vary by a large amount. There are varying factors influencing the risk of developing deficiency of vitamin B12 in each patient and thus it becomes mandatory to locate the key factor to reduce the compounding phenomena. Metformin is one the most commonly used anti-diabetic agent for the past few decades in the treatment of type 2 diabetes mellitus. It comes from the biguanide class of drug and is an euglycemic agent. The proposed mechanism of action of biguanides is reduction of the glucose output through the stimulation of cyclic AMP mediated protein kinase. Other mechanisms which are postulated are interference with hepatic

gluconeogenesis, decreased rate of absorption of glucose from intestine, reduced plasma glucagon level, accelerated conversion of glucose to lactate in intestinal epithelial cells, enhancement of glycolysis in peripheral tissues. Metformin also improves the lipid profile of the treated patient, by decreasing the adipose tissue mobilization from the periphery, decreasing the free fatty level in the blood, also lowers the VLDL. But the precise molecular mechanism for metformin action is not known. Recent studies show some evidence towards the action of metformin in respiratory chain complex. This interfere with the mitochondrial respiratory cycle.

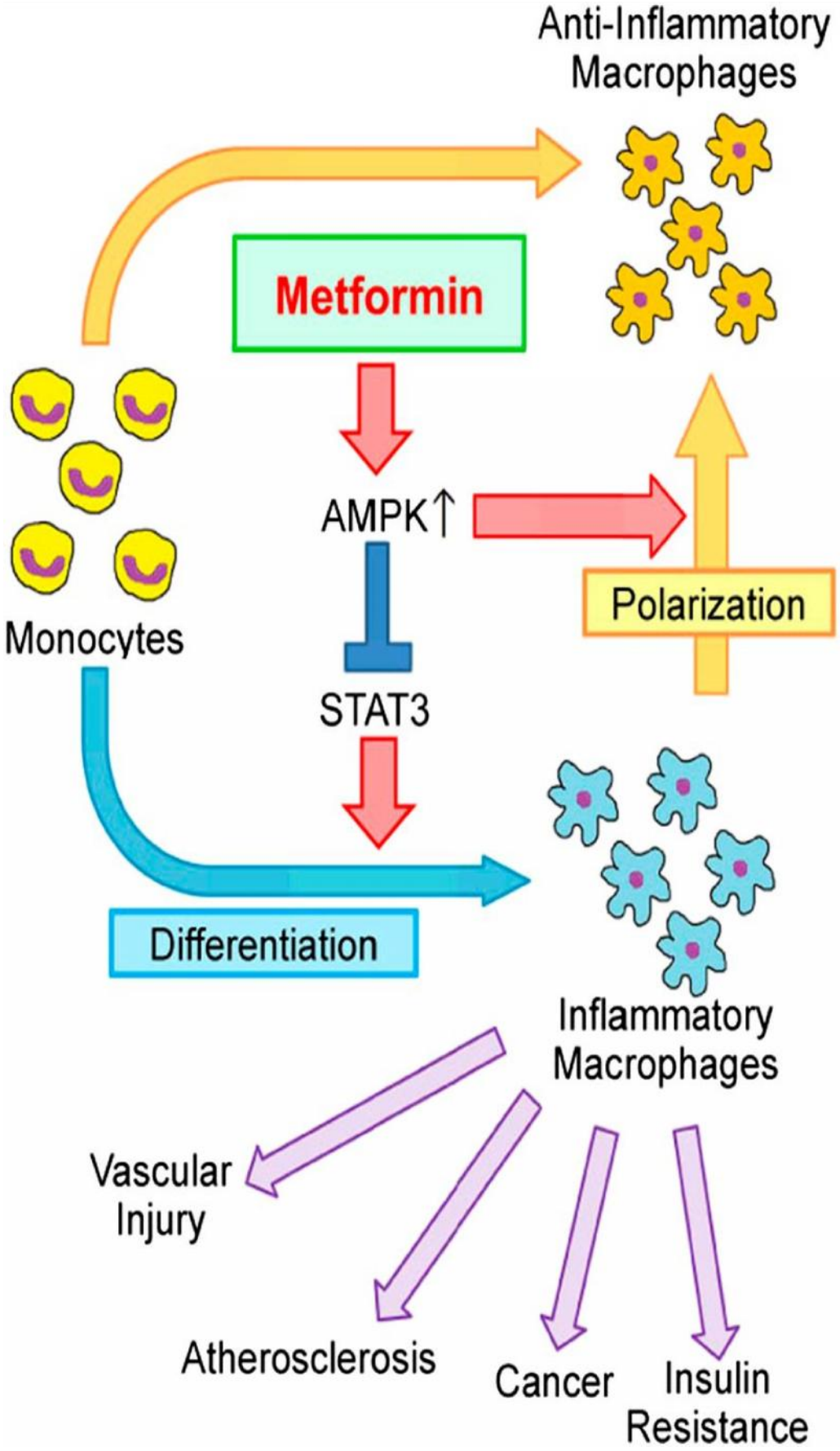
In the UKPDS study, Metformin showed to decrease the death due to diabetes such as stroke and myocardial infarction. Among the best known effects of metformin are the increased sensitivity of insulin by increasing the peripheral glucose usage and decreased hepatic glucose output and improved tyrosine kinase activity(6). Metformin prevents the cardiovascular mortality and morbidity in type 2 diabetic patients(5). Also it is weight neutral and associated with very low hypoglycemic episodes. Hence it is being considered first in treating the type 2 diabetic patients and one of the most prescribed drug too (7).

Targeting of AMPK

Cyclic AMP mediated protein kinase is a vital member of AMPK/SNF1 family. This kinase family is seen in eukaryotes, including plants, mammals, yeasts, Drosophila. It is a heterotrimeric subunit with α, β, ϒ subunits. The principal subunit is the α subunit. The α subunit turnover decides the action of the enzyme. The β/ϒ subunit regulates the turnover and action of enzymes. The enzyme is easily activated by AMP and inhibited in abundance of ATP. This

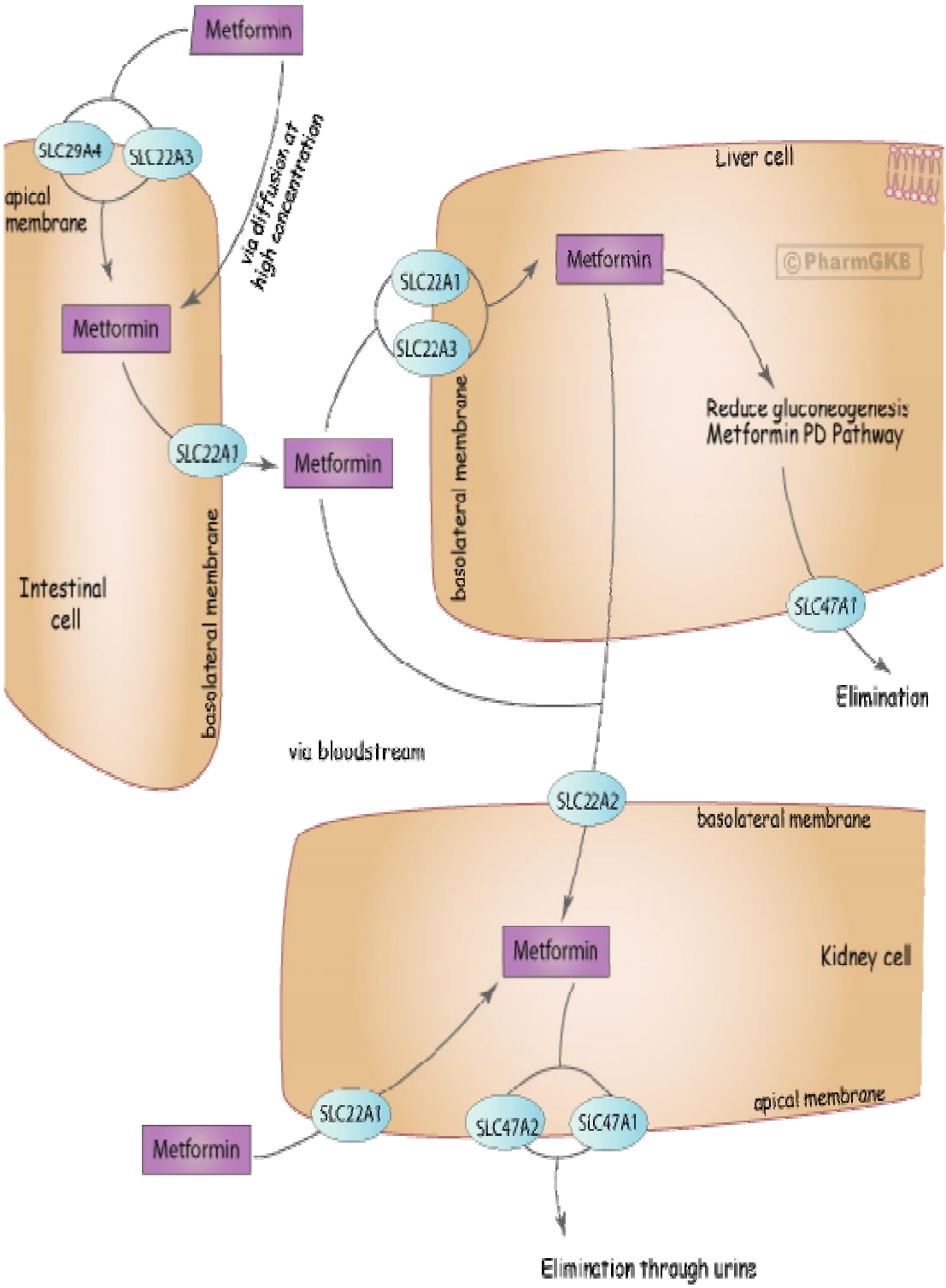
ADP to ATP cycle acts as a metabolic switch between synthesis and utilization of ATP. Creatine phosphate is a negative allosteric inhibitor of the kinase. Thus the AMPK activating effect of the

Metformin is measured by alteration in the cellular adenine nucleotide pool, which manifest as decreased cellular respiration. This leads to the various pleiotropic benefits of metformin.


Anti-Inflammatory Macrophages
Metformin
AMPK↑
Polarization
Monocytes
STAT3
Differentiation
Inflammatory Macrophages
Vascular Injury
Atherosclerosis
Cancer
Insulin Resistance

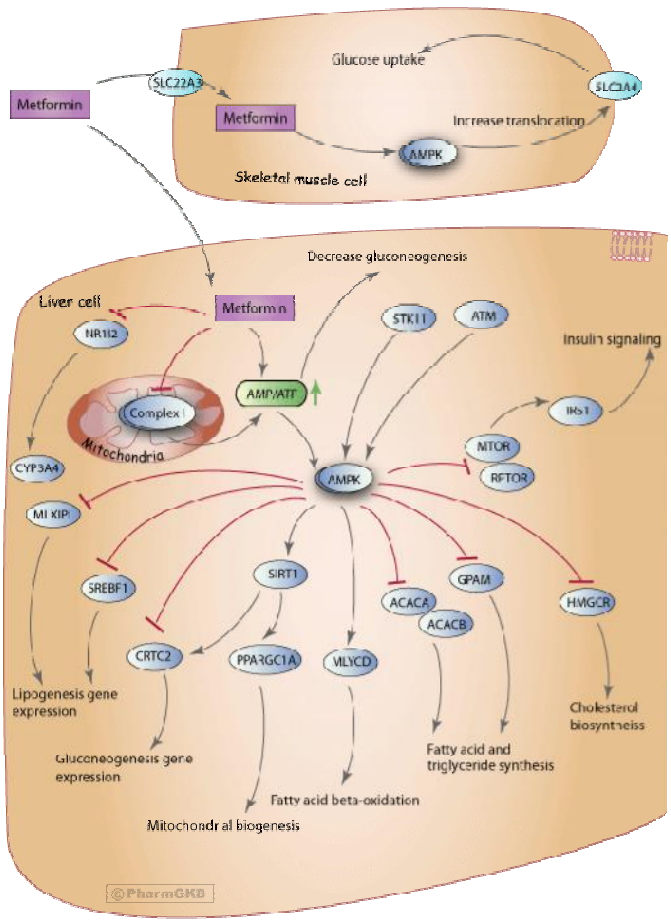
PHARMACOKINETICS

The main mode of elimination of metformin is via kidney. Tubular excretion is predominant in renal system. The evidence for liver mediated removal of metformin in humans is less. Intestinal uptake is mediated by plasma membrane monoamine transporter (PMAT/SLC29A4) and OCT3 (Organic cation transporter). Transfer of metformin from enterocytes to interstitial fluid is done by OCT1 (SLC22A1). OCT1 and OCT3 plays the similar role in liver in uptake of metformin, where it inhibits gluconeogenesis and decreases glucose output. In kidney, transfer of metformin from circulation into tubular cells is mediated by OCT2(SLC22A2). Elimination from cell into the tubule is done by MATE1 (Multidrug and toxin extrusion – 1) (SLC47A1) and MATE2-K(SLC47A2). Liver doesn't take part in excreting metformin. Hence drug interactions can occur due to polymorphisms in drug transporters. For example PPIs (Proton pump inhibitors) inhibits Organic cation transporters.


Metformin
SLC29A4
SLC22A3
apical membrane
via diffusion at high concentration
Metformin
SLC22A1
Metformin
Intestinal cell
basolateral membrane
Liver cell
SLC22A1
SLC22A3
Metformin
©PharmGKB
basolateral membrane
Reduce gluconeogenesis
Metformin PD Pathway
SLC47A1
Elimination
via bloodstream
SLC22A2
basolateral membrane
Metformin
Kidney cell
SLC22A1
SLC47A2
SLC47A1
apical membrane
Metformin
Elimination through urine

PHARMACODYNAMICS

Metformin exerts its effect on fasting and prandial sugar level by various mechanisms discussed before. It acts by inhibiting gluconeogenesis, increasing fatty acid oxidation and decreased lipid synthesis. So it favours both the glycemic and lipid profile of the patient. The postulated mode of action of metformin as discussed before is through the AMPK pathway. The compiled effect of AMPK stimulation in the liver includes the activation of fatty acid oxidation with inhibition of cholesterol and triglyceride synthesis. Peripheral effects include the stimulation of fatty acid oxidation and glucose uptake in skeletal muscle as well as a systemic increase in insulin sensitivity. However, the role of metformin in insulin mediated glucose uptake has been debated.



ADVERSE EFFECTS

Nausea, vomiting, stomach upset, diarrhoea, weakness, or a metallic taste in the mouth may occur. Also there are some other disadvantages too. It can cause gastrointestinal problems, like discomfort and diarrhoea which may cause the patient to discontinue the drug. Other important treatable clinical situations are anemia, peripheral neuropathy in the setting of low vitamin B12 caused by chronic metformin usage in these patients (7).

Lactic acidosis occurs in drug overdose, liver, renal failure, any type of shock, dehydration, alcohol intoxication. Not noted in regular patients. Hypoglycemia due to metformin perse is not documented well. But it can occur when it is combined with other OHA (Oral hypoglycemic agents). This drug is found to be one of the cause of vitamin B12 deficiency. Among all the patients undergoing therapy with metformin around 10% - 30% is developing biochemical deficiency. This can be asymptomatic or with biochemical deficiency alone or symptomatic deficiency.

Another study showed a 22% prevalence of B12 deficiency in type 2 DM on metformin therapy (8). The mechanism for vitamin B12 deficiency induced by metformin therapy is not yet precisely defined. Studies during 1970s by Stovers and smith showed that the deficiency is not only due to prolonged 30 duration of therapy with metformin but also due to various other factors like diet, duration of diabetes, overall dosage used in each patient. Yet metformin being used as a first line drug in all type 2 diabetics it is essential to screen all the patients annually for their deficiency. Recent evidence related to this cause is due to interaction of metformin with the calcium channel and impairment of its activity. Soon after stopping metformin a detectable reduction in vitamin B12 can be noted, which can occur

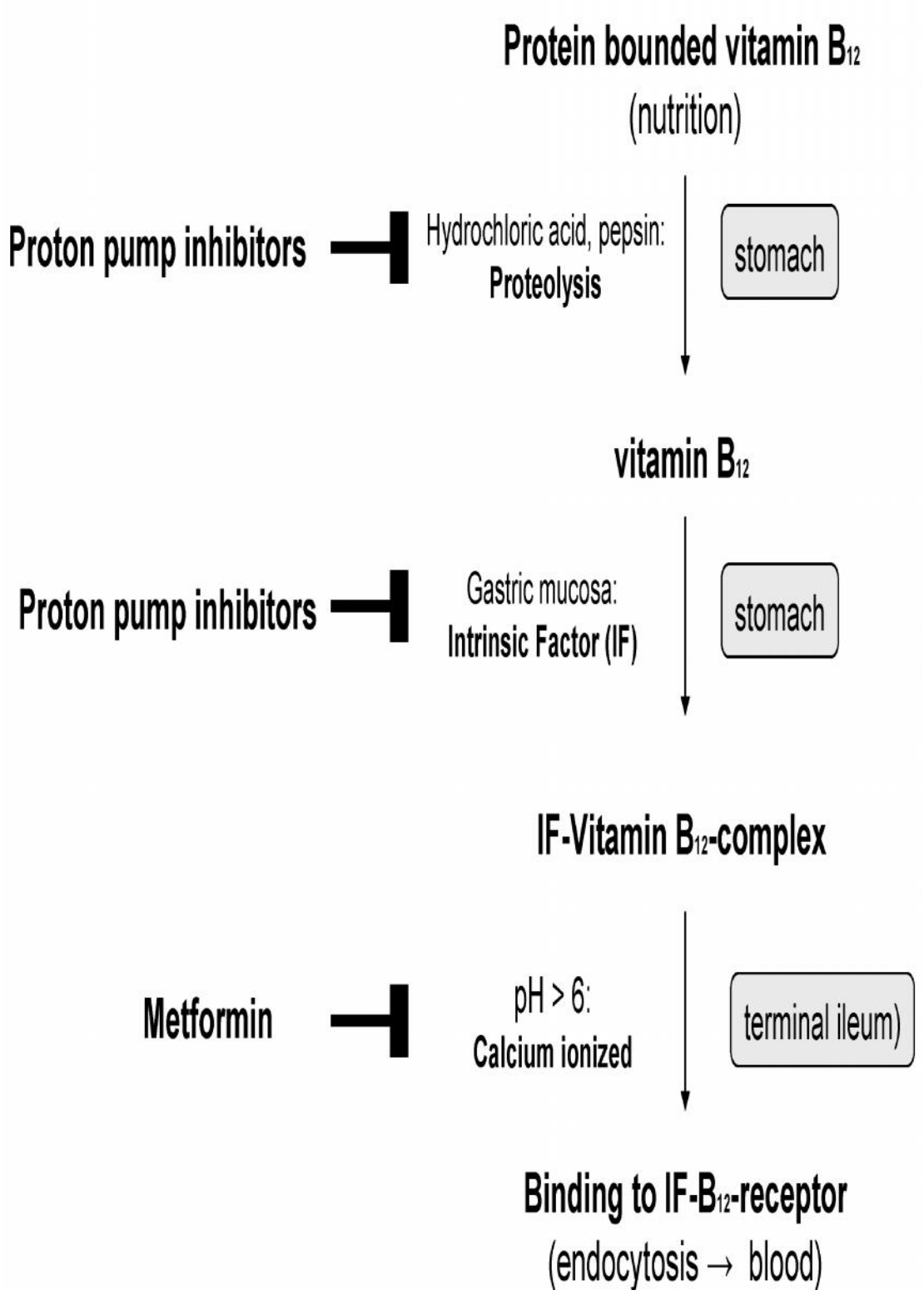
within 5 months. Yet, most of the patients are asymptomatic. For a patient to become symptomatic it may take atleast 5 to 10 years.

For otherwise it is easy to miss a case of macrocytic anemia with or without signs of subacute combined regeneration of cord. So it is prudent to annually screen all patients who are on metformin therapy.The mechanisms causing the deficiency of vitamin B12 are controversial and were subjected to various studies(10). The postulated mechanisms are competitive inactivation and inhibition of cobalamin, individual variation in intrinsic factor level, gastrointestinal motility disorders, alteration in bowel bacterial flora, the inhibition at or alteration of the cubilin receptors(10). More appropriate explanation could be antagonism of the calcium mediated transport in the terminal ileum of the B12 31 complex.

This is substantiatedby calcium supplementation improving the vitamin B 12 level in these patients(9).The cause of vitamin B12 deficiency with metformin is due to defective absorption of vitamin B12 at the terminal ileum. First it was believed that metformin caused modified proliferation of bacteria in the small bowel either due to intestinal dysmotility or an elevated intestinal glucose level. The current, appropriate and more suitable explanation for metformin causing vitamin B12 malabsorption and deficiency is that metformin has the effect on calcium mediated membrane action in the terminal ileum.

Absorption of the vitamin B12-intrinsic factor complex is calcium dependent and metformin interferes with this absorption. In support of this hypothesis, it is evident that dietary calcium supplementation brings back metformin-induced vitamin B12 malabsorption. In the view of varying pathogenic causes of this deficiency there is no absolute mode of treatment in these patients.

The most common method of treatment used in these patients could be using intramuscular injection of Hydroxycobalamin as a loading dose, followed up with oral supplementation. But as the main interference occurs in the absorption process, it is wise to administer the sublingual form of vitamin B12. So parenteral followed by sublingual supplementation is better than oral supplementation(11). But there are no studies that has clearly assessed this however. Intramuscular injections of vitamin B12 were proved superior than oral supplementation in studies with patients who have undergone gastric bypass surgery. But the relevance of sublingual group was not established in that also(12).


Protein bounded vitamin B12
(nutrition)
Proton pump inhibitors
Hydrochloric acid, pepsin:
Proteolysis
stomach
vitamin B12
Proton pump inhibitors
Gastric mucosa:
Intrinsic Factor (IF)
stomach
IF-Vitamin B12-complex
Metformin
pH > 6:
Calcium ionized
terminal ileum)
Binding to IF-B12-receptor
(endocytosis → blood)

The effect of metformin on vitamin B12 status is an intriguing topic given that many studies assumed that metformin treatment is associated (15,16) or causally related to vitamin B12 deficiency (17 18). The association between low serum B12 and metformin treatment was confirmed in a recent study on 1621 type 2 diabetics from the National Health and Nutrition Examination Survey (1999e 2006) (16). Moreover, in a 3-month trial, metformin treatment caused significant decreases of total vitamin B12 (by 24%) and holohaptocorrin concentrations in plasma (vitamin B12-bound to haptocorrin) (by 19%) (19). Metformin caused also a slight reduction of plasma holoTC concentrations (by 14%) (19).

Plasma MMA was not changed during this short period of metformin treatment. The study confirms a reduction in serum B12, but because of the short duration, changes in MMA cannot be excluded in long-term studies. One early study suggested that metformin can inhibit the intestinal absorption of vitamin B12 (17). An effect of metformin on calcium ion homeostasis has been suggested (17). Oral calcium supplementation enhanced vitamin B12 absorption in patients taking metformin. However, because the effect of oral calcium alone was not tested in individuals not taking metformin, the study lacks a control group and an independent effect of calcium on vitamin B12 absorption cannot be excluded.

Vitamin B12-intrinsic factor complex uptake by ileal receptors is mediated by a process dependent on calcium availability. This calcium dependent uptake action is deranged by Metformin. The malabsorption is said to be corrected by calcium supplementation. But there is no parallel increase in biochemical B12 level. The effect of calcium was not researched independently without metformin, and therefore it is not known whether calcium increases vitamin B12 absorption or it corrects metformin induced deficiency. Calcium is said to increase the cardiac mortality and morbidity in

already predisposed diabetic patients, inspite of improving the vitamin B12 absorption.

Also, there can be normal serum level of vitamin B12 with abnormal metabolites of vitamin B12 pathway within the cell in diabetic patients. Analysis of RBC extracts and metabolite estimation in it (methylmallonic acid) proves this concept. The metabolite level is low within the cell, but the extracellular level of metabolites is elevated in diabetics not using Metformin. So there is elevated vitamin B12 level in diabetics with deficiency inside the cell. This is manifested as increased serum homocysteine and this acts as a marker of vitamin B12 resistance in diabetics not taking metformin.

There is no recent evidence to suggest that the treatment with metformin in type 2 diabetics will unmask the vitamin B12 metabolic status of the patient. By altering the metabolic marker levels within the cell, it improves the cobalamin metabolic pathways (13). A study which was done by Greibi Etal was aimed at detecting the different available absorption pathways for vitamin B12 in presence of metformin. Rats were used as study population. They were given S.C injection of metformin and saline for subjects and control groups respectively for a period of three weeks. Following this procedure the level and the quantity of vitamin B12 was assessed and the regions of distribution was detected using radioisotope B12.

The results were analysed and it showed similar patterns with other studies such that the treatment with metformin decreased vitamin B12 level. The results were significant as the 3 week exposure to metformin reduced vitamin B12 in 22% of the rats. But, in this study, the exact mechanism causing this reduction was not evaluated completely. Regionalization of the vitamin B12 level in the subjects was done and it showed increased concentration of vitamin in the liver. In both control and subject

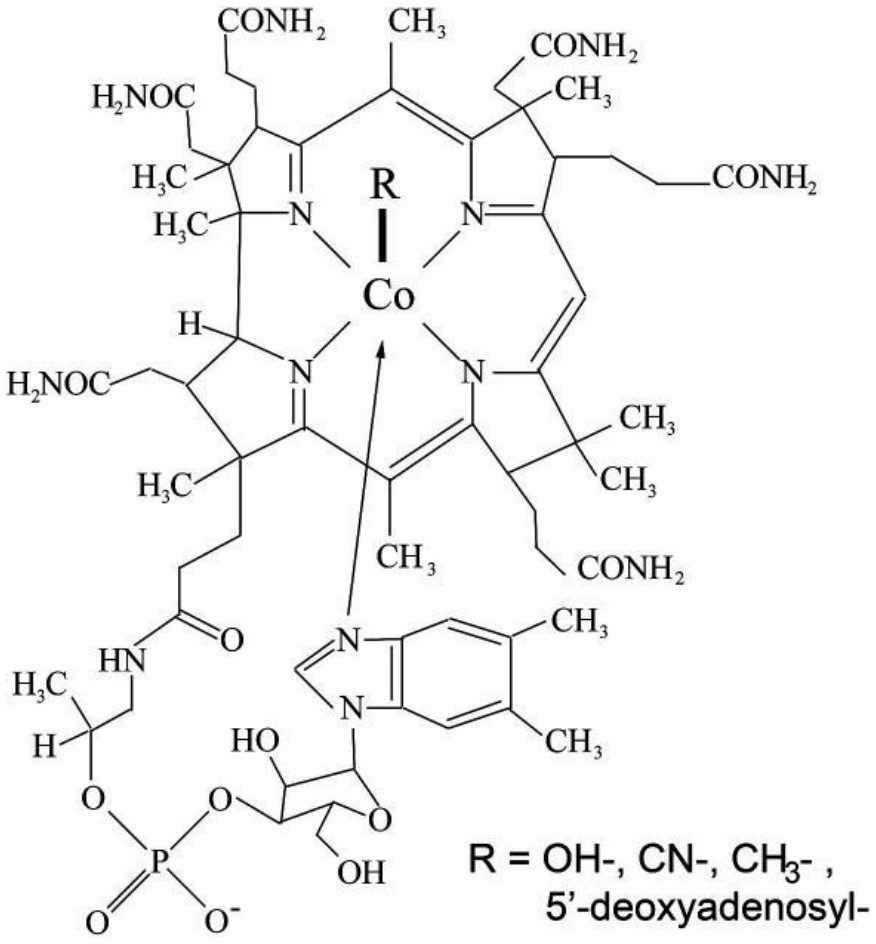
rats, the total absorbed Vitamin B12 level was similar. This suggests that there are no absorption defects induced by Metformin, rather the reduction in level is due to redistribution.

Kidneys of the subject rats treated with metformin showed 36% reduction in vitamin B12 level than control rats treated with saline. This also reflects the redistribution of vitamin B12 to liver. But the shortcoming of the study is we cannot translate the exact findings into the humans because the pathogenesis of diabetes varies highly between two different species. As we have seen before, if the diabetic patients have B12 resistance at cellular level this study did not provide a solution to this resistance. Yet the crucial outcome of the study is the mode of administration that is used. It is a gastric bypass system.

Hence sublingual, subcutaneous or intramuscular administration will mask the malabsorption produced by metformin interaction at the ileal level or at the small bowel. Metformin treatment and its outcomes have resulted in useful data in decreasing the mortality and morbidity of different carcinomas in further studies (14). This is attributed to the glycemic control caused by metformin which increases glucose utilization by peripheral large tissues like muscles. The proliferation of cancerous cells is thus reduced due to the limited availability of glucose. Some investigations showed that there are some alternate mechanisms for metformin like inhibition of mTOR and AMPK or LKB1 axis in the cancer cells. These pathways are concerned with energy production and protein synthesis inside the cells. A meta-analysis showed reduction in the risk of developing hepatic, breast, colon and pancreatic tumors by 78%, 6%, 23%, 46% respectively (14).

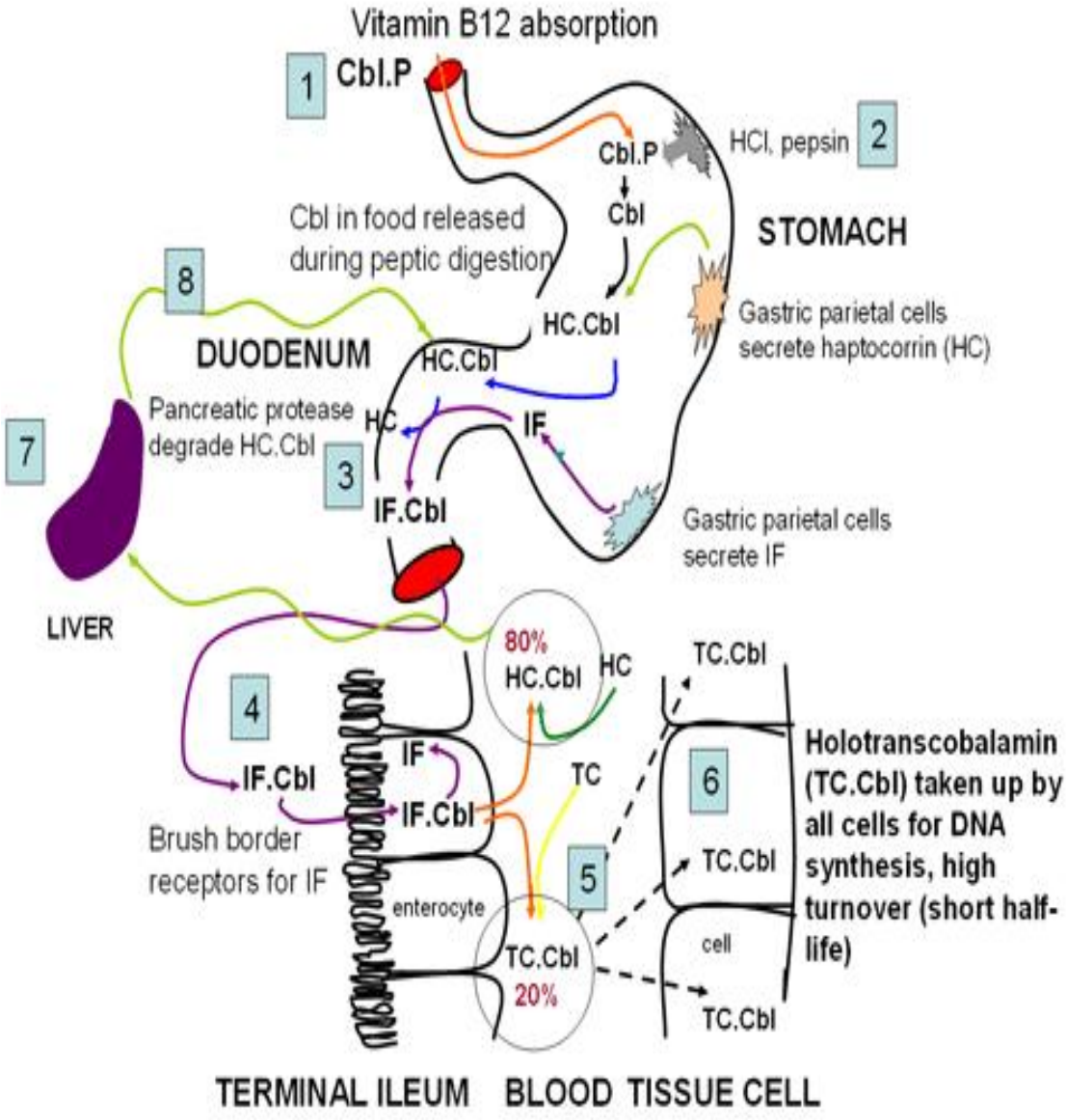
VITAMIN B 12

Vitamin B12 which is also called Cobalamin, is a member of B group of vitamins. The biochemical active form of vitamin is said to be in different forms depends on method of synthesis. It is said to play a vital role in blood, brain, and nerve function. Meat and eggs are the richest sources of vitamin B12. Milk, fortified cereals, fish are some of the other rich sources of vitamin B12. So, it goes without saying that vegetarians are at a risk of developing vitamin B12 deficiency. The daily required adult dose is around 1-3 microgram, which is only 0.1% of total body store. The total body stores are of 2-3 milligram. So the total body store is sufficient almost for half a decade, in the absence of external supplies.



DIETARY RECOMMENDED INTAKE

Recommended Dietary Allowance (RDA) for Vitamin B12			
Life Stage	**Age**	**Males (mcg/day)**	**Females (mcg/day)**
Infants	0-6 months	0.4 (AI)	0.4 (AI)
Infants	7-12 months	0.5 (AI)	0.5 (AI)
Children	1-3 years	0.9	0.9
Children	4-8 years	1.2	1.2
Children	9-13 years	1.8	1.8
Adolescents	14-18 years	2.4	2.4
Adults	19-50 years	2.4	2.4
Adults	51 years and older	2.4	2.4
Pregnancy	all ages	.	2.6
Breast-feeding	all ages	.	2.8


Vitamin B12 absorption
1
Cbl.P
Cbl.P
HCl, pepsin
2
Cbl
STOMACH
Cbl in food released
during peptic digestion
8
HC.Cbl
Gastric parietal cells
secrete haptocorrin (HC)
DUODENUM
HC.Cbl
Pancreatic protease
degrade HC.Cbl
HC
IF
7
3
IF.Cbl
Gastric parietal cells
secrete IF
LIVER
80%
HC.Cbl
HC
TC.Cbl
4
IF
TC
6
IF.Cbl
IF.Cbl
Holotranscobalamin
(TC.Cbl) taken up by
all cells for DNA
synthesis, high
turnover (short half-
life)
Brush border
receptors for IF
5
TC.Cbl
enterocyte
cell
TC.Cbl
20%
TC.Cbl
TERMINAL ILEUM
BLOOD
TISSUE CELL

ABSORPTION AND TRANSPORT

Vitamin B12 is absorbed by basically two mechanisms, active and passive absorption. The passive process occurs through small intestinal mucosa. But this process is highly inefficient and extremely fast. Thus the normal physiological absorption process occurs by active diffusion at the level of terminal ileum in the presence of gastric intrinsic factor. Cobalamin which is present in the diet is separated from its protein complexes by the action of gastric and small intestinal enzymes. After this, it binds to the R- binder with which it is transported to the terminal ileum. Stomach parietal cells then secrete the intrinsic factor. It combines with cobalamin and forms IFCobalamin complexes and this gets transported to the terminal ileum. This complex attaches itself to receptor called as cubilin. Cubilin is an endocytic receptor protein which helps in the translocation of complex into the enterocytes, where the intrinsic factor is destroyed. With a lag period of six hours, the cobalamin appears in the portal circulation combined with transcobalamin II. Large amount of cobalamin undergoes enterohepatic circulation from the denuded intestinal epithelial cells. Hence there is a higher risk of vitamin B12 deficiency in patients with malabsorption than in vegetarians. The transport of cobalamin occurs in one to one molecule manner. Transcobalamin I is formed from the granules of neutrophils. It has no primary role in transport of cobalamin into the tissues. The major transport protein is transcobalamin II. It is produced from the liver endothelial cells, ileal enterocytes and macrophages. This takes up cobalamin to areas of high demand like marrow, placenta.

The different forms Vitamin B12 are playing an important role in vital physiological chemical reactions in the body. Adenosylcobalamin is the coenzyme for, the methymalonyl-CoA conversion to succinyl- CoA, where methylmalonyl-CoA

mutase acts as enzyme. Methylcobalamin is the co-enzyme in the conversion of homocysteine to methionine, where transfer of a methyl group occurs. The methyl group is donated by methylcobalamin. This methyl transfer is catalyzed by methionine synthetase. In the subsequent reactions methyl cobalamin is reproduced by one carbon transfer mechanism with the contribution from folate. SAM(S-Adenosyl methionine) is a derivative of methionine, where the methyl transfer to methionine has taken place. S-Adenosyl methionine is useful for life molecule synthesis like DNA and RNA, neuro transmitter formation and methylation that occurs in myelin synthesis (20). In the deficiency of vitamin B12, the generation of S-Adenosyl methionine is hampered which ultimately predisposes the patient for defective myelination and nucleotide synthesis. This is done by methyl transfer that occurs from SAM. The methionine synthase action needs a balance of carbon molecules which directs towards synthesis of nucleotides or the methylation of substrate compounds by S-adenosylmethionine (SAM).

The role of Cbl in this function may alter some epigenetic functions of an individual through specific methylation of DNA, RNA, histone and gene expression which can result in different physiological differences, depending on the site of methylation(21) The clinical picture in a vitamin B12 deficiency patient is very different to differentiate as the symptoms of early disease is highly nonspecific. Most of the patients being of elderly age group and having long term diabetic history and they are predisposed to multiple micronutrient deficiency. Some of the most common presentations are easy fatigability or “general tiredness”. This shows the role of vitamin B12 in the regulation of sleep cycle. The two other routinely noted complications in these patients are burning sensation, numbness of feet and in very deficient cases,anemia.Both conditions overlap with the chronic conditions these

patients may be having, yet they are one of the most important treatable conditions. This easy fatigability can be due to hypoglycemia due to drugs, or due to hyperglycemia, or the dietary habits of the patient like taking low carbohydrate diet. The peripheral nerve involvement can occur in the diabetic patients itself. So these are difficult to differentiate in the first clinical instance.

The currently used biochemical markers for diagnosis of Vitamin B12 deficiency are under scanner and controversy. The routinely used serum B12 assay is said to be not sufficient for the diagnosis of vitamin B12 deficiency (13). The use of vitamin B12 in the diagnosis of this depends on the range of values where level under 149 pmol/L is deficient status, with low or borderline levels being in the level of 148-220 pmol/L. Normal ranges of Vitamin B12range between 220- 800 pmol/L. Values highly exceeding this values are to be seen with suspicion, as it may be associated with myeloproliferative status of these patients(22). The estimation of the metabolite biochemical markers such as methyl malonic acid (MMA) and total homocysteine (tHcy) are said to be more appropriate for a correct diagnosis of deficiency with levels >0.28 µmol/L and >15 µmol/Lrespectively. These two are the markers of vitamin B12 deficiency. But when comparing the cost of both methods, estimation of MMA and tHcy is very costlier (22).

DIABETES MELLITUS

Definition: It is an endocrine disorder which is characterized by polyuria, polyphagia, polydipsia clinically and features of hyperglycemia biochemically. It occurs due to absolute or relative insulin deficiency. Primarily it is divided into type 1 and type 2 diabetes mellitus.

Type 2 diabetes mellitus occurring in a middle aged to elderly people, is due to relative insulin deficiency and also insulin resistance.

SYMPTOMATOLOGY

Diagnosis of diabetes mellitus depends on medical history and few simple biochemical tests. The hyperglycemic triad namely polyuria, polyphagia, polydipsia is an indirect evidence. Other associated features predominate in specific forms of diabetes. For example features of malabsorption and acute abdomen occurring in cases of pancreatitis. Most of the time the disease is asymptomatic, and it is identified in screening the patients for some other illness.

Generalized symptoms like weight loss, emaciation, paresthesias, acidotic breathing, recurrent vomiting, malaise, ocular disturbances, balanoposthitis, recurrent respiratory, urinary tract infections, dry tongue, glossitis, tuberculosis, skin infections, poor wound healing, non healing ulcers, typical infections like sinonasal fungal infections all may indicate the underlying cause as diabetes mellitus. There can be acute presentations like ketoacidosis, diabetic coma, seizures.

The prevalence of diabetes has increased in the last two decades, presumably due to changing pattern of life style , changing dietary habits , increased consumption of refined sugar, high trans fatty acid intake, reduced physical activity etc. According

to CDC estimation, the countries with maximum number of diabetics are China, India, United states, Brazil.

Diabetes mellitus is the reason behind most of the mortality that occurs. But the background evidence of diabetes being the cause of those deaths were underreported. Diabetes will be the cause of 11% of total medical expenditures in few decades worldwide.

CLASSIFICATION OF DIABETES (AMERICAN DIABETES ASSOCIATION)

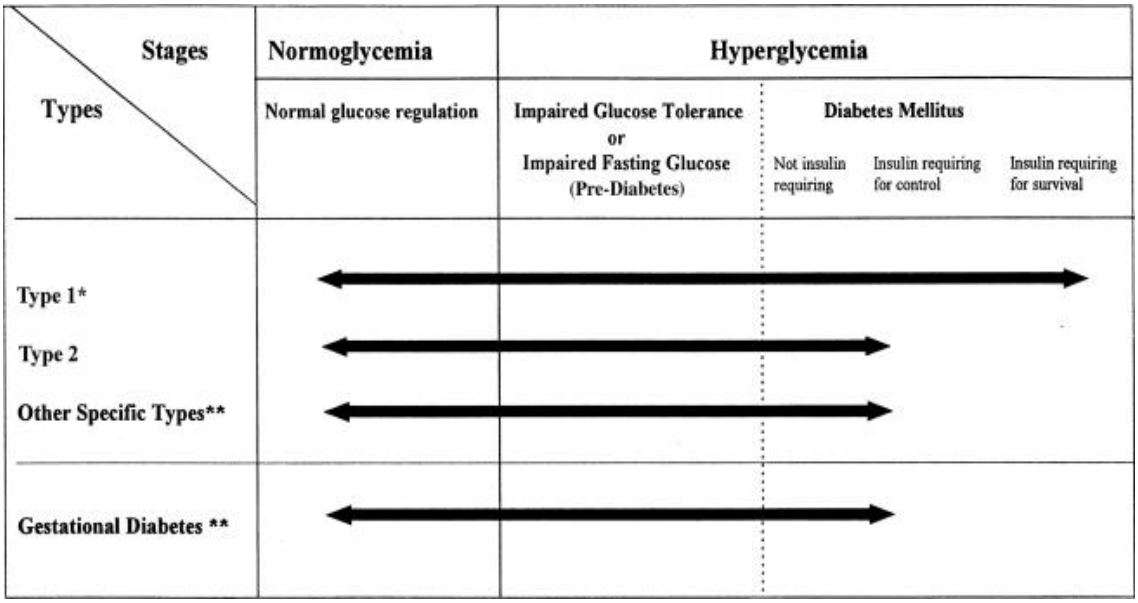


Table 1

Etiologic classification of diabetes mellitus (AMERICAN DIABETES ASSOCIATION)

I. Type 1 diabetes (β-cell destruction, usually leading to absolute insulin deficiency)

A. Immune mediated

B. Idiopathic

II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)

III. Other specific types

A. Genetic defects of β-cell function

1. Chromosome 12, HNF-1α (MODY3)
2. Chromosome 7, glucokinase (MODY2)
3. Chromosome 20, HNF-4α (MODY1)
4. Chromosome 13, insulin promoter factor-1 (IPF-1; MODY4)
5. Chromosome 17, HNF-1β (MODY5)
6. Chromosome 2, *NeuroD1* (MODY6)
7. Mitochondrial DNA
8. Others

B. Genetic defects in insulin action

1. Type A insulin resistance
2. Leprechaunism
3. Rabson-Mendenhall syndrome

4. Lipoatrophic diabetes
5. Others

C. Diseases of the exocrine pancreas

1. Pancreatitis
2. Trauma/pancreatectomy
3. Neoplasia
4. Cystic fibrosis
5. Hemochromatosis
6. Fibrocalculous pancreatopathy
7. Others

D. Endocrinopathies

1. Acromegaly
2. Cushing's syndrome
3. Glucagonoma
4. Pheochromocytoma
5. Hyperthyroidism
6. Somatostatinoma
7. Aldosteronoma
8. Others

E. Drug or chemical induced

1. Vacor
2. Pentamidine
3. Nicotinic acid
4. Glucocorticoids

5. Thyroid hormone
6. Diazoxide
7. β-adrenergic agonists
8. Thiazides
9. Dilantin
10. γ-Interferon
11. Others

F. Infections

1. Congenital rubella
2. Cytomegalovirus
3. Others

G. Uncommon forms of immune-mediated diabetes

1. "Stiff-man" syndrome
2. Anti-insulin receptor antibodies
3. Others

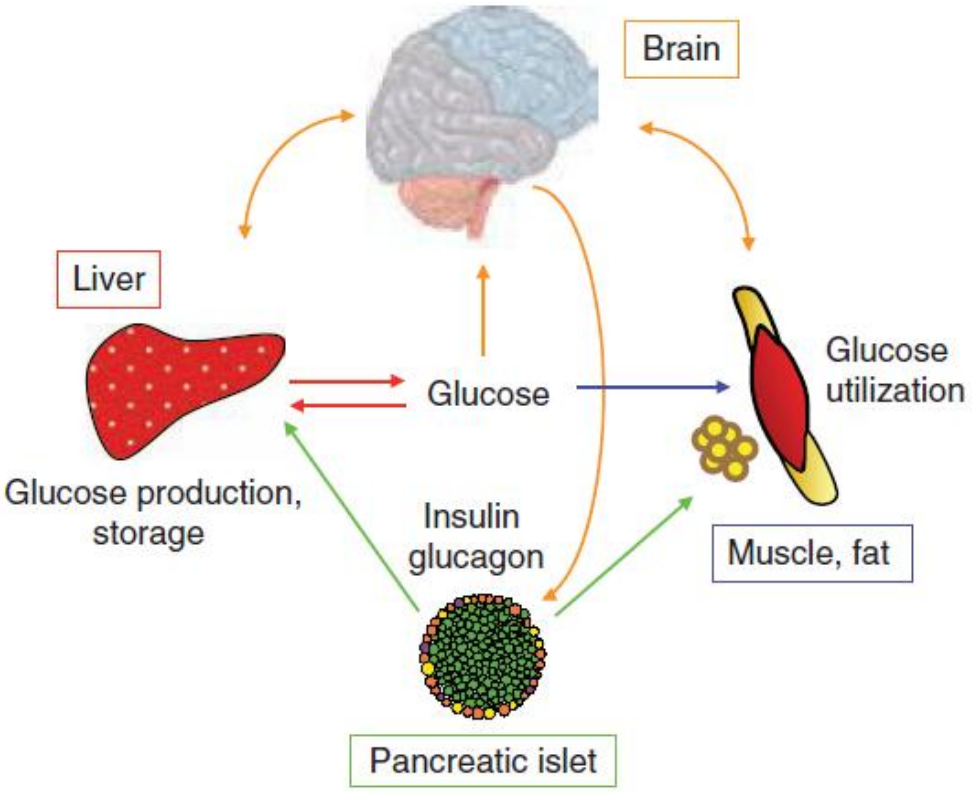
H. Other genetic syndromes sometimes associated with diabetes

1. Down syndrome
2. Klinefelter syndrome
3. Turner syndrome
4. Wolfram syndrome
5. Friedreich ataxia
6. Huntington chorea
7. Laurence-Moon-Biedl syndrome
8. Myotonic dystrophy

9. Porphyria
10. Prader-Willi syndrome
11. Others

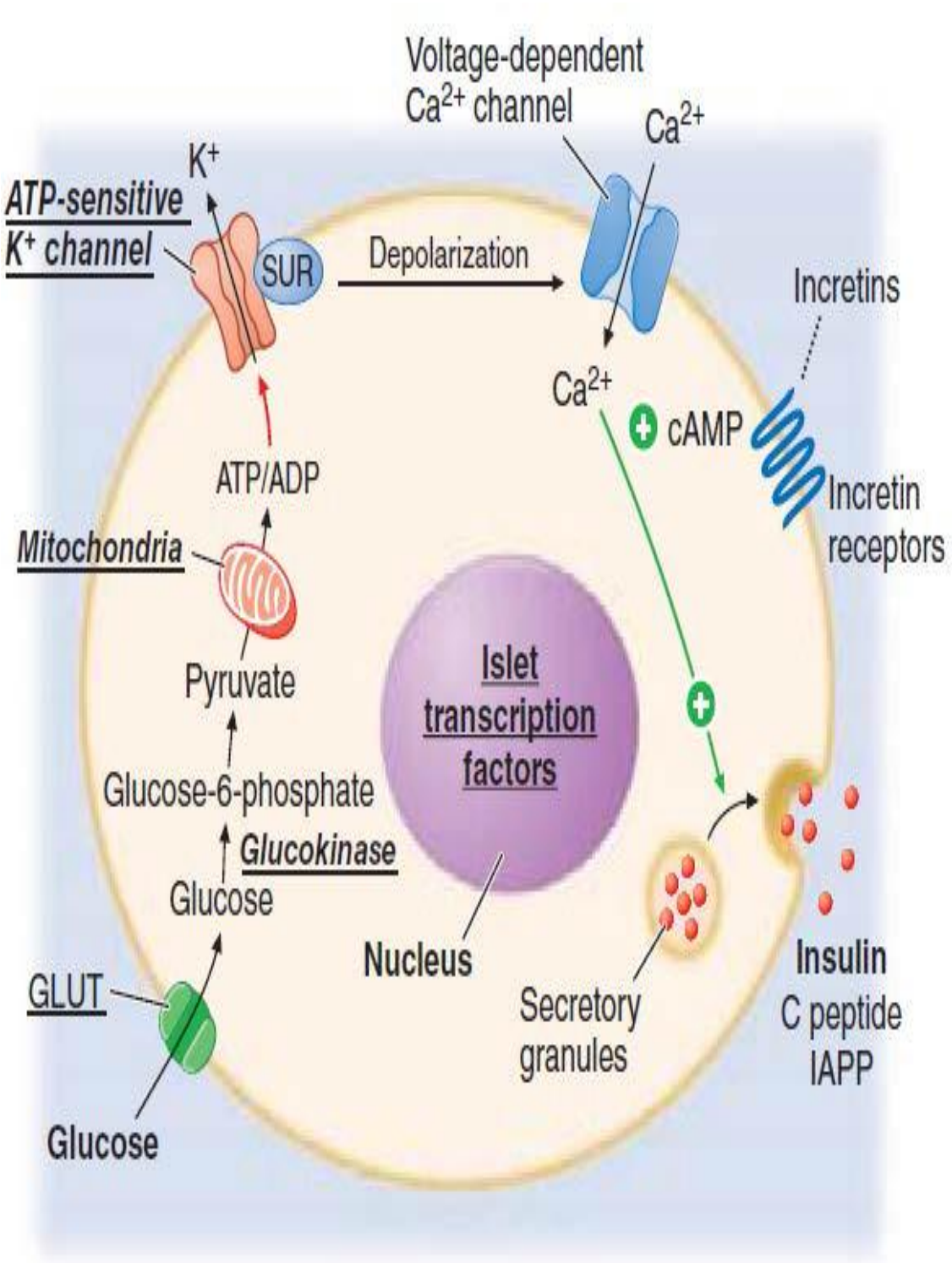
IV. Gestational diabetes mellitus

GLUCOSE METABOLISM

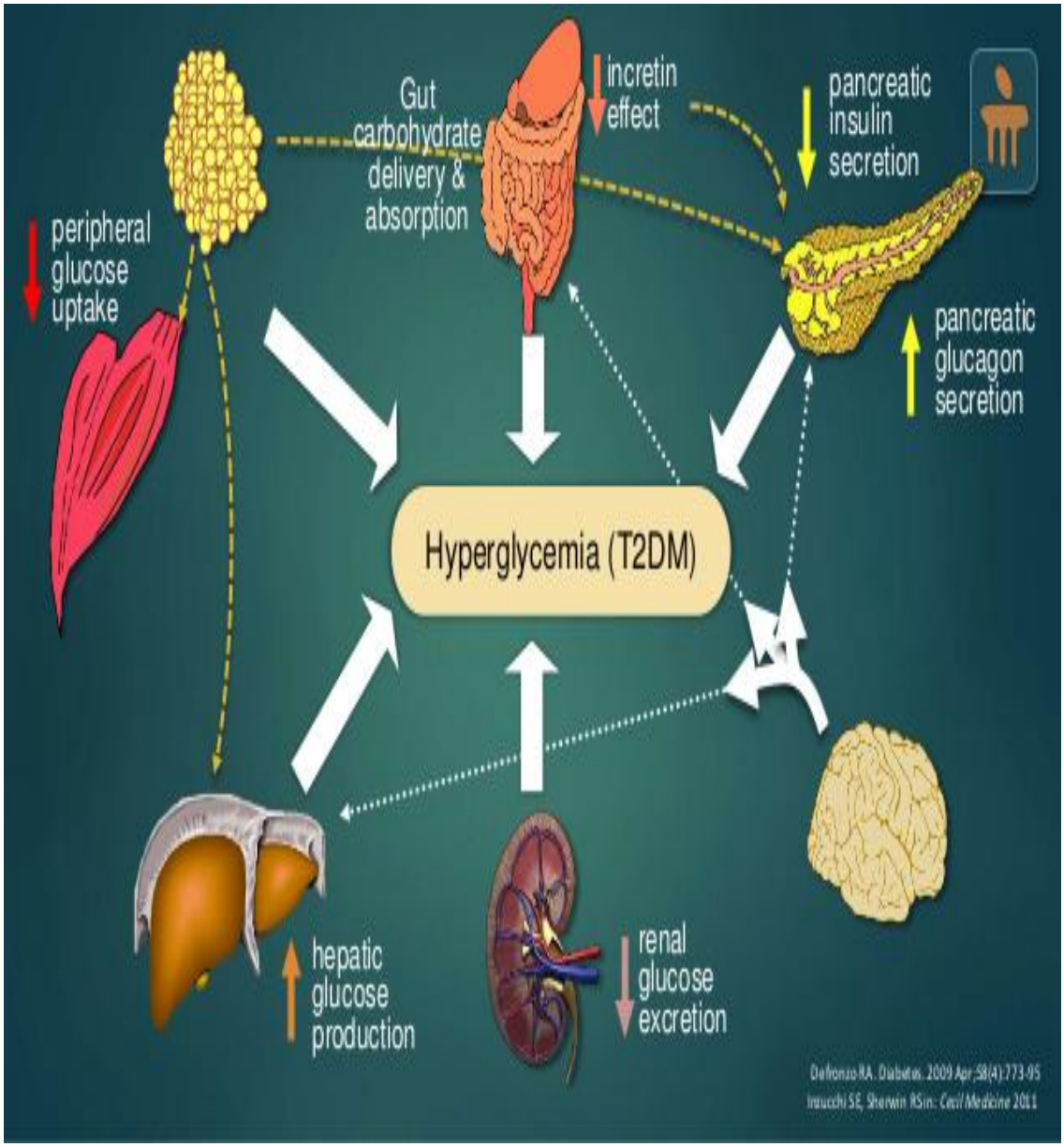


The overall glucose homeostasis is based on the balance between the liver glucose output and the peripheral utilization in the muscle, adipose tissue etc. The primary hormone involved in this homeostasis is Insulin. Other hormones, lipid derived factors, neural mechanisms are also involved in the glucose homeostasis.

INSULIN PRODUCTION AND SECRETION



PATHOPHYSIOLOGY OF TYPE 2 DM



PERIPHERAL NEUROPATHY

The prevalence of peripheral neuropathy in the general population is 2.4% and it increases with age to 8% in those older than 55 years(23)(24). Common causes of peripheral neuropathy include diabetes mellitus, human immunodeficiency virus infection, and dysproteinemic disorders and in those receiving chemotherapy. Annual screening for peripheral neuropathy is recommended especially in diabetic patients(25)(26) .Most recommendations for office screening for neuropathy have suggested light touch perception to a 10-g Semmes-Weinstein monofilament, vibration testing with a 128-Hz tuning fork, superficial pain (pinprick) perception, or testing of ankle deep tendon reflexes(27-31)

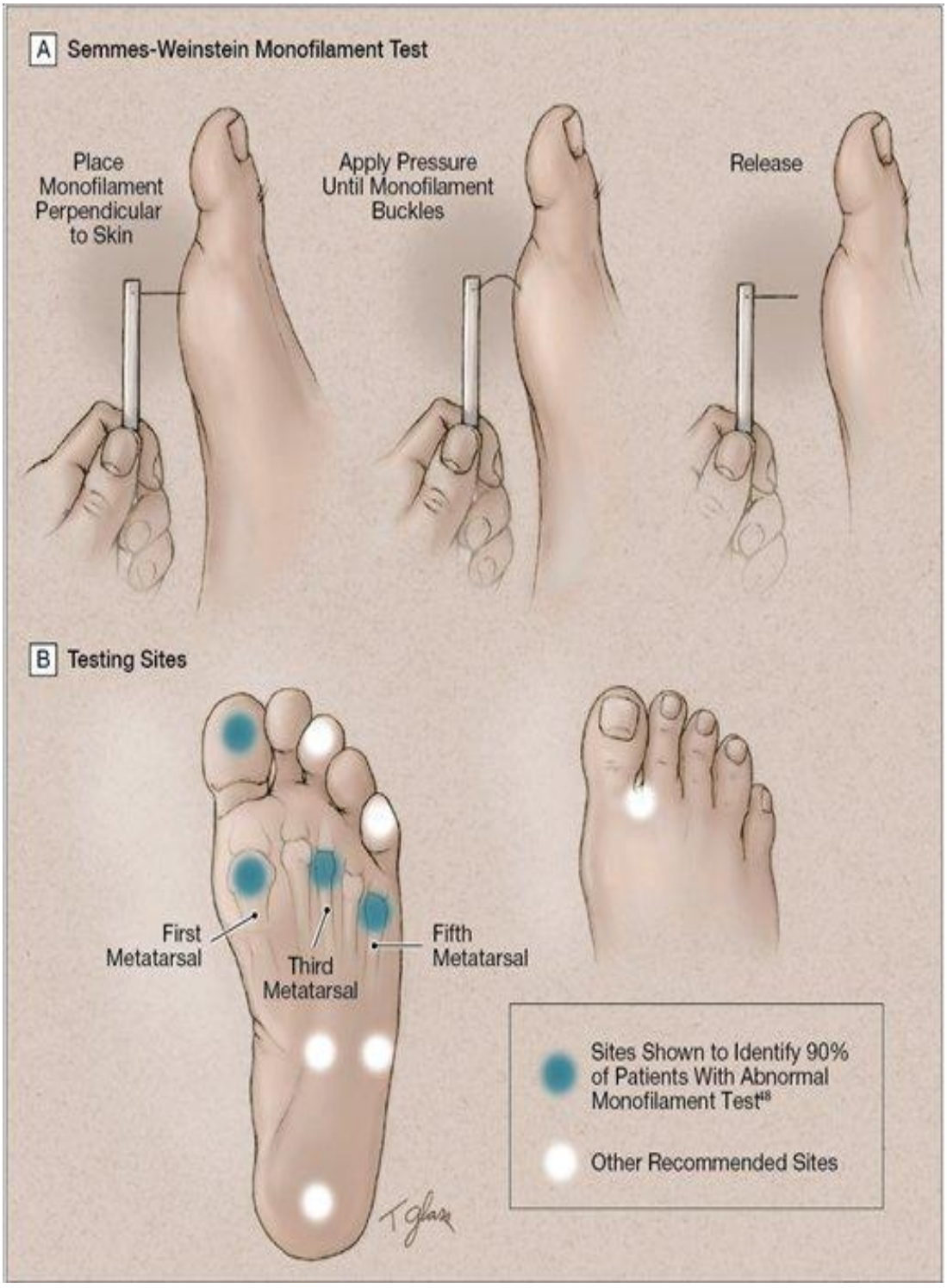
Clinical history alone is not sufficient to recognize peripheral neuropathy(30) Although most patients with objective evidence of diabetic length-dependent peripheral neuropathy are clinically asymptomatic, they remain at risk for injury to insensitive feet(32) If single-modality screening is to be used, monofilament light touch or vibration testing appears to be more sensitive and specific than superficial pain (pinprick) or ankle reflex testing(27)(28)(30) As peripheral neuropathies may affect different types of nerve fibers to different degrees, single-modality testing may miss 25% to 50% of those with diabetic neuropathy(30).

In diabetic cohorts, combination testing of vibration plus 10-g monofilament testing provides the best balance of an efficient (less than 2-minute), sensitivity being 90%, and specificity being 85%-89% for diabetic peripheral neuropathy and correlates with the development of diabetic foot ulcers(30-32) Light touch with a cotton swab is often substituted for monofilament testing in clinical practice, although its sensitivity and specificity is unknown. There is an age-related decline in vibration sensation, with almost one-quarter of the population older than age 65 years and one-

third of those older than 75 years having absent vibration sensation on clinical examination (33) Thus, reduced or absent vibration sensation in isolation should not be overinterpreted in elderly patients and should instead prompt further history and consideration of other sensory modalities to determine its relevance.

Clinically, the patients can be stratified by looking for the following symptoms :- Sensory symptoms (eg, numbness, tingling), weakness, autonomic symptoms (eg, early satiety, impotence, orthostatic hypotension, sweat abnormalities), or neuropathic (burning, stabbing, electrical) . The most common pattern of clinical involvement is that of a length-dependent peripheral neuropathy. This form of neuropathy is symmetric, and symptoms begin in the longest nerves at their terminals (ie, distal foot). Negative (lack of feeling) or positive (prickling, tingling, burning) sensory symptoms usually precede motor weakness.

Proprioception is spared relative to other sensory modalities in mild to moderate length dependent neuropathies and only becomes affected as the neuropathy severity progresses. Patients with notable early proprioceptive deficits (gait ataxia, imbalance with eyes closed) require further evaluation for posterior column disease (eg, vitamin B12 deficiency)


A Semmes-Weinstein Monofilament Test
Place Monofilament Perpendicular to Skin
Apply Pressure Until Monofilament Buckles
Release
B Testing Sites
First Metatarsal
Third Metatarsal
Fifth Metatarsal
Sites Shown to Identify 90% of Patients With Abnormal Monofilament Test[48]
Other Recommended Sites

DIABETIC NEUROPATHY

Diabetes mellitus is the most common cause of peripheral neuropathy in the world, with a prevalence of up to 30% to 66%(34-37) of all diabetic patients, which is dependent on whether the neuropathy is defined by clinical or electrophysiologic criteria. Despite the objective evidence of neuropathy, according to studies, only 10% to 15% of patients with diabetic neuropathy are neurologically symptomatic (from motor, sensory, or autonomic dysfunction)(36) whereas 11% to 26% are limited to neuropathic pain.

Diabetic neuropathy has been defined as presence of symptoms and/or signs of peripheral nerve dysfunction in diabetics after exclusion of other causes, which may range from hereditary, traumatic, compressive, metabolic, toxic, nutritional, infectious, immune mediated, neoplastic, and secondary to other systemic illnesses. Since the manifestations of diabetic neuropathy closely mimic chronic inflammatory demyelinating polyneuropathy, alcoholic neuropathy, and other endocrine neuropathies, hence, before labelling diabetic neuropathy it is mandatory to exclude all other causes of peripheral nerve dysfunction.

Table I : Classification of diabetic neuropathy.

A. Diffuse
1. Distal symmetric sensori-motor polyneuropathy
2. Autonomic neuropathy
   a. Sudomotor
   b. Cardiovascular
   c. Gastrointestinal
   d. Genitourinary
3. Symmetric proximal lower limb motor neuropathy (amyotrophy)

B. Focal
1. Cranial neuropathy
2. Radiculopathy/plexopathy
3. Entrapment neuropathy
4. Asymmetric lower limb motor neuropathy (amyotrophy)

The precise pathogenesis of diabetic peripheralneuropathy despite recent advances remains obscure; however, consensus is that neuropathy in diabetes mellitus is a multifactorial disease14. The possible aetiologic factors suggested include, hyperglycaemia, polyol pathway, non-enzymatic glycation, free radical and oxidative stress. Available evidence suggests that these various pathogenetic factors act synergistically (40). Many of these hypotheses are based on studies of different animal models of diabetes, but none of these truly reproduce the changes as seen in diabetic neuropathies in humans (41). Generally the nerve involvement has been correlated with glycaemic control, hyperglycaemia induced metabolic derangements and neurophysiological alterations, serum lipid changes, vascular coagulation, and thrombotic abnormalities (42)

Diagnosis of Sensorimotor Neuropathy

In DPN, sensory deficits usually overshadow motor nerve dysfunction and appear first in the distal portions of the extremities and progress proximally in a ‘stocking-glove' distribution with increasing duration or severity of diabetes (43) . In the typical form, the large nerve fibres are damaged later than the small ones (44). The signs and symptoms of DPN vary depending on fibre type involved, with large fibre disease impairing proprioception and light touch. Small-fibre disease impairs pain and temperature perception, leading to paraesthesia, dysaesthesia and/or neuropathic pain (43) (table 1). Distal weakness occurs only in the most severe cases. Diminished or absent deep-tendon reflexes, particularly the Achilles tendon reflex, often indicate mild and otherwise asymptomatic DPN. More advanced asymptomatic neuropathy may first present with late complications such as ulceration or neuroarthropathy (Charcot's joints) of the foot (43).

For diagnosis of DPN, bedside examination should include assessment of muscle power, sensations of pinprick, joint position, touch and temperature. Vibration test should be done by a 128-Hz tuning fork. For touch sensation monofilament of 10 g is recommended (45,46). A number of questionnaires have been developed to help practitioners diagnose neuropathic pain (44,45,46). The DN4 questionnaire is of particular interest as it can be rapidly completed, is easy to use and has a good diagnostic performance: for a score ≥4/10, it has a sensitivity of 83% and a specificity of 90% for diagnosing neuropathic pain (44). The main advantage of screening tools is to identify potential patients with neuropathy, particularly by non-specialists. However, these tools fail to identify 10-20% of patients with clinician-diagnosed neuropathy, showing that they cannot replace careful clinical judgement (48).

Electrophysiological tests are usually not recommended in the diagnosis of chronic sensorimotor diabetic neuropathy, as they can be normal when only small-diameter fibres are damaged, but it is a reliable procedure in the case of mononeuropathies or radiculopathies to exclude any other aetiology (demyelinating polyneuropathies, etc.). Such procedures are really useful when the clinical presentation is atypical and the diabetic origin uncertain (asymmetrical symptoms or involvement of the upper limbs) [44,46,47]. Among laboratory tests, laser-evoked potentials may be the best tool for assessing Aδ pathway dysfunction (small-fibre neuropathy), and skin biopsy for assessing neuropathies with distal loss of unmyelinated nerve fibres (48).

Diagnosis of Autonomic Neuropathy

Questionnaires have been developed to investigate orthostatic symptoms and their severity in dysautonomic conditions, although they have not been specifically validated for CAN and validated translations in different languages are lacking (49). Diabetic patients with features of cardiac autonomic dysfunction such as unexplained tachycardia, orthostatic hypotension and poor exercise tolerance, or with other symptoms of autonomic dysfunction, should be evaluated for the presence of CAN. Screening for CAN should be performed at the diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes, particularly in patients at greater risk of CAN due to a history of poor glycaemic control, cardiovascular risk factors, DPN, and macro- and microangiopathic diabetic complications (47). Diagnosis of CAN is based on the use of cardiovascular autonomic reflex tests for heart rate response to deep breathing, standing and Valsalva manoeuvre, as well as for blood pressure response to standing (47,49).

A number of instruments are available to quantify gastrointestinal symptoms, including the Diabetes Bowel Symptom Questionnaire. Objective gastric emptying measurement is advocated for the diagnosis of gastroparesis. Unfortunately, there is no specific test in the detection of diabetic gastroparesis - it is only an exclusion diagnosis after detailed gastrointestinal examinations (47).

Key diagnostic procedures of ED include comprehensive patient history (sexual, medical, drugs, alcohol, tobacco and psychosocial). The use of validated questionnaires is the most appropriate method to characterize the frequency and severity of ED symptoms (47). Due to the potential risks of adverse or unanticipated drug interactions, cardiac risk factors should be evaluated and managed in all patients with ED and cardiovascular disease (47). Specific testing may be recommended in patients not responding to phosphodiesterase-5 inhibitors (47).

The type of bladder dysfunction is most readily characterized with complete urodynamic testing (47). Assessment of sudomotor dysfunction contributes to the detection of autonomic dysfunction in DPN. The quantitative sudomotor axon reflex test is capable of detecting distal small-fibre polyneuropathy with a sensitivity of 75% (47).

METHODOLOGY

Study site:

Study was conducted in the Department of Medicine of K.L.E'S Dr. Prabhakar Kore Hospital And Medical Research Centre, Belagavi.

Study population:

All the patients having Diabetes Mellitus on Metformin, attending Medicine OPD of K.L.E'S Dr Prabhakar Kore Hospital And Medical Research Centre, Belagavi.

Study design:

The current study was a cross-sectional study.

Sample size:

100

Sampling method:

All the eligible subjects were recruited into the study consecutively by convenient sampling till the sample size is reached.

Study duration:

The data collection for the study was done between January 2017 to December 2017 for a period of 1 year.

Inclusion criteria:

Known cases of Type 2 Diabetes Mellitus on metformin therapy for more than 3 years.

Exclusion criteria:

Elevated Sr Creatinine levels, Known Vitamin B12 deficiency, Pregnancy, Known thyroid disorder, Hematological malignancy, Inflammatory Bowel Disease (IBD)

Ethical considerations:

Study was approved by institutional human ethics committee. Informed written consent was obtained from all the study participants and only those participants willing to sign the informed consent were included in the study. The risks and benefits involved in the study and voluntary nature of participation were explained to the participants before obtaining consent. Confidentiality of the study participants was maintained.

Data collection tools:

All the relevant parameters were documented in a structured study proforma.

Methodology:

Outpatients with Diabetes Mellitus fulfilling the Inclusion and Exclusion criteria were taken in to the study after obtaining written informed consent in their own vernacular language. Further they were subjected to a detailed history and examination as per predesigned proforma. Examination included general physical examination, systemic examination and specific examination for peripheral neuropathy. Semmes-Weinstein monofilament was used to assess neuropathy over the foot and grading was done accordingly. Also, biochemical tests were done which included routine blood investigations like complete blood count, renal function tests, serum TSH. To find out the glycemic control of the patients, HbA1c was also done.

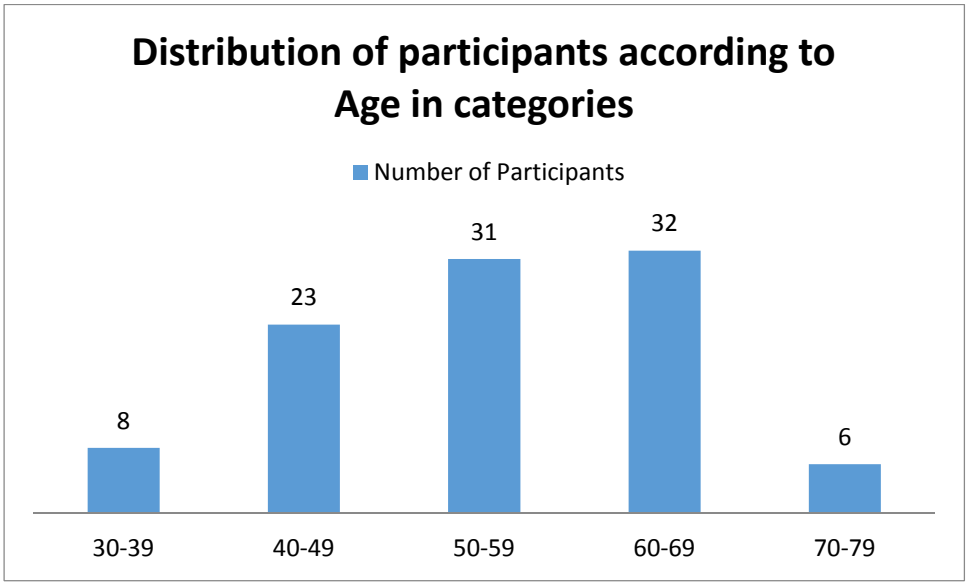
Mainly, all patients were subjected to Serum Vitamin B12 testing. Thus, all biochemical findings were correlated clinically.

RESULTS

A total of 100 patients were included in the study. Socio-demographic characteristics and biochemical profile of the participants are described in following tables.

Age Category (Yrs)	Number of Participants	Percent (%)
30-39	08	08
40-49	23	23
50-59	31	31
60-69	32	32
70-79	06	**6**
Total	100	**100**

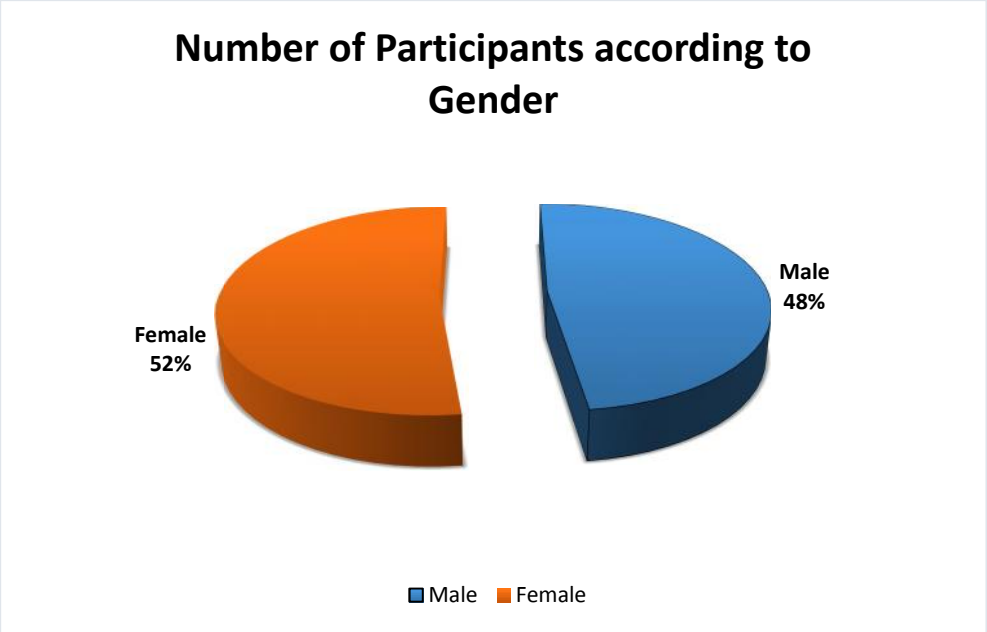
Table 1: Distribution of participants according to Age in categories



The **mean age of study participants was 55.3** years (SD ± 10.6) within range of 32 to 78 years of age

Gender	Number of Participants	Percent (%)
Male	48	48
Female	52	52
Total	100	**100**

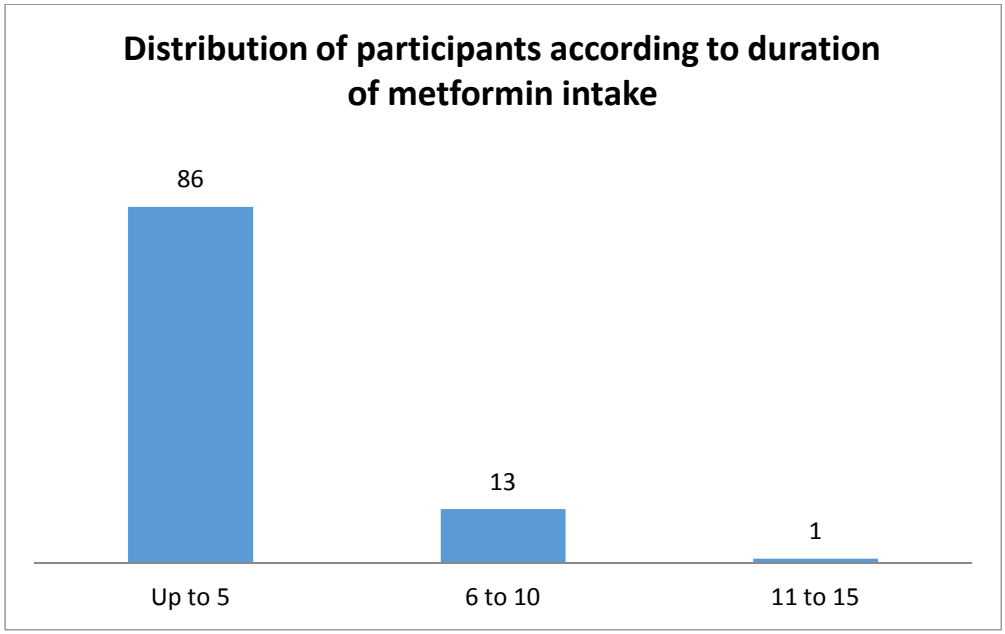
Table 2: Distribution of participants according to Gender



Majority (52%) of the study participants were females.

Duration of Metformin use(Years)	Number of Participants	Percent (%)
Upto 5	86	86
6 to 10	13	13
11 to 15	1	1
Total	100	100

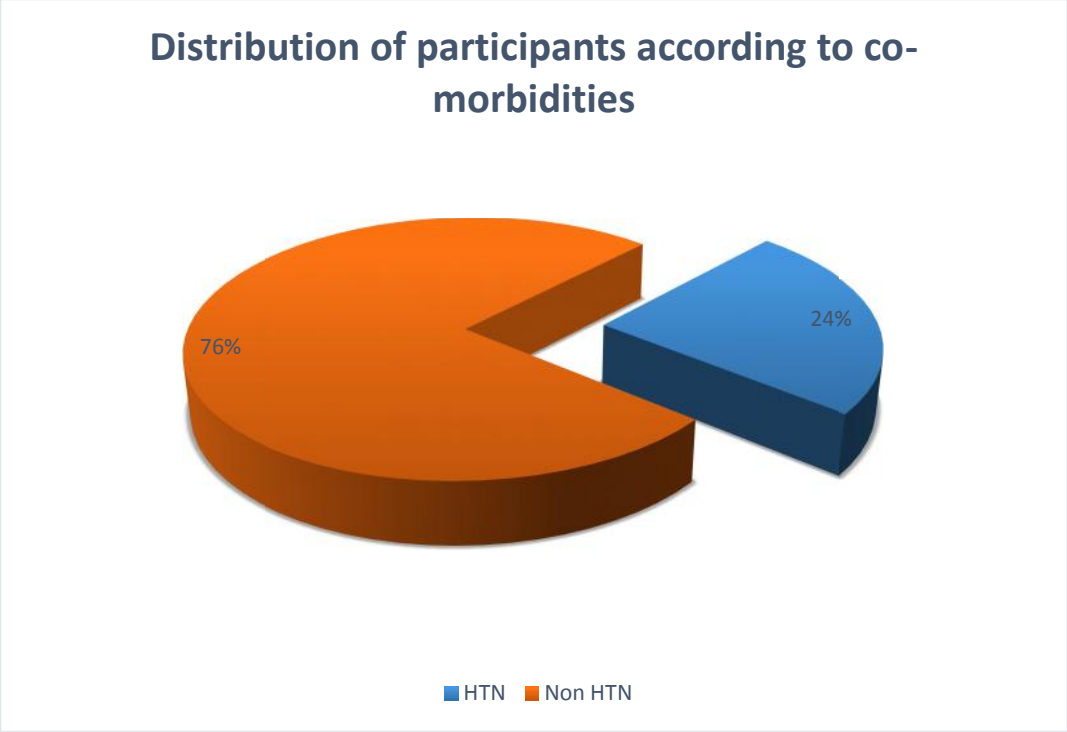
Table 3: Distribution of participants according to duration of metformin intake



Mean duration for metformin usage is years 3.05 (SD ± 2.5) with maximum participants among group of 0 to 5 yrs of metformin use.

Co-morbidities	Number of Participants	Percent (%)
HTN	24	24
Absent	76	76
Total	100	100

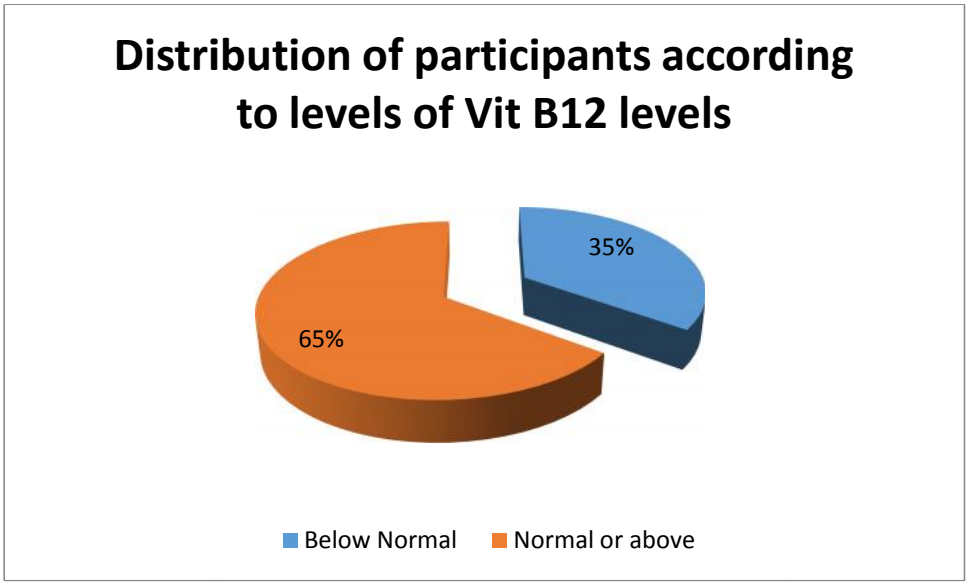
Table 4: Distribution of participants according to co-morbidities



Most of the study participants presented with hypertension (24%) as co-morbidity.

Vit B12 level	Number of Participants	Percent (%)
Below Normal	35	35
Normal or above	65	65
Total	100	100

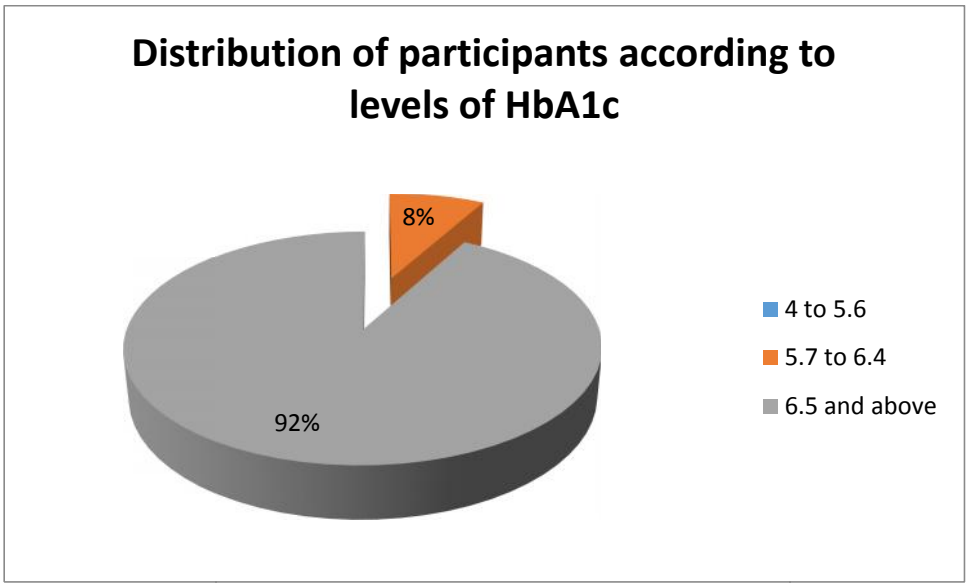
Table 5: Distribution of participants according to levels of Vit B12 levels



Most of the study participants were having normal or above (65%) level of Vitamin B 12 levels with mean 619.8 ± 669.9 within the range of 50 to 2000.

HbA1c Levels (ng/ml)	Number of Participants	Percent (%)
4 to 5.6	00	0
5.7 to 6.4	08	8
6.5 and above	92	92
Total	**100**	**100**

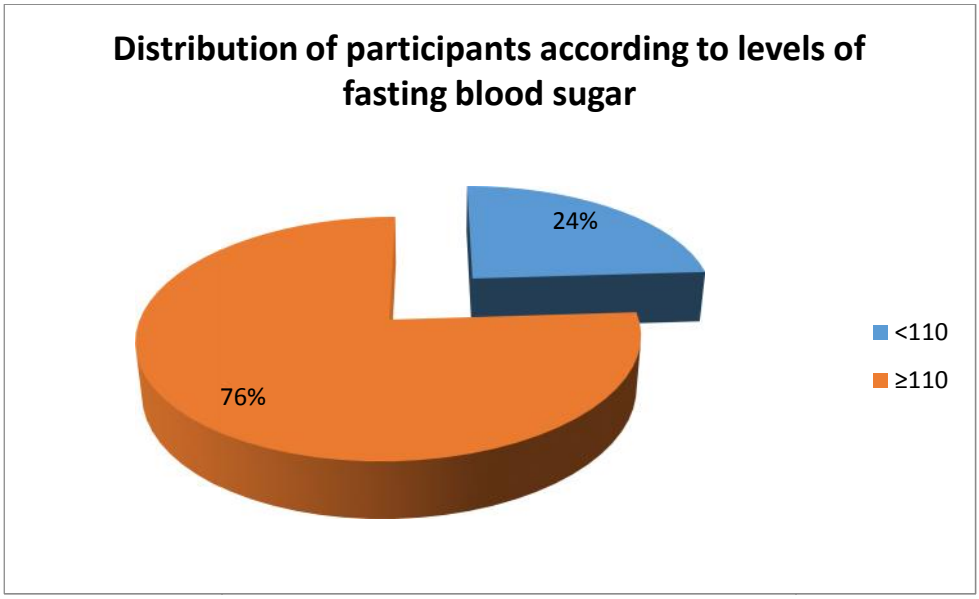
Table 6: Distribution of participants according to levels of HbA1c



Most of the study participants presented with high level of HbA1c (92%) with mean 8.1 ± 1.4 within range of 6.2 to 11.2.

FBS levels	Number of Participants	Percent (%)
<110	24	24
≥110	76	76
Total	100	100

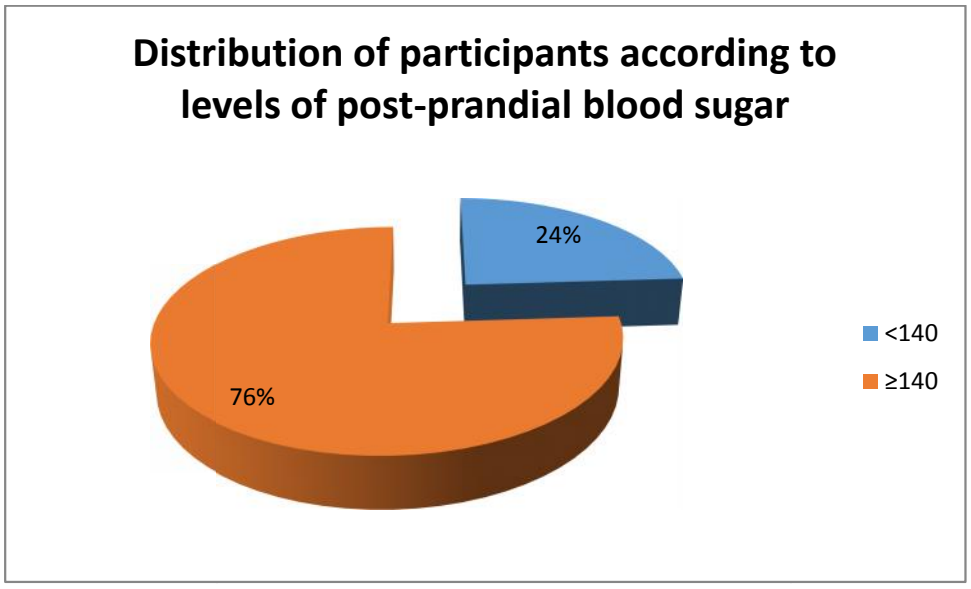
Table 7: Distribution of participants according to levels of fasting blood sugar



Most of the study participants presented with mean level of fasting blood sugar as with 128.9 ± 26 within the range of 88 to 198.

PPBS levels	Number of Participants	Percent (%)
<140	24	24
≥140	76	76
Total	100	100

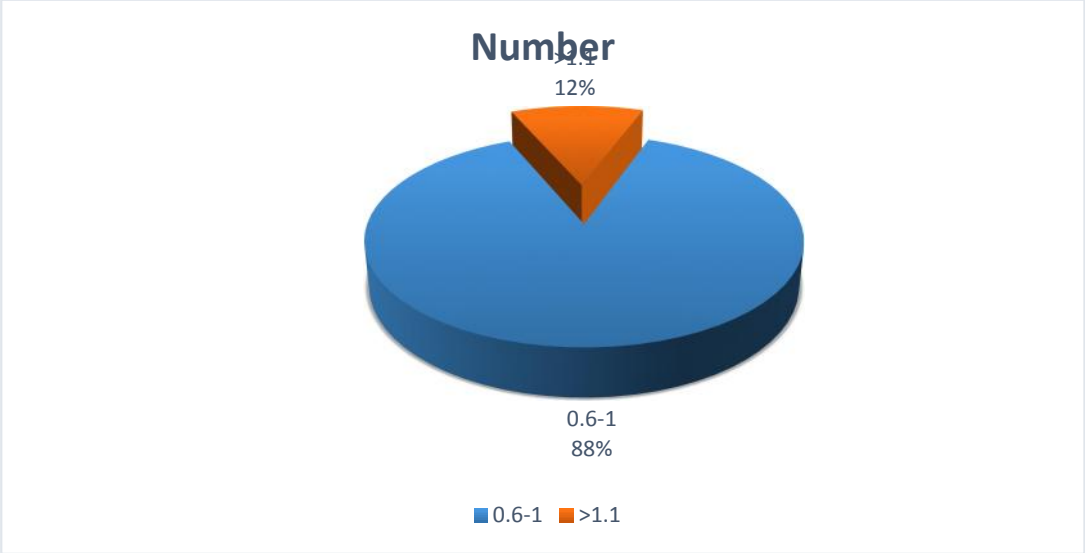
Table 8: Distribution of participants according to levels of post-prandial blood sugar



Most of the study participants presented with mean level of post prandial blood sugar as with 180.6 ± 43.3 within the range of 124 to 302.

Sr. Creatinine levels	Number of Participants	Percent (%)
0.6 -1	88	88
>1.1	12	12
Total	**100**	**100**

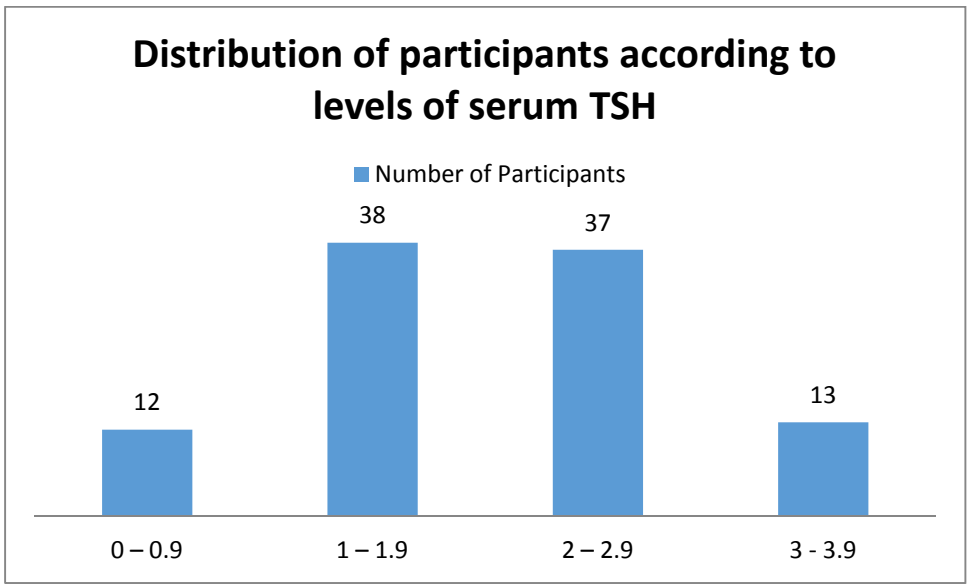
Table 9: Distribution of participants according to levels of serum creatinine



Most of the study participants presented with mean level of serum creatinine of 0.88 ± 0.14, which is well within the normal range.

Sr. TSH levels	Number of Participants	Percent (%)
0 – 0.9	12	12
1 – 1.9	38	38
2 – 2.9	37	37
3 - 3.9	**13**	**13**
Total	**100**	**100**

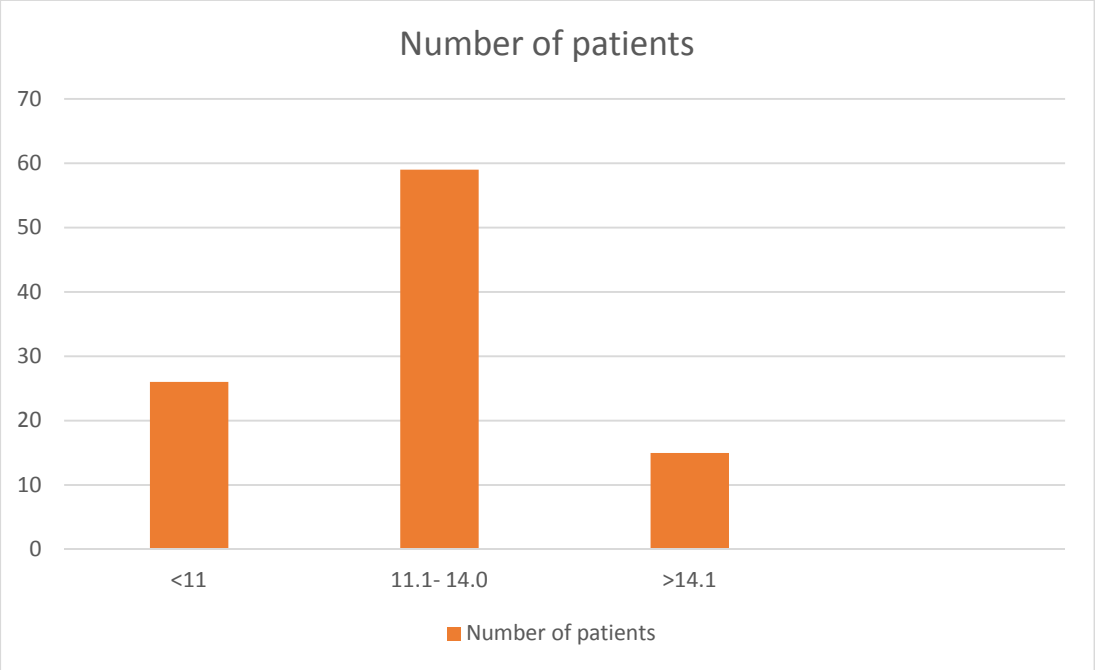
Table 10: Distribution of participants according to levels of serum TSH



Most of the study participants presented with mean level of serum TSH of 1 to 1.9 and mean of 1.94 ± 0.74.

Hb levels	Number of Participants	Percent (%)
<11	26	26
11.1-14.0	59	59
>14.1	15	15
Total	**100**	**100**

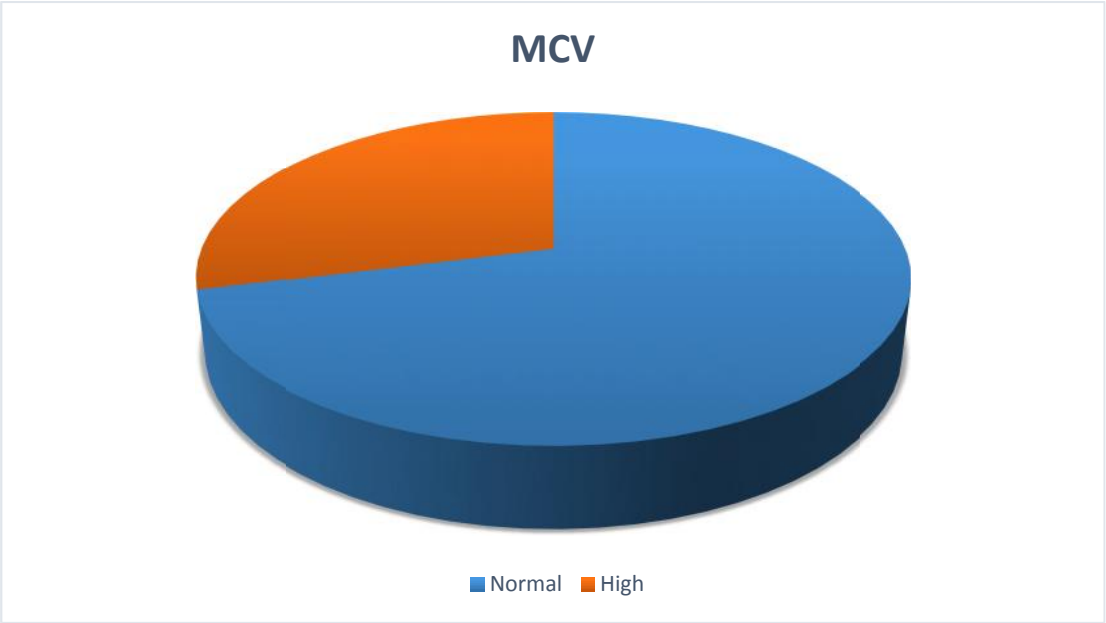
Table 11: Distribution of participants according to levels of haemoglobin



Most of the study participants presented with level of haemoglobin ranging between 11.1 to 14.0 mg/dl.

MCV	Distribution (n=100)	Percentage(%)
Normal	71	71
High	29	29

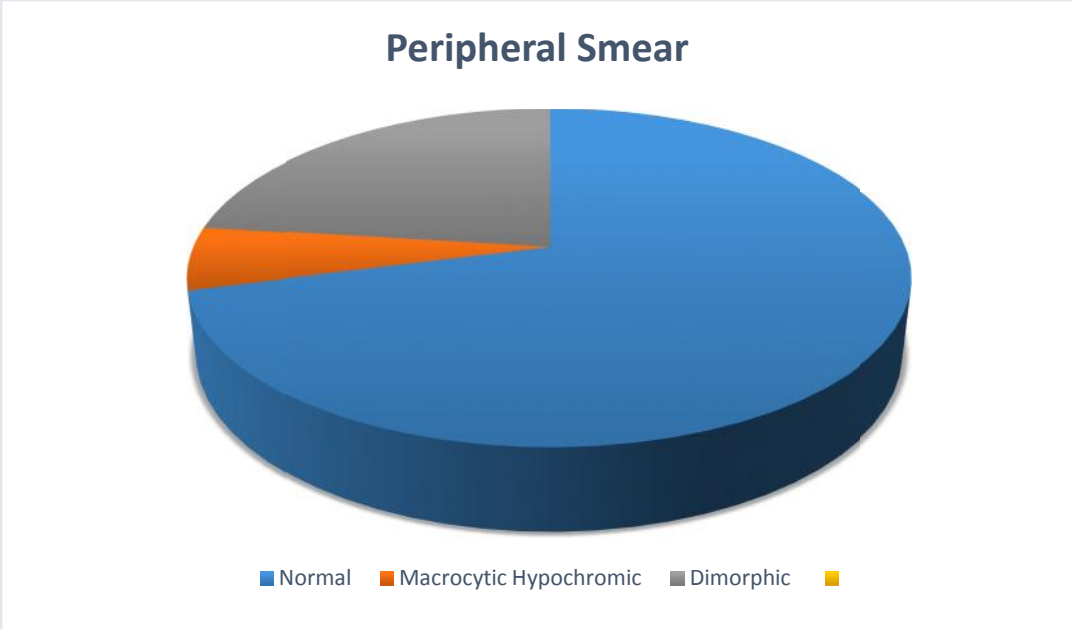
Table 12: Distribution of participants according to levels Mean Corpuscular Volume (MCV)



In our study, we observed, 71 patients had normal Mean Corpuscular Volume of RBC, while, 29 patients had high Mean Corpuscular Volume

Peripheral Smear	Distribution No. (n=100)	Distribution Percentage (%)
Normal	71	71
Dimorphic	23	23
Macrocytic	6	6

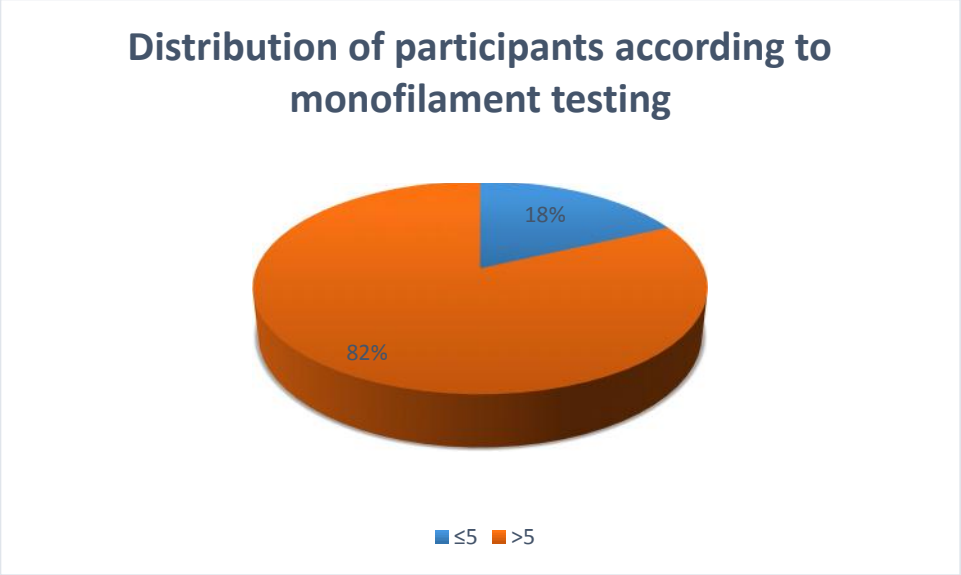
Table 13: Distribution of participants according to Peripheral Smear



In our study, we observed that 71 patients had a normal peripheral smear, while, 23 patients had dimorphic picture and 6 had macrocytic picture.

Monofilament testing score	Number of Participants	Percent (%)
≤5	18	18
>5	82	82
Total	100	100

Table 14: Distribution of participants according to monofilament testing



Most of the study participants (82 %) were having monofilament score of >5 showing presence of neuropathy.

Bivariate Analysis

	MFT Positive	MFT Negative	Total
B12 Deficiency	16	19	35
B12 Normal	02	63	65
Total	18	82	100

OR – 26 (5 – 125), CI – 95%, P <0.0001

Table 15: 2x2 table of B12 deficiency and monofilament test

By applying Chi square test as test of significance, odds of positive outcome for monofilament test in Vit B 12 deficient person is 25.5 and p value is highly significant (P<0001).

DISCUSSION

Metformin, a biguanide, is the most commonly used oral hypoglycemic agent for the treatment of diabetes mellitus. There are proposed mechanisms**,** through which metformin interacts with vitamin B12 absorption and causes deficiency of vitamin B12. A cross sectional study where the serum Vitamin B12 level of type 2 Diabetic patients who are on metformin therapy for >3 yrs was measured and correlated with various other basic parameters like demographic status, fasting, post prandial glucose status, duration of metformin therapy, associated co-morbidities etc .

Age

In the present study, it was found out that 32 % of the study subjects belonged to 60-69 years of age group and mean age of the study subjects was 55.3 years with standard deviation of 10.6 years, the range being 32 -78 years of age. The study conducted by **Holay MP et al (2017)**(50) found the mean age of study subjects was 63.65 ± 11.37 years, maximum number of study subjects their study belongs to age group 60-70 years.

Sex

In our study, it was found that majority were females 52% than males 48%. In contrast to our findings, males were 54.5% in the study conducted by **Raizada N et al.(2017).**(51)

Metformin duration

In our study, it was observed that the mean duration for metformin usage is 3.05 (SD ± 2.5) years with maximum participants 86% among group of 0 to 5 yrs of

metformin use. While in the study conducted by **Atif Rauf et al (2015)**(52) the mean duration of metformin use was 5.1 (SD ± 1.9)years and range was 1.5 years to 8.4 years.

Co morbidities

In the present study most of the study participants were presented with as hypertension (24%) as co-morbidity. While almost 51% of the study participants having having hypertension as comorbidity in the study conducted by **Kang D. et al (2014)**(53)**.** It is almost double as compared to our study findings as there is combination of metformin and sulfonylureas use in study subjects.

Monofilament test

In the present study, we found out that most of the study participants (82 %) were having monofilament score of >5 showing presence of neuropathy. While in the study conducted by **Sharon L Edelstein et al (2016)**(55), there was higher prevalence of monofilament-defined neuropathy which correlated with our study.

Vitamin B12 level

In our study most of the study participants 65% were having normal or above level of Vitamin B 12 levels with mean 619.8 ± 669.9pg/mL within the range of 50 to 2000. While study done by **Kang D. et al(2014)**(53) it was found that the mean vitamin B12 levels of the normal B12 level group were 704.56 ± 244.3 pg/mL. In their study there was comparison with the subjects without vitamin B12 deficiency, the patients with vitamin B12 deficiency were older in age, used more sulfonylurea, and had lower levels of HbA1c and hemoglobin

HbA1c

our study most of the study participants (92%) were presented with high level of HbA1c mean and standard deviation of 8.1 ± 1.4%.While similar higher level was found in the study conducted by **Ahmed et al (2016)**(54) where the mean and standard deviation of HbA1c was 9.1 ± 2.5%.

Fasting and PPbs

In the present study, subjects were presented with mean level of fasting blood sugar as with 128.9 ± 26 mg/dL. While in the study conducted by **Holay MP et al(2017)**(50) and **Atif Rauf et al(2015)**(52) fasting plasma glucose was calculated to be 155.15 ± 52.33mg/dL and 208± 46.3mg/dL respectively.

Also most of the study participants 76% in our were presented with mean level of post prandial blood sugar as with 180.6 ± 43.3 mg/dL. While in the study conducted by **Holay MP et al(2017)**(50) post prandial blood sugar was calculated to be 229.58 ± 69.86 mg/dL.

Serum Creatinine

Most of the study participants 57% in the present were presented with mean level of serum creatinine of 0.88 ± 0.14, which is well within the normal range. While consistent findings, mean level of serum creatinine of 0.8 ± 0.2 was observed by **Kang D. et al(2014)**(53)

Serum TSH

Most of the study participants 38 % were presented with mean level of serum TSH of 1 to 1.9 and mean of 1.94 ± 0.74 which is well within the normal range. While

consistent findings were observed by **Omar Marar et al (2011)** (56) of serum TSH with a mean level of 2.01 ± 1.21.

Mean Hb level

In this study the level of haemoglobin was found to between be 11 and 14. Similar findings were found by **Kang D et al. (2014)**(53) and **Sharon L Edelstein et al (2016)**(55) where mean level of haemoglobin was 13.9 ± 5.3 and 13.8 ± 1.3 respectively

MCV level

In this study, it was observed that 29 patients (29%) had high Mean Corpuscular Volume. In contrast to these findings, study conducted by **Sun-Hye Ko et al (2014)**(57) showed only 4 patients from the total study population (0.5%) having a high mean corpuscular volume (MCV). The high MCV findings in this study could be attributed to high incidence of vegetarianism found in the Indian population.

Peripheral smear

In our study, we observed that 71 patients had a normal peripheral smear, while, 23 patients had dimorphic picture and 6 had macrocytic picture. , in contrast to these findings, study conducted by **Vijaya Lakshmi Koduri et al (2018)** (58) 41.1% of the peripheral smears indicating the presence of megaloblastic anaemia. These findings indicated presence of concomitant iron deficiency anaemia which further need to be investigated.

Vit B 12 Deficiency and monofilament test

By applying Chi square test as test of significance, odds of positive outcome for monofilament test in Vit B 12 deficient person is 25.5 and p value is highly significant (P<0001). It is consistent with the findings of the study conducted by **Sharon L Edelstein et al (2016)**(55) which showed higher prevalence of monofilament-defined neuropathy in metformin-treated participants with low vitamin B12 levels.

CONCLUSIONS

In the present study of 100 patients with Type II Diabetes Mellitus taking Metformin therapy, the commonest age group was between 60 to 69 years followed by 50 to 59 years. Majority of the participants were females compared to males. The mean duration of metformin therapy was 3 years and most of the participants had Hypertension as a co-morbidity.

All the participants presented with a normal value of Serum Creatinine. The study also compares the Serum TSH values which was found to be within normal limits in all the study participants.

HbA1c values were also analyzed and it was found that maximum number of participants had high levels of HbA1c thus indicating poor glycemic control. Also, the present study showed high levels of Fasting Blood Sugar levels and Post Prandial Blood Sugar levels, which provided further evidence of poor glycemic control.

Along with this, Haemoglobin levels were also studied and maximum number of participants were found to be between 11 – 14 gm/dl . 30% of the total number of participants had anaemia which can be attributed not only to Vitamin B12 deficiency only, but also iron deficiency. Other hematological parameters which were assessed include Mean Corpuscular Volume and Peripheral Smear.

Higher MCV levels (29%) were found in this study which can't be attributed to Vitamin B12 deficiency per se, as maximum Indian population tends to be vegetarian. Also, Peripheral Smear analysis showed more of a Dimorphic picture, indicating the presence of co-existing Nutritional anaemia.

The Serum Vitamin B12 levels were found to be normal in about 65% of all participants while 35% were found to be deficient which is highly significant.

In majority of our patients who were found to be Vitamin B12 deficient, there was associated peripheral neuropathy which was confirmed by monofilament testing, using the standard Semmes-Weinstein monofilament. Thus, simple Vitamin B12 supplementation in the form of tablets or injections may help such patients to control symptoms of neuropathy. But, proper glycemic control is necessary as if the patient is having poor glycemic control, he or she may progress to diabetic neuropathy and Vitamin B12 supplementation would not be of any help.

There were some limitations pertaining to this study. Mainly, the diagnosis of peripheral neuropathy could have been more specific if Nerve Conduction Velocity testing could be done in these patients. Monofilament assessment is subjective evidence of neuropathy. But since this was an out-patient study, carrying out NCV testing was difficult.

Also, estimation of Serum Holotranscobalamin (Htc) and Serum Methyl Malonyl Acid (MMA) provides solid evidence of Vitamin B12 deficiency, but this was not done in this study.

Due to the short duration of the study, follow up of the patients could not be done.

SUMMARY

- Chronic metformin therapy causes Vitamin B12 deficiency
- Various mechanisms are associated with metformin induced Vitamin B12 deficiency.
- This Vitamin B12 deficiency can manifest as peripheral neuropathy
- Peripheral neuropathy can be confirmed by bedside testing methods which include Semmes-Weinstein monofilament testing.
- Peripheral Neuropathy secondary to Vitamin B12 deficiency is a treatable condition, by giving simple Vitamin B12 supplements.

BIBLIOGRAPHY

1. Marianna Karamanou, Athanase Protogerou, Gregory Tsoucalas, George Androutsos, Effie Poulakou-Rebelakou , Milestones in the history of diabetes mellitus: The main contributors World J Diabetes. 2016 Jan 10; 7(1): 1–7. Published online 2016 Jan 10. doi: 10.4239/wjd.v7.i1.1 PMCID: PMC4707300

2. Mazokopakis EE, Starakis IK., Recommendations for diagnosis and management of metformin-induced vitamin B12 (Cbl) deficiency. Diabetes Res Clin Pract. 2012; 97:359–67.

3. Bouchoucha M, Uzzan B, Cohen R (2011) Metformin and digestive disorders. Diabetes Metab 37: 90–96.

4. Vitamin B12 deficiency & levels of metabolites in an apparently normal urban south Indian elderly population. Vineeta Shobhaa, Subhash D. Tareya, Ramya G. Singhc, Priya Shettyc, Uma S. Unnid, Krishnamachari Srinivasane & Anura V. Kurpadb

5. The U.K. Prospective Diabetes Study A review ROBERT C. TURNER, MD, FRCP

6. Cusi, K, Defronzo, RA. Metformin: a review of its metabolic effects. *Diabetes Reviews* 1998. 6:89-131.

7. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomized placebo controlled trial. Jolien de

Jager, resident,1,2 Adriaan Kooy, internist,2,3 Philippe Lehert, professor of statistics,4 Michiel G Wulffele

8. Matthew C. Pflipsen, Robert C. Oh, Aaron S, Dean A. Seehusen, and Richard Topolski. The Prevalence of Vitamin B12 Deficiency in Patients with Type 2 Diabetes: A Cross-Sectional Study.
9. Increased Intake of Calcium Reverses Vitamin B12 Malabsorption Induced by Metformin. william a. bauman, md spencer shaw, md elizabeth jayatilleke, ms ann m. spungen, edd victor herbert, md, jd.
10. Metformin Associated B12 Deficiency:Anand Ajit Kumthekar* , Hitesh Vinod Gidwani**, Ajit Bhaskar Kumthekar***
11. Sharabi, A., Cohen, E., Sulkes, J., & Garty, M. (2003). Replacement therapy for vitamin B12 deficiency: comparison between the sublingual and oral route. *British Journal of ClinicalPharmacology, 56*(6), 635-638. doi: 10.1046/j.1365- 2125.2003.01907.x
12. Majumder, S., Soriano, J., Cruz, A. L., & Dasanu, C. A. (2013). Vitamin B-12 deficiency in patients undergoing bariatric surgery: Preventive strategies and key recommendations. *Surgery for Obesity and Related Diseases, 9*(6), 1013-1019. doi: 10.1016/j.soard.2013.04.01717.
13. Obeid, R., Jung, J., Falk, J., Herrmann, W., Geisel, J., Friesenhahn-Ochs, B., .Kostopoulos, P. (2013). Serum vitamin B12 not reflecting vitamin B12 status in patients with type 2 112 diabetes. *Biochimie, 95*(5), 1056-1061. doi: 0.1016/j.biochi.2012.10.028
14. Zhang, P., Li, H., Tan, X., Chen, L., & Wang, S. (2013). Association of metformin use with cancer incidence and mortality: a meta-analysis.*Cancer epidemiology, 37*(3), 207-218. doi: 10.1016/j.canep.2012.12.009

15. S. Tal, Y. Shavit, F. Stern, S. Malnick, Association between vitamin B12 levels and mortality in hospitalized older adults, J. Am. Geriatr. Soc. 58 (2010) 523e526

16. L. Reinstatler, Y.P. Qi, R.S. Williamson, J.V. Garn, G.P. Oakley Jr., Association of biochemical B(1)(2) deficiency with metformin therapy and vitamin B(1)(2) supplements: the National Health and Nutrition Examination Survey, 1999- 2006, Diabetes Care 35 (2012) 327e333

17. W.A. Bauman, S. Shaw, E. Jayatilleke, A.M. Spungen, V. Herbert, Increased intake of calcium reverses vitamin B12 malabsorption induced by metformin, Diabetes Care 23 (2000) 1227e1231.

18. G.H. Tomkin, Malabsorption of vitamin B12 in diabetic patients treated with phenformin: a comparison with metformin, Br. Med. J. 3 (1973) 673e675.

19. S. Leung, A. Mattman, F. Snyder, R. Kassam, G. Meneilly, E. Nexo, Metformin induces reductions in plasma cobalamin and haptocorrin bound cobalamin levels in elderly diabetic patients, Clin. Biochem. 43 (2010) 759e760

20. Gherasim, C., Lofgren, M., & Banerjee, R. (2013). Navigating the B-12 Road: Assimilation, and Disorders of Cobalamin. *Journal of Biological Chemistry, 288*(19), 13186-13193. doi:10.1074/jbc.R113.458810

21. Gnimpieba, E. Z., Eveillard, D., Gueant, J.-L., & Chango, A. (2011). Using logic programming for modeling the one-carbon metabolism network to study the impact of folate deficiency on methylation processes**.***Molecular Biosystems, 7*(8), 2508-2521. doi: 10.1039/c1mb05102d

22. Mazokopakis, E. E., & Starakis, I. K. (2012). Recommendations for diagnosis and management of metformin-induced vitamin B12 (Cbl) deficiency. *Diabetes Research and Clinical Practice,97*(3), 359-367. doi: 10.1016/j.diabres.2012.06.001

23. Martyn CN, Hughes RA. Epidemiology of peripheral neuropathy. J Neurol Neurosurg Psychiatry. 1997;62(4):310-318.

24. Italian General Practitioner Study Group (IGPSG). Chronic symmetric symptomatic polyneuropathy in the elderly: a field screening investigation in two Italian regions, I: Prevalence and general characteristics of the sample. Neurology. 1995;45(10): 1832-1836.

25. American Diabetes Association. Standards of medical care in diabetesd2014. Diabetes Care. 2014;37(suppl 1):S14-S80.

26. Boulton AJ, Armstrong DG, Albert SF, et al. Comprehensive foot examination and risk assessment: a report of the Task Force of the Foot Care Interest Group of the American Diabetes Association, with endorsement by the American Association of Clinical Endocrinologists. Diabetes Care. 2008;31(8): 1679-1685.

27. Perkins BA, Olaleye D, Zinman B, Bril V. Simple screening tests for peripheral neuropathy in the diabetes clinic. Diabetes Care. 2001;24(2):250-256.

28. Olaleye D, Perkins BA, Bril V. Evaluation of three screening tests and a risk assessment model for diagnosing peripheral neuropathy in the diabetes clinic. Diabetes Res Clin Pract. 2001;54(2):115-128.

29. Kamei N, Yamane K, Nakanishi S, et al. Effectiveness of Semmes-Weinstein monofilament examination for diabetic peripheral neuropathy screening. J Diabetes Complications. 2005; 19(1):47-53.

30. Al-Geffari M. Comparison of different screening tests for diagnosis of diabetic peripheral neuropathy in primary health care setting. Int J Health Sci (Qassim). 2012;6(2):127-134.

31. Armstrong DG, Lavery LA, Vela SA, Quebedeaux TL, Fleischli JG. Choosing a practical screening instrument to identify patients at risk for diabetic foot ulceration. Arch Intern Med. 1998;158(3):289-292.

32. Boulton AJ, Vinik AI, Arezzo JC, et al. Diabetic neuropathies: a statement by the American Diabetes Association. Diabetes Care. 2005;28(4):956-962.

33. Odenheimer G, Funkenstein HH, Beckett L, et al. Comparison of neurologic changes in 'successfully aging' persons vs the total aging population. Arch Neurol. 1994;51(6):573 580.

34. Partanen J, Niskanen L, Lehtinen J, Mervaala E, Siitonen O, Uusitupa M. Natural history of peripheral neuropathy in patients with non-insulin-dependent diabetes mellitus. N Engl J Med. 1995;333(2):89-94.

35. Boulton AJM. Management of diabetic peripheral neuropathy. Clin Diabetes. 2005;23(1):9-15.

36. Dyck PJ, Kratz KM, Karnes JL, et al. The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy Study [published correction appears in Neurology. 1993;43(11):2345]. Neurology. 1993;43(4):817-824.

37. Gregg EW, Sorlie P, Paulose-Ram R, et al. Prevalence of lowerextremity disease in the US adult population _40 years of age with and without diabetes: 1999-2000 National Health and Nutrition Examination Survey. Diabetes Care. 2004;27(7): 1591-1597.

38. Viollet B, Guigas B, Sanz Garcia N, Leclerc J, Foretz M, Andreelli F. Cellular and molecular mechanisms of metformin: an overview. Clin Sci (Lond). 2012;122(6):253–70.

39. Tomkin GH, Hadden DR, Weaver JA, Montgomery DA. Vitamin-B12 status of patients on long-term metformin therapy. Br Med J. 1971;2(5763):685–7.

40. Feldman EL, Stevens MJ, Greene DA. Pathogenesis of diabetic neuropathy. *Clin Neuro Sci* 1997; 4: 365-70.

41. Sharma AK, Thomas PK. Animal Models : Pathology and pathophysiology. In Dyck PJ Thomas PK, Asbely AK *et al* (eds): *Diabetic Neuropathy*. Philadalphia, WB Saunders 1987; p 237.

42. Harati Y. Diabetes and the nervous system. *Endo Metab Clin North Am* 1996; 25: 325-59.

43. Edwards JL, Vincent AM, Cheng HT, Feldman EL: Diabetic neuropathy: mechanisms to management. Pharmacol Ther 2008;120:1-34.

44. Hartemann A, Attal N, Bouhassira D, Dumont I, Gin H, Jeanne S, Said G, Richard JL; Working Group on the Diabetic Foot from the French-speaking Society of Diabetology: Painful diabetic neuropathy: diagnosis and management. Diabetes Metab 2011;37:377-388.

45. Baron R, Binder A, Wasner G: Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. Lancet Neurol 2010;9:807-819.

46. Bansal V, Kalita J, Misra UK: Diabetic neuropathy. Postgrad Med J 2006;82:95-100.

47. Tesfaye S, Boulton AJ, Dyck PJ, Freeman R, Horowitz M, Kempler P, Lauria G, Malik RA, Spallone V, Vinik A, Bernardi L, Valensi P; Toronto Diabetic Neuropathy Expert Group: Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care 2010;33:2285-2293.

48. Cruccu G, Sommer C, Anand P, Attal N, Baron R, Garcia-Larrea L, Haanpaa M, Jensen TS, Serra J, Treede RD: EFNS guidelines on neuropathic pain assessment: revised 2009. Eur J Neurol 2010;17:1010-1018.

49. Spallone V, Ziegler D, Freeman R, Bernardi L, Frontoni S, Pop-Busui R, Stevens M, Kempler P, Hilsted J, Tesfaye S, Low P, Valensi P; Toronto Consensus Panel on Diabetic Neuropathy: Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management. Diabetes Metab Res Rev 2011, DOI: 10.1002/dmrr.1239.

50. Holay M, Vyawahare M, Shekar K. Serum B12 Levels in Type II Diabetics on Metformin Therapy and its association with Clinical Neuropathy. Int J Biomed Adv Res. 2017;8(8):321–6.

51. Raizada N, Viveka P. Serum Vitamin B12 Levels in Type 2 Diabetes Patients on Metformin Compared to those Never on Metformin : A Cross - sectional Study. Indian J Endocr Metab 2017;21424-8. 2017;21(3):424–8.

52. Atif Rauf, Khan M, Arshad A. Frequency of Vitamin B12 Deficiency in patients with Type 2 Diabetes Mellitus Taking Metformin. P J M H S. 2015;9(4):1316–8.

53. Kang D, Yun J, Ko S, Lim T, Ahn Y, Park Y, et al. Higher Prevalence of Metformin-Induced Vitamin B 12 Deficiency in Sulfonylurea Combination Compared with Insulin Combination in Patients with Type 2 Diabetes : A Cross-Sectional Study. PLoS One. 2014;9(10).

54. Ahmed MA, Muntingh G, Rheeder P. Vitamin B12 deficiency in metformin-treated type-2 diabetes patients , prevalence and association with peripheral neuropathy. BMC Pharmacol Toxicol [Internet]. 2016;1–10. Available from: http://dx.doi.org/10.1186/s40360-016-0088-3

55. Aroda VR, Edelstein SL, Goldberg RB, Knowler WC, Marcovina SM, Orchard TJ, et al. Long-term Metformin Use and Vitamin B12 Deficiency in the Diabetes Prevention Program Outcomes Study. J Clin Endocrinol Metab. 2018;101(April 2016):1754–61.

56. Omar Marar, Sera Senturk, Amar Agha, Chris Thompson, Diarmuid Smith 1RCSI medical students 2Department of Endocrinology/RCSI Medical School, Beaumont Hospital, Dublin - The prevalence of vitamin B12 deficiency in patients with type 2 diabetes mellitus on metformin

57. Sun-Hye Ko,[1] Sun-Hee Ko,[1] Yu-Bae Ahn,[1] Ki-Ho Song,[1] Kyung-Do Han,[2] Yong-Moon Park,[3,4] Seung-Hyun Ko,[1] andHye-Soo Kim, Association of Vitamin B_{12} Deficiency and Metformin Use in Patients with Type 2 Diabetes

58. Vijaya Lakshmi Koduri , Srinivas N. S. Nori , Aditya Sai Rama Krishna K , Suhas Madaboina , Sindhuja A. B. K , Swati Sappa , Haematological Parameters And Vitamin B12 Levels In Type Ii Diabetic Patients On Metformin- A Prospective Case Control Study.

ANNEXURE I – CONSENT FORM

Dear Mr./Mrs./Dr. _____, you are kindly requested to enroll yourself in a research study tilted, "**PREVALENCE OF VITAMIN B12 DEFICIENCY AND CLINICAL NEUROPATHY WITH METFORMIN USE IN TYPE 2 DIABETES MELLITUS PATIENTS**" being conducted by Dr._____ , a post graduate student in M.D. General Medicine and the study will be carried out under the direct supervision and guidance of Dr. _____, Professor, Department of General Medicine, Jawaharlal Nehru Medical College, Belgaum.

You have been requested to participate in this as you fit into the laid out criteria for a study 'subject'/ participant.

Your participation in study is voluntary. During the study you will be asked some questions and you are supposed to answer to the best of your knowledge. Your decision whether or not to participate in the study will not affect your treatment in any form. If you decide to participate you are free to withdraw at any time.

TITLE OF THE STUDY:

"**PREVALENCE OF VITAMIN B12 DEFICIENCY AND CLINICAL NEUROPATHY WITH METFORMIN USE IN TYPE 2 DIABETES MELLITUS PATIENTS**."

PURPOSE OF THE STUDY:

To compare the prevalence of Vitamin B12 deficiency and peripheral neuropathy in patients with Type 2 Diabetes Mellitus treated with and without Metformin

PROCEDURES INVOLVED:

If you agree to enroll yourself in my study, you will be interviewed regarding your present, past and family history then you will be clinically examined in detail and investigated accordingly.

After detailed history taking you will be subjected to detailed clinical examination which mainly includes foot examination with the help of **10 g monofilaments and 128 Hz tuning fork**, to check for "Loss of pressure sensation (LOPS)", both of which are non-invasive methods of examination.

Then you will be subjected to a few blood investigations, namely **FBS/PPBS, HbA1C (Glycocylated Haemoglobin), Serum Vitamin B12, Serum TSH (Thyroid Stimulating Hormone), CBC (Complete Blood Count), Serum Creatinine**.

RISKS AND BENEFITS:

There are no potential risks involved in this study.

Benefits of taking part in this research:

By taking part in this study, diabetic neuropathy can be differentiated from peripheral neuropathy caused by B12 deficiency by the diagnosis of the same. As Vitamin B12 deficiency is a treatable condition, it can be immensely beneficial to you.

VOLUNTARY PARTICIPATION / WITHDRAWAL FROM THE STUDY:

Taking part in the study is voluntary. You may choose not to enroll yourself in this study and may choose to leave the study anytime in between.

ALTERNATIVES:

Your decision regarding participation in study will not change present or future health care services offered to you at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. You would simply be excluded from the study if you wish to, and all your details shall be kept confidential and you will get the routine line of management.

PRIVACY AND CONFIDENTIALITY:

All data collected or disclosed by you during the course of participation of study, will be kept fully confidential. If however during the course it becomes necessary for the progress of the course to disclose the identity, it would be done so only after your informed & written consent.

The only people to know that you are a research subject are members of the research team. No information about you will be disclosed to other

without your written permission except:

- In emergency to protect your rights AND welfare.
- If required by law.

AUTHORIZATION TO PUBLISH RESULT:

The results of the study may be used to publish an article. When the results of research published or discussed, in a conference, no information will be displayed that would disclose your identity. Any information obtained in connection with this study and that can be identified with you will remain confidential.

FINANCIAL INCENTIVES FOR PARTICIPATION:

No additional costs shall be incurred upon you for the purpose of this study.

It is purely being done with the idea of research and all the cost of study will be borne by the investigator.

COMPENSATION:

In the event that you become injured as a result of taking part in this study, treatment will be offered to you at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum, or you will be given information about where to receive medical care. However, no reimbursement, compensation or free medical care will be given.

QUESTIONS/CONTACT DETAILS:

You shall be free to contact the below mentioned name & addresses anytime during the study period for any clarification or help as you may desire for.

Dr. _____

Department of General Medicine,

Jawaharlal Nehru Medical College,

Nehru Nagar, KLE Hospital Road,

Belagavi- 590010

Dr. _____

MD (GENERAL MEDICINE),

Department of General Medicine,

Jawaharlal Nehru Medical College,

Nehru Nagar, KLE Hospital Road,

Belagavi- 590010

In case you need any further information regarding your rights as study participant you may contact:

Dr. GANGA. S. PILLI

Professor of Pathology & Chairman,

JNMC Institutional Ethics Committee

on Human Subjects Research,

Jawaharlal Nehru Medical College

Nehru Nagar, KLE Hospital Road

Mobile – 9480275601

CONSENT STATEMENT:

I the undersigned Mr/Mrs/Dr_____ do hereby give consent for my participation in this research study after being explained in-depth about the important elements of this study in my own vernacular language.

I give this consent voluntarily in my sound mind and good faith, knowing very well the risks involved and been given enough time to clear my doubts and other queries to participate as a 'subject' in this study. I do hereby also give consent for publication of this article in any media / journal and have no objections whatsoever.

Signature or left thumb print of participant or legally authorized representative

Participants name: _____

Signature: _____

Witness/guardian name: _____

Signature_____

Investigator's name:

Signature_____

Guide's name:

Signature_____

Date: ___/___/_____ Place: _____

माहिती मिळाल्यानंतर दिलेली सहमति

* माननीय श्री /श्रीमती /डॉक्टर : ----------यांना

या संशोधन अभ्यासक्रमात तुम्ही आपले नांव द्यावे अशी मी आपणास विनंती करतो.

"टाईप-२ मधूमेहाच्या रोग्यामध्ये मोठ्या प्रमाणात व्हिटॅमिन बी-१२ ची शरीरातील कमतरता आणि वैद्यकिय दृष्टिकोणातून मज्जा संस्थेच्या रोगाचा, मेटफॉरमीन चा वापर करुन केलेला अभ्यास" जो डॉ. पोस्ट ग्रॅज्युएट विद्यार्थी, सामान्य औषोधोपचार पध्दतीचा एम.डी पदवी मिळविण्यासाठी अभ्यास करत आहेत, ते हा आपला अभ्यासक्रम डॉ. , प्रोफेसर आणि सामान्य औषोधपचार विभाग, जवाहरलाल नेहरु मेडिकल कॉलेज, बेळगांव यांच्या देखरेखीखाली व मार्गदर्शनानुसार करणार आहेत.

या अभ्यासक्रमामध्ये सामिल होण्याची मी विनंती करतो. कारण तुम्ही या अभ्यासक्रमात भाग घेण्याच्या कसोटीत योग्य असे आहात.

तुमचा या अभ्यासक्रमातील सहभाग हा स्वयंभू आहे. या अभ्यासक्रमामध्ये तुम्हास तुमच्याविषयी प्रश्न विचारले जातील व त्याची उत्तरे तुम्ही तुमच्या क्षमतेनुसार योग्य अशी द्यावयाची आहेत. तुमच्या या अभ्यासक्रमात भाग घेणे किंवा न घेण्याच्या निर्णयामुळे तुम्हास येथे मिळणाऱ्या उपचार पध्दतीवर कोणताही परिणाम होणार नाही. जर का तुम्ही या अभ्यासक्रमात सहभागी झालात तरीसुध्दा तुम्ही या आपल्या सहभागातून कोणत्याही क्षणी मुक्ती प्राप्त करु शकता.

* **अभ्यासाचे नांव :**

"टाईप-२ मधूमेहाच्या रोग्यामध्ये मोठ्या प्रमाणात व्हिटॅमिन बी-१२ ची शरीरातील कमतरता आणि वैद्यकिय दृष्टिकोणातून मज्जा संस्थेच्या रोगाचा, मेटफॉरमीन चा वापर करुन केलेला अभ्यास"

* **अभ्यासाचा उद्देश :**

टाईप-२ मधूमेहाच्या रोग्यामध्ये मेटफॉरमीनचा उपयोग करुन किंवा न करुन, मोठ्या प्रमाणात व्हिटॅमिन बी-१२ ची शरीरातील कमतरता आणि मज्जा संस्थेच्या रोगांची तुलना करणे असा आहे.

*** अभ्यासक्रमाची पध्दती :**

जर का तुम्ही या अभ्यासक्रमात सहभागी झालात तर, तुमच्या घराण्याचा (कुटुंबाचा) संपूर्ण पूर्व इतिहास विचारला जाईल. आणि नंतर तुमची वैद्यकिय दृष्टिकोणातून तपासणी केली जाईल.

याअभ्यासामध्ये तुमच्या पायाची तपासणी केली जाईल व त्यावेळी 10 ग्रॅम मोनोफिलामेटस पायावर लावून आणि 128 हडर्स कंपनसंख्या असलेल्या दुतोंडी काटयाच्या मदतीने तुमच्या **"कमी प्रमाणात झालेला संवेदनाचा अभ्यास"** करण्यात येईल.

तसेच तुमचे एफबीएस, पीपीबीएस, एचबी.ए.सी. (रक्तशर्करा) रक्ताच्यामध्ये व्हिटॅमिन बी-१२ ची मात्रा, टीएसएच, (थॉयरॉईड ग्रंथातील प्रवाहित झालेला हार्मोन) झीबीसी तसेच रक्ताच्या पातळ पदार्थात असलेली क्रियाटीनीन मात्रा किती आहे हे पाहिले जाईल.

*** धोके व फायदे :**

या अभ्यास क्रमामध्ये कोणतेही धोके नाहीत.

- **या संशोधनात भाग घेतल्यामुळे मिळणारे फायदे :**

या अभ्यासक्रमात तुम्ही भाग घेतल्यामुळे मधुमेहामध्ये झालेले मज्जातंतूचे रोग आणि व्हिटॅमिन बी-12च्या कमतरतेमुळे निर्माण झालेल्या मज्जातंतूच्या रोगांची तुलना करता येईल. कारण व्हिटॅमिन बी-12 ची कमतरता असणारे रोग बरे करता येतात व त्यामुळे तुम्हास मोठ्याप्रमाणात आरोग्याचे फायदे होतील.

*** या अभ्यासक्रमात स्वतःहून सहभागी होणे /त्यामधून आपले नांव कमी करुन घेणे:**

आपण या अभ्यासक्रमात स्वतःहून सहभागी होवू शकता. तुम्ही या अभ्यासक्रमात भाग घेणे सुध्दा नाकारु शकता आणि भाग घेतल्यास कोणत्याही वेळी आपले नाव कमी करु शकता.

*** पर्याय उपाय :-**

या संशोधन अभ्यासामध्ये तुम्ही भाग घेतल्याने के.एल.ई प्रभाकर कोरे हॉस्पीटल व वैद्यकिय संशोधन केंद्र बेळगाव याव्दारे भविष्यात मिळण्याच्या कोणत्याही वैद्यकिय सेवेवर परिणाम होणार नाही. तुमचे नाव फक्त या

अभ्यासक्रमातून कमी करण्यात येईल. तुमचे नाव व सहभाग हा गुप्त राखला जाईल. आणि तुम्हाला मिळणाऱ्या सुविधा तुम्हास मिळतील.

* गुप्तता :-

या संशोधनामध्ये तुमच्या सहभागामुळे घेतलेली संपूर्ण माहिती किंवा तुम्ही दिलेली माहिती ही गुप्त राखण्यात येईल. तथापि जरुरत असेल तर या संबंधीची माहिती तुम्हास पूर्व सूचना देवून व तुमची लेखी परवानगी घेऊन उघड करण्यात येईल.

या संशोधनाची माहिती फक्त संशोधकांना व त्या संबंधीत जोडलेल्या व्यक्तिनाच माहीत असेल. तुमच्या विषयीची माहिती कोणासही तुमच्या परवानगी देण्यात येणार नाही. ते तुमच्या सूरक्षसोयी व आधिकार सुरक्षित राखून आणिबाणीच्या प्रसंगी /निगडीच्या प्रसंगी ते उपयोगात आणले जातील.

- ती तुमच्या कल्याणासाठी आणि आणिबाणीच्या प्रसंगी तुमचे अधिकार सुरक्षित राखण्यासाठी आणले जातील.
- तसेच कायद्याच्या जरुरीनुसार ते उपयोगात आणले जाईल.

*** अभ्यासाचे निष्कर्ष प्रसिध्द करण्याचे आधिकार :-**

या अभ्यासक्रमाचे निष्कर्ष लेखाद्वारे प्रसिध्द करण्यात येतील. हे संशोधाचे निष्कर्ष प्रसिध्द करण्यासाठी किंवा परिषदेमध्ये चर्चा करण्यासाठी उपयोगात आणले जातील परंतु तुमची ओळख ही उघड करण्यात येणार नाही. यासंबंधीत अभ्यासक्रमामध्ये तुमच्या विषयीची मिळालेली संपूर्ण माहिती ही गुप्त ठेवण्यात येईल.

*** कार्यक्रमात भाग घेतल्याबद्दल मिळणारी आर्थिक मदत:**

या अभ्यासक्रमात भाग घेतल्याबद्दल कोणताही खर्च तुम्हास करावा लागणार नाही. हे फक्त संशोधनासाठी करण्याचा विचार आहे आणि संशोधक हे फक्त अभ्यासक्रमावर खर्च करणार आहे.

*** नुकसान भरपाई:**

जर का हा अभ्यासक्रम करताना तुम्हास कोणतीही इजा पोहचली तर के.एल.ई. डॉ. प्रभाकर कोरे हॉस्पीटल आणि वैद्यकिय संशोधन केंद्र येथे तुमच्यावर उपचार करण्यात ये ईल. किंवा तुम्हास कोठे वैद्यकिय सेवा मिळू शकेल हे सांगण्यात येईल. तुम्हास नुकसानभरपाई, केलेल्या खर्चाची भरपाई किंवा मुफ्त वैद्यकिय सेवा त्या ठिकाणी मिळणार नाही.

*** प्रश्न व संपर्क:**

या अभ्यास क्रमाच्या काळामध्ये कोणत्याही वेळी तुम्ही याबाबत खालील व्यक्तिशी संपर्क करु शकता. व तुमचे शंका समाधान करु शकता.

डॉ.
एम. डी. पोस्ट ग्रॅज्युएट विद्यार्थी
सामान्य औषधोपचार विभाग
जवाहरलाल नेहरु, के .एल.ई. हॉस्पीटल रोड,
बेळगांव ५९००१०
मोबाईल :

डॉ.
एम.डी. (सामान्य औषधोपचार)
प्रोफेसर सामान्य औषधोपचार विभाग जे. एन. एम सी. मेडिकल कॉलेज, नेहरु नगर, के.एल.ई. हॉस्पीटल रोड, बेळगांव ५९००१०
मोबाईल :

जर का तुमच्या अधिकार संबंधी माहिती पाहिजे असल्यास तुम्ही खालील व्यक्तिशी संपर्क साधू शकता.

डॉ. गंगा एस. पिल्ली,
पॅथॉलॉजी विभाग के प्रोफेसर व चेअरमन,
मानव संशोधन, जे.एन.एम.सी. इथिक्स कमिटी,
प्रोफेसर, पॅथॉलॉजी विभाग, जे.एन.एम. सी. बेळगाव
फोन नं: 9480275601

सहमतीचा नमुना

मी या अभ्यासक्रमामध्ये खाली दिलेल्या संबंधीत रेषेवर सही करुन स्वतःहून भाग घेत आहे. मी या अभ्यासक्रममधून कोणत्याही वेळी मुक्त होवू शकतो. मी माझे कोणतेही कायदेशीर अधिकार या सहमतीच्या नमुन्यावर सही केल्याने गमवून बसलेलो नाही. मी खाली सही करणार सांगतो कि, हा संपूर्ण नमुना फार्म मी वाचून पाहिला आहे किंवा मला तो वाचून दाखविला आहे व माझ्या भाषेमध्ये तो मला समजावून सांगितला आहे व माझे संपूर्ण शंकासमाधान झालेले आहे. मला या नमुन्या फॉर्म ची कॉपी देण्यात येईल.

या अभ्यासक्रमात भाग घेणाऱ्यांची किंवा त्याच्यातर्फे त्याचे प्रतिनिधीत्व करण्याऱ्यांची सही/डाव्या हाताचा अंगठा

अभ्यासात भाग घेणाऱ्याचे नांव : ----------

सही ----------

साक्षीदाराची किंवा प्रतिनिधीत्व करणाऱ्याचे नांव : ----------

सही ----------

संशोधकाचे नांव : डॉ. नहुष चाफेकर

सही :----------

मार्गदर्शकाचे नांव : डॉ. प्रकाश बबलिचे

सही :----------

तारीख : **स्थळ :**

ತಿಳುವಳಿಕೆ ಒಪ್ಪಿಗೆ ಪತ್ರ

ಆತ್ಮೀಯ ಶ್ರೀ/ಶ್ರೀಮತಿ/ಡಾ. _____

"ಪ್ರಿವ್ಯಾಲೆನ್ಸ್ ಆಫ್ ವಿಟಾಮಿನ್ ಬಿ12 ಡೆಫಿಸಿಯನ್ಸಿ ಆಂಡ್ ಕ್ಲಿನಿಕಲ್ ನ್ಯುರೊಪಥಿ ವಿತ್ ಮೆಟ್‌ಫಾರ್ಮಿನ್ ಯುಸ್ ಇನ ತೈಪ್ 2 ಡಯಾಬಿಟಿಸ್ ಮೆಲ್ಲಟಸ್ ಪೇಷಂಟ್ಸ್" ಎಂಬ ಸಂಶೋಧನಾ ಅಧ್ಯಯನದಲ್ಲಿ ತಾವು ಪಾಲ್ಗೋಳ್ಳಬೇಕೆಂದು ತಮ್ಮಲ್ಲಿ ವಿನಂತಿಸಿಕೊಳ್ಳುತ್ತೇನೆ. ಈ ಸಂಶೋಧನಾಯನ್ನು ಡಾ. , ಸ್ನಾತಕೋತ್ತರ ವೈದ್ಯಕೀಯ ವಿದ್ಯಾರ್ಥಿಯು ಮಾಡುತ್ತಿದ್ದು ಡಾ. ಪ್ರಾಧ್ಯಾಪಕರು, ಜನರಲ್ ಮೆಡಿಸಿನ್ ವಿಭಾಗ ಜವಾಹರಲಾಲ ನೆಹರು ವೈದ್ಯಕೀಯ ಮಹಾವಿದ್ಯಾಲಯ ಬೆಳಗಾವಿ ಇವರ ಮಾರ್ಗದರ್ಶನ ಮಾಡುತ್ತಿದ್ದಾರೆ.

ತಾವುಗಳು ಈ ಸಂಶೋಧನೆಯಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳಲು ಬೇಕಾಗಿರುವ ಎಲ್ಲಾ ಮಾನದಂಡಗಳನ್ನು ಪೂರೈಸಿರುತ್ತೀರಿ ಮತ್ತು ಅರ್ಹರಾಗಿರುತ್ತೀರಿ.

ತಾವು ಈ ಸಂಶೋಧನೆಯಲ್ಲಿ ಸ್ವ–ಇಚ್ಛೆಯಿಂದ ಪಾಲ್ಗೊಳ್ಳಬಹುದು ಸಂಶೋಧನೆಯ ಸಮಯದಲ್ಲಿ ನಿಮಗೆ ಕೆಲವು ಪ್ರಶ್ನೆಗಳನ್ನು ಕೇಳಲಾಗುವುದು ಹಾಗೂ ತಾವು ಈ ಪ್ರಶ್ನೆಗಳಿಗೆ ತಮಗೆ ಗೊತ್ತಿರುವ ಮಟ್ಟಿಗೆ ಸರಿಯಾಗಿ ಉತ್ತರಿಸಬೇಕು. ನೀವು ಸಂಶೋಧನೆಯಲ್ಲಿ ಪಾಲ್ಗೋಳ್ಳಲು ಬಯಸದೇ ಇದ್ದರೂ ಸಹ ಅದು ನಿಮ್ಮ ಚಿಕಿತ್ಸೆಯ ಮೇಲೆ ಯಾವುದೇ ಪರಿಣಾಮ ಬೀರುವುದಿಲ್ಲ ಮತ್ತು ನೀವು ಸಂಶೋಧನೆಯ ಭಾಗವಾಗಿ ನಂತರ ನೀವು ಇದರಿಂದ ಹಿಂದೆ ಸರಿಯಲು ಬಯಸಿದರೆ ಅದಕ್ಕೂ ನಮ್ಮ ಸಮ್ಮತಿ ಇರುತ್ತದೆ.

ಶೀರ್ಷಿಕೆ :–

"ಪ್ರಿವ್ಯಾಲೆನ್ಸ್ ಆಫ್ ವಿಟಾಮಿನ್ ಬಿ12 ಡೆಫಿಸಿಯನ್ಸಿ ಆಂಡ್ ಕ್ಲಿನಿಕಲ್ ನ್ಯುರೊಪಥಿ ವಿತ್ ಮೆಟ್‌ಫಾರ್ಮಿನ್ ಯುಸ್ ಇನ ತೈಪ್ 2 ಡಯಾಬಿಟಿಸ್ ಮೆಲ್ಲಟಸ್ ಪೇಷಂಟ್ಸ್"

ಸಂಶೋಧನೆಯ ಉದ್ದೇಶ :–

ವಿಟಾಮಿನ್ ಬಿ12 ಮತ್ತು ಬಾಹ್ಯ ನರರೋಗದಿಂದ ಉಂಟಾಗುವ ಮಧುಮೇಹ ಮೆಲ್ಲಿಟಸ್‌ನ ಚಿಕಿತ್ಸೆಯನ್ನು ಮೆಟ್‌ಫಾರ್ಮಿನ್‌ನಿಂದ ಅಥವಾ ಮೆಟ್‌ಫಾರ್ಮಿನ್ ಇಲ್ಲದಯೇ ನೀಡುವ ಚಿಕಿತ್ಸೆಯನ್ನು ಅಭ್ಯಸಿಸುವುದು.

ವಿಧಾನಗಳು :–

ರೋಗದ ಇತಿಹಾಸವನ್ನು ತಿಳಿದುಕೊಂಡ ನಂತರ ನಿಮಗೆ ಕೆಲವು ಪರೀಕ್ಷೆಗಳನ್ನು ಮಾಡಲಾಗುವುದು, ಮುಖ್ಯವಾಗಿ ನಿಮ್ಮ ಪಾದಗಳಲ್ಲಿ ಒತ್ತಡ ಸಂವೆದನ ನಷ್ಟವಾಗಿದಯೇ ಎಂಬುದನ್ನು

10g ಮೊನೋಫಿಲಾಮೆಂಟ್ಸ್ ಮತ್ತು 128Hz ಟ್ಯೂನಿಂಗ್ ಫೋರ್ಕ್ ಮುಖಾಂತರ ಪರೀಕ್ಷಿಸಿಲಾಗುವುದು. ಈ ವಿಧಾನದ ಪರೀಕ್ಷೆಯಲ್ಲಿ ನಿಮಗೆ ಯಾವುದೇ ತರಹದ ನೋವು ಆಗುವುದಿಲ್ಲ.

ಇದಾದ ನಂತರ ಕೆಲವು ರಕ್ತದ ಮಾದರಿಗಳನ್ನು ಪರೀಕ್ಷಿಸಿಲಾಗುವುದು, ಅವುಗಳೆಂದರೆ ಊಟದ ಮೊದಲಿನ ಹಾಗೂ ಊಟದ ನಂತರದ ರಕ್ತದಲ್ಲಿನ ಸಕ್ಕರೆ ಪ್ರಮಾಣದ ಪರೀಕ್ಷೆ, HbA1C (ಗ್ಲೈಕೋಸಿಲೇಟೆಡ ಹಿಮೋಗ್ಲೋಬಿನ್), ಸಿರಮ್ ವಿಟಾಮಿನ್ ಬಿ12, ಸಿರಮ್ ಟಿ.ಎಸ್.ಎಚ್ (ಥೈರಾಯಿಡ್ ಸ್ಟಿಮ್ಯೂಲೇಟಿಂಗ್ ಹಾರ್ಮೋನ್), ಸಿ.ಬಿ.ಸಿ (ಕಂಪ್ಲೀಟ್ ಬ್ಲಡ್ ಕೌಂಟ್), ಸಿರಮ್ ಕ್ರಿಯೇಟಿನೈನ್.

ಪ್ರಯೋಜನಗಳು ಮತ್ತು ಅಪಾಯಗಳು :

ಈ ಸಂಶೋಧನಾ ಅಧ್ಯಯನದಲ್ಲಿ ಯಾವುದೇ ಅಪಾಯಗಳಿಲ್ಲ.

ಸಂಶೋಧನೆಯಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳುವುದರಿಂದಾಗುವ ಪ್ರಯೋಜನೆಗಳು :

ಈ ಸಂಶೋಧನೆಯಲ್ಲಿ ನೀವು ಪಾಲ್ಗೊಳ್ಳುವುದರಿಂದ ವಿಟಾಮಿನ್ ಬಿ12 ಕೊರತೆಯಿಂದ ಉಂಟಾಗುವ ಬಾಹ್ಯ ನರ ದೌರ್ಬಲ್ಯ ಮತ್ತು ಮಧುಮೇಹ ನರದೌರ್ಬಲ್ಯಗಳ ನಡುವಿನ ವ್ಯತ್ಯಾಸವನ್ನು ರೋಗ ನಿರ್ಧಾರಕ ಪರೀಕ್ಷೆಗಳಿಂದ ತಿಳಿದುಕೊಳ್ಳಬಹುದು. ಇಟಾಮಿನ್ ಬಿ12 ಕೊರತೆಯನ್ನು ಚಿಕಿತೆಯಮೂಲಕ ಸರಿಪಡಿಸಬಹುದಾಗಿದೆ. ಇದರಿಂದ ನಿಮಗೆ ತೊಂಬಾ ಪ್ರಯೋಜನವಾಗುವುದು.

ಸ್ವಯಂಪ್ರೇರಿತ ಪಾಲ್ಗೋಳ್ಳುವಿಕೆ/ ಹಿಂದೆ ಸರಿಯುವಿಕೆ :

ಈ ಸಂಶೋಧನಾ ಅಧ್ಯಯನದಲ್ಲಿ ನೀವು ಸ್ವಯಂ ಪ್ರೇರಿತರಾಗಿ ಪಾಲ್ಗೋಳ್ಳಬಹುದು ಅಥವಾ ಪಾಲ್ಗೋಳ್ಳದೇ ಇರಬಹುದು, ಅಥವಾ ನೀವು ಪಾಲ್ಗೋಳ್ಳಲು ನಿರ್ಧರಿಸಿ ನಂತರದ ದಿನಗಳಲ್ಲಿ ಅದರಿಂದ ಹಿಂದೆ ಸರಿಯಬಹುದು.

ಪರ್ಯಾಯಗಳು :

ಈ ಸಂಶೋಧನೆಯಲ್ಲಿ ಪಾಲ್ಗೋಳ್ಳುವುದರಿಂದ/ ಪಾಲ್ಗೋಳ್ಳದೇ ಇರುವ ನಿರ್ಧಾರದಿಂದ ನಿಮಗೆ ಕೆ.ಎಲ್.ಇ ಡಾ. ಪ್ರಭಾಕರ ಕೋರೆ ಆಸ್ಪತ್ರೆ ಮತ್ತು ವೈದ್ಯಕೀಯ ಸಂಶೋಧನಾ ಸಂಸ್ಥೆಯಲ್ಲಿ ನೀಡಲಾಗುತ್ತಿರುವ ಚಿಕಿತ್ಸೆಯ ಮೇಲೆ ಯಾವುದೇ ಪರಿಣಾಮ ಬೀರುವುದಿಲ್ಲ. ಒಂದು ವೇಳೆ ನೀವು ಸಂಶೋಧನೆಯ ಭಾಗವಾದರೆ ನಿಮ್ಮ ಹೆಸರನ್ನು ಗೌಪ್ಯವಾಗಿಡಲಾಗುವುದು.

ಗೌಪ್ಯತೆ :–

ಸಂಶೋಧನೆಯ ಸಂದರ್ಭದಲ್ಲಿ ಸಂಗ್ರಹಿಸಿರುವ ಎಲ್ಲಾ ಮಾಹಿತಿಯನ್ನು ಕಾನೂನಿಗನುಸಾರವಾಗಿ ಗೌಪ್ಯವಾಗಿಡಲಾಗುವುದು. ಎಲ್ಲಿಯೂ ನಿಮ್ಮ ಹೆಸರು ಪ್ರಕಟವಾಗದೇ ನಿಮ್ಮನ್ನು ಗೌಪ್ಯ ಸಂಖ್ಯೆಯಿಂದ ಗುರುತಿಸಲಾಗುವುದು. ಮುಂದಿನ ದಿನಗಳಲ್ಲಿ ಈ ಸಂಶೋಧನಾ ವರದಿಯು ಪ್ರಕಟಗೊಂಡಾಗಲೂ ಸಹ ನಿಮ್ಮ ಹೆಸರನ್ನು ಗೌಪ್ಯವಾಗಿಡಲಾಗುವುದು. ಅಕಸ್ಮಾತ್ತಾಗಿ ಯಾವುದೇ ಕಾರಣಕ್ಕಾಗಿ ನಿಮ್ಮ ಹೆಸರನ್ನು ಬಹಿರಂಗಪಡಿಸುವ ಸಂದರ್ಭ ಎದುರಾದರೇ, ನಿಮ್ಮಿಂದ ಲಿಖಿತ ಅನುಮತಿಯನ್ನು ಪಡೆದುಕೊಂಡ ನಂತರವಷ್ಟೇ ಬಹಿರಂಗಪಡಿಸಲಾಗುವುದು.

ನೀವು ಈ ಸಂಶೋಧನೆಯಲ್ಲಿ ಪಾಲ್ಗೊಂಡಿರುವುದು ಕೇವಲ ಸಂಶೋಧನಾ ತಂಡಕ್ಕೆ ಮಾತ್ರ ಗೊತ್ತಿರುತ್ತದೆ, ನಿಮ್ಮ ಬಗ್ಗೆ ಎಲ್ಲ ಮಾಹಿತಿಯನ್ನು ಗೌಪ್ಯವಾಗಿಡಲಾಗುವುದು ಮತ್ತು ಕೆಳಗಿನ ಸಂದರ್ಭಗಳಲ್ಲಿ ಬಿಟ್ಟರೆ ನಿಮ್ಮಿಂದ ಲಿಖಿತ ಅನುಮತಿಯನ್ನು ಪಡೆಯದೇ ನಿಮ್ಮ ಹೆಸರನ್ನು ಬಹಿರಂಗಪಡಿಸಲಾಗುವುದಿಲ್ಲ.

- ತುರ್ತು ಸಂದರ್ಭಗಳಲ್ಲಿ ನಿಮ್ಮ ಹಕ್ಕುಗಳನ್ನು ರಕ್ಷಿಸಲು
- ಕಾನೂನಿಗನುಸಾರವಾಗಿ ಅವಶ್ಯಕತೆ ಕಂಡು ಬಂದಲ್ಲಿ

ಫಲಿತಾಂಶ ಪ್ರಕಟಿಸಲು ಇರುವ ಅಧಿಕಾರಗಳು :–

ಈ ಸಂಶೋಧನೆಯ ಫಲಿತಾಂಶವನ್ನು ಕೆ.ಎಲ್.ಇ. ವಿಶ್ವವಿದ್ಯಾಲಯ ಬೆಳಗಾವಿ ಇವರಿಗೆ ಎಮ್.ಡಿ. ಪದವಿ ಪೂರ್ಣಗೊಳಿಸಲು, ವಿಮರ್ಶಿಸಲು ಹಾಗೂ ಪ್ರಕಟಿಸಲು ಕಳುಹಿಸಿಕೊಡಲಾಗುವುದು.

ಪ್ರೋತ್ಸಾಹ ಧನ :–

ನಿಮಗೆ ಈ ಸಂಶೋಧನೆಯ ಭಾಗವಾಗಲು ಯಾವುದೇ ರೀತಿಯ ಹಣ, ಉಡುಗೊರೆಯನ್ನು ನೀಡಲಾಗುವುದಿಲ್ಲ.

ಸಂಶೋಧನೆಯ ಸಂದರ್ಭದಲ್ಲಿ ಅಥವಾ ಮುಂದೆ ಯಾವುದಾದರೂ ಪ್ರಶ್ನೆಗಳು ಅಥವಾ ಅನುಮಾನಗಳಿದ್ದಲ್ಲಿ ಈ ಕೆಳಗಿನವರನ್ನು ಸಂಪರ್ಕಿಸಬಹುದಾಗಿದೆ.

ಸಂಪರ್ಕಿಸುವ ವಿಳಾಸ :

ಈ ಕೆಳಗಿನ ವ್ಯಕ್ತಿಗಳನ್ನು ನೀಡಿರುವ ವಿಳಾಸದಲ್ಲಿ ಶೋಧನೆಯ ಸಂದರ್ಭದಲ್ಲಿ ನಿಮಗೆ ಯಾವುದಾದರೂ ಪ್ರಶ್ನೆಗಳಿದ್ದಲ್ಲಿ ಅಥವಾ ಸಂಶಯಗಳಿದ್ದಲ್ಲಿ ಸಂಪರ್ಕಿಬಹುದಾಗಿದೆ.

ಡಾ.

ಸ್ನಾತಕೋತ್ತರ ವಿದ್ಯಾರ್ಥಿ

ಜನರಲ್ ಮೆಡಿಸಿನ್ ವಿಭಾಗ

ಜವಾಹರಲಾಲ್ ನೆಹರು ವೈದ್ಯಕೀಯ ಕಾಲೇಜು

ನೆಹರು ನಗರ ಕೆ.ಎಲ್.ಇ ಆಸ್ಪತ್ರೆ ರಸ್ತೆ

ಬೆಳಗಾವಿ 590010

ಮೋ ನಂ.

ಡಾ.

ಎಂ.ಡಿ (ಜನರಲ್ ಮೆಡಿಸಿನ್)

ಪ್ರಾಧ್ಯಾಪಕರು

ಜನರಲ್ ಮೆಡಿಸಿನ್ ವಿಭಾಗ

ಜವಾಹರಲಾಲ್ ನೆಹರು ವೈದ್ಯಕೀಯ ಕಾಲೇಜು

ನೆಹರು ನಗರ ಕೆ.ಎಲ್. ಇ. ಆಸ್ಪತ್ರೆ ರಸ್ತೆ

ಬೆಳಗಾವಿ 590010

ಮೋ ನಂ.

ಡಾ. ಗಂಗಾ ಪಿಳ್ಳಿ

ಪ್ರಾಧ್ಯಾಪಕರು ಪ್ಯಾಥೋಲಾಜಿ ವಿಭಾಗ ಮತ್ತು ಛೇರಮನ್,

JNMC Institutional Ethics committee

On Human Subjects Research

ಜವಾಹರಲಾಲ್ ನೆಹರು ವೈದ್ಯಕೀಯ ಕಾಲೇಜ

ನೆಹರು ನಗರ ಕೆ.ಎಲ್.ಇ. ಆಸ್ಪತ್ರೆ ರಸ್ತೆ

ಬೆಳಗಾವಿ 590010

ಮೊ–9480275601

ಒಪ್ಪಿಗೆ ಪತ್ರ

ನಾನು ಶ್ರೀ/ಶ್ರೀಮತಿ/ಡಾ. _____ ನನ್ನ ಸ್ವ-ಇಚ್ಛೆಯಿಂದ್ನೀ ಸಮ್ಮತಿ ಪತ್ರಕ್ಕೆ ಸಹಿ ಮಾಡಿರುತ್ತೇನೆ. ನಾನು ನನ್ನ ಸಮ್ಮತಿಯನ್ನು ಯಾವಾಗ ಬೇಕಾದರೂ ಹಿಂಪಡೆಯಬಹುದು. ಕೇವಲ ಸಹಿ ಮಾಡಿದ ಮಾತ್ರಕ್ಕೆ ನನ್ನ ಕಾನೂನಾತ್ಮಕ ಹಕ್ಕುಗಳನ್ನು ಬಿಟ್ಟು ಕೊಟ್ಟಂತಾಗುವುದಿಲ್ಲ. ನಾನು ಈ ಸಮ್ಮತಿ ಪತ್ರವನ್ನು ಸಂಪೂರ್ಣವಾಗಿ ಓದಿ, ನನ್ನ ಭಾಷೆಯಲ್ಲಿ ಓದಿಸಿ ತಿಳಿದುಕೊಂಡಿರುತ್ತೇನೆ. ಸಮ್ಮತಿ ಪತ್ರಕ್ಕೆ ಸಹಿ ಮಾಡಿದ ನಂತರ ಇದರ ಒಂದು ಪ್ರತಿಯನ್ನು ನಾನು ಕಾಯ್ದಿರಿಸಿಕೊಳ್ಳುತ್ತೇನೆ.

ಭಾಗಿದಾರರ ಸಹಿ / ಎಡಗೈ ಹೆಬ್ಬೆರಳಿನ ಗುರುತು ಅಥವಾ ಅವರ ಕಾನೂನಾತ್ಮಕ ಪ್ರತಿನಿಧಿಗಳು.

ಭಾಗವಹಿಸುವವರ ಹೆಸರು

ಭಾಗಿದಾರರ ಸಹಿ / ಎಡಗೈ ಹೆಬ್ಬೆರಳಿನ ಗುರುತು

ಸಹಿ / ಎಡಗೈ ಹೆಬ್ಬೆರಳಿನ ಗುರುತು

ಸಾಕ್ಷಿದಾರರ ಸಹಿ

ಸಹಿ / ಎಡಗೈ ಹೆಬ್ಬೆರಳಿನ ಗುರುತು

ತನಿಖಾಧಿಕಾರಿಯ ಹೆಸರು
ಡಾ.ನಹುಷ ಡಿ. ಚಾಫೆಕರ
ಸಹಿ

ಮಾರ್ಗದರ್ಶಕರ ಹೆಸರು
ಡಾ. ಪ್ರಕಾಶ ಬಬಲಿಚೆ

ಸಹಿ

ದಿನಾಂಕ: ಸ್ಥಳ:

जानकारी प्राप्त होने के बाद दी गई सम्मति

माननीय श्री. श्रीमती. डॉ/ ----------

इस संशोधन अभ्यास में आप आपका नाम देनेकी विनंती करता हूँ। "टाईप-२ मधूमेह के रोगीयोंमें बडे पैमानेपर व्हिटॅमिन बी-12 की कमी होना और वैद्यकिय बाते ध्यान में रखकर मज्जासंस्थाके रोग का मेटफारसीन का इस्तेमाल करके किया हुआ अभ्यासक्रम ।" जो डॉ. पोस्ट ग्रॅजुएट छात्र, सामान्य औषधोपचार का उपयोग करके एम.डी पदवी हासील करने के लिए कर रहे है। वे उनका यह अभ्यासक्रम डॉ.
और सामान्य औषधोपचार विभाग जवाहरलाला नेहरु मेडीकल कॉलेज बेलगाम इसके मार्गदर्शकके नुसार कर रहा हूँ ।

इस अभ्यासक्रम में आप शामिल होनेकी मैं आपको विनंति करता हूं क्योंकि, आप इस अभ्यासक्रममें हिस्सा लेने के लिए योग्य है।

इस अभ्यासक्रम में आप स्वयंम् हिस्सा लेंगे ऐसी मैं आशा करता हूं। इस अभ्यासक्रम के बारेमें, आपको प्रश्न पुछे जाएंगे और आप, आपके बुध्दीके नुसार उनके उत्तर देंगे। आप इस अभ्यासक्रममें शरीक होने से या न होनेसे आपको यहाँ पर मिलनेवाली उपचार पध्दतिपर कोईभी असर नही होगा। यदि आप इस अभ्यासक्रम में शरीक होते है तो भी आप इस अभ्यासक्रमसे किसी भी वक्त मुक्त हो सकते है।

***अभ्यास का नाम :**

"टाईप-२ मधूमेह के रोगीयोंमें बडे पैमानेपर व्हिटॅमिन बी-१२ की कमी होना और वैद्यकिय बाते ध्यान में रखकर मज्जासंस्थाके रोग का मेटफारसीन का इस्तेमाल करके किया हुआ अभ्यासक्रम"

***अभ्यास का उद्देश :**

टाईप-२ मधूमेह के रोगीयों में मेटफॉरसीन का इस्तेमाल करके या न करके, बडे पैमानेपर व्हिटॅमिन बी-12 की शरीरमें कमी होना और मज्जासंस्थाके रोगी तुलना करना ऐसा है।

गोपनिय रखा जायेगा और आपको यहाँपर मिलनेवाली सुविधाये यहाँपर ही बहाल की जायेगी।

*** गोपनियता :**

इस अभ्यासक्रममे आप सम्मिलित होने से जो जानकारी मिलेगी या अपने दी हुई जानकारी गोपनीय रखी जायेगी। परंतु जरुरत होगी तो इसकी जानकारी आपको पूर्वसूचित करके और आपकी लेखी सम्मति लेकर दुसरों को दी जायेगी।

इस संशोधन की जानकारी सिर्फ संशोधकों को और इस संबंधमें आनेवाले व्यक्तियों को ही होगी। आपकी जानकारी, आपके अनुमति के बिगर किसी को भी नही दी जायेगी।

- यह आपके हिपाजत के लिए और आपके अधिकार सुरक्षित रखने हेतु

उपयोग में लायी जायेगी।

- उसीप्रकार यह कानून मुताबिक इस्तेमाल में लायी जायेगी।

*** निष्कर्ष प्रकाशित करने के अधिकार :**

इस अभ्यासक्रम के निष्कर्ष लेखाद्वारे प्रसिध्द कीये जायेंगे। इस अभ्यास क्रम के निष्कर्ष प्रकाशित करनेहेतु या परिषद में विचार-विनिमय करने हेतु उपयोग किये जायेंगे। लेकिन आपकी पहचान नही दी जायेगी। इस अभ्यासक्रम में आपके विषयमें प्राप्त मिली हुई पूरी जानकारी गोपनिय रखी जाएंगी।

*** कार्यक्रम में सम्मिलित होने से मिलनेवाली आर्थिक सहायता:**

इस अभ्यासक्रम में हिस्सा लेने वालोंको कोई भी खर्चा नही करना पडेगा। संशोधन करने के इरादेसे यह सब कर रहे हैं और संशोधक इस अभ्यासक्रम करने हेतु खर्चा करेंगे।

*** नुकसान भरपाई :**

यदी अभ्यास के दौरान आपको कोई जखम हो गयी तो, के.एल.ई.एस. डॉ, प्रभाकर कोरे हॉस्पीटल और वैद्यकिय संशोधन केंद्र बेलगाम में आपके ऊपर उपचार किये जायेंगे, या आपको कहाँपर वैद्यकिय सेवा प्राप्त होगी यह बताया जायेगा। तथापि किया हुआ खर्चा या नुकसान भरपाई आपको नही मिलेगी या इस मामले में आपको कहाँपर मुक्त सेवा मिल सकती है यह बताया जायेगा ।

यदी आप इस अभ्यास में सम्मिलित होते हैं तो आपको आपके परीवार का संपूर्ण इतिहास पुछा जायेगा और उसके बाद आपकी वैद्यकिय हिसाबसे चिकित्सा की जायेगी।

*इसमें आपके पावों की जाँच की जायेगी और उस समय 10 ग्रॅम मोनोफिलामेटस पावोंको लगाया जाएगा और 128 हडर्स कंपनसख्या के ट्यूनिंग फोर्क की मदतसे पाव में "**कम होनेवाले संवेदनों की**" जाँच की जायेगी।*

इसके आलावा आपकी एफ बी एस /पीपीबीएस, एचबीए१सी (रक्तशर्करा)रक्त में व्हिटॅमिन बी-12 की मात्रा टी एस एच (थॉयराईड ग्रंथीसे प्रवाहीत होनेवाला हार्मोन) सीबीसी, और रक्त पतला करनेवाले क्रियाटीनीन की मात्रा कितनी है यह देखा जाएगा।

*** आपत्ती और फायदे:**

इस अभ्यासक्रम से आपको कोई भी आपत्ती नही होगी।

- **इस संशोधन में हिस्सा लेने से मिलनेवाले फायदे :**

इस अभ्यासक्रम में आज हिस्सा लेनेसे, मधुमेह में होनेवाले मज्जातंतू के

रोग और व्हिटॅमिन बी-12 की कमी से निर्माण होनेवाली मज्जातंतू के रोगीकी तुलना की जायेगी। यह करनेका कारण व्हिटॅमिन बी-12 की कमीसे होनेवाले रोग ठिक हो सकते है। और इसके कारण आपको बडे पैमाने पर स्वास्थ लाभ होगा।

**** अभ्यासक्रम में सम्मिलित होना या उसमें से आपका नाम निकाल लेना:***

आप इस अभ्यासक्रममे खुद सम्मिलित हो सकते हो। इस अभ्यासक्रममें आप हिसा नही भी ले सकते हो, और आपने इस अभ्यासक्रम में हिस्सा ले लिया तो आप इसमेंसे आपका नाम किसी भी वक्त कम करते हो।

**** पर्याय :***

इस अभ्यासक्रम में हिस्सा लेने से आपको के.एल.ई. डॉ. प्रभाकर कोरे हॉस्पीटल और वैद्यकिय केंद्र बेलगांम के द्वारा मिलनेवाली कोई भी वैद्यकिय सेवेपर परिणाम नही होगा। यदि आपकी इच्छा है तो, आपका नाम इस अभ्यासक्रमसे कम कर सकते हो। आपका नाम और सम्मिलित होना यह

*** प्रश्न और संपर्क:**

इस अभ्यासक्रम के दौरान आप निचे लिखे नामपर या पत्तेपर संपर्क कर सकते है और आपके प्रश्न पुछ सकते है, और उनका समाधान आपके इच्छा के मुताबिक किया जायेगा।

डॉ.
एम. डी. पोस्ट ग्रॅज्युएट छात्र
सामान्य औषधोपचार विभाग
जवाहरलाल नेहरु, के.एल.ई. हॉस्पीटल रोड,
बेळगांव ५९००१०
मोबाईल :

डॉ.
एम.डी. (सामान्य औषधोपचार)
प्रोफेसर सामान्य औषधोपचार विभाग जे. एन. एम सी. मेडिकल कॉलेज, नेहरु नगर, के.एल.ई. हॉस्पीटल रोड, बेळगांव ५९००१०
मोबाईल :

यदि आपको आपके अधिकार संबंधी जानकारी चाहिए तो आप निम्नलिखित व्यक्तिसे संपर्क कर सकते हो।

डॉ. गंगा एस. पिल्ली,
पॅथॉलॉजी विभाग के प्रोफेसर व चेअरमन,
मानव संशोधन, जे.एन.एम.सी. इथिक्स कमिटी,
प्रोफेसर, पॅथॉलॉजी विभाग, जे.एन.एम. सी. बेळगाव
फोन नं: 9480275601

सम्मतीका नमुना

मैं इस अभ्यास में, निचे किये हुए मेरे लिए लागू होनेवाले लाईनपर सही करके स्वयं इसमें भाग ले रहा हूँ। मैं इस अभ्यास क्रम से कभी भी, किसी भी वक्त मुक्त हो सकता हूँ। मैने मेरे कोई भी कानूनी अधिकार इस सम्मति नमुनेपर हस्ताक्षर करके नही गमाये हुए है। मैं निचे सही करनेवाला यह बताना चाहता हूँ कि, यह नमुना फार्म मैंने पढ लिया है या मुझे यह पढकर समझाया गया है और मुझे मेरी भाषामें यह समझाया है और मेरा पूरा शंकासमाधान किया है। मुझे इस नमुना फार्म की कॉपी दी गई है।

अभ्यास में भाग लेनेवालों की या उसकी तरफसे उसके प्रतिनिधीत्व करनेवाले की सही /बाये हात के अंगुठेका निशान

अभ्यास में भाग लेनेवाले का नाम : ----------

सही :----------

साक्षीदार का या प्रतिनिधी करनेवाले का नाम: ----------

सही:----------

संशोधक का नाम : डॉ. नहुष चाफेकर

सही :----------

मार्गदर्शकाचे नांव : डॉ. प्रकाश बबलिचे

सही :----------

तारीख : **स्थळ :**

ANNEXURE-II PROFORMA

PROFORMA / QUESTIONNAIRE TO BE USED FOR DATA COLLECION

The proposed proforma/questionnaire to be used for data collection for the study tilted, "**PREVALENCE OF VITAMIN B12 DEFICIENCY AND CLINICAL NEUROPATHY WITH METFORMIN USE IN TYPE 2 DIABETES MELLITUS PATIENTS**" is as follows:

1) Patient Details:

- O.P.D NO.:
- NAME:
- SEX:
- AGE:
- ADDRESS:

2) Chief Complaints:

- Polyurea /polydipsia/polyphagia:
- Numbness:
- Burning sensation:
- Muscle weakness:
- Any other complaints :

3) General Examination:

- Built and Nourishment:
- Weight:
- Pulse:
- BP: Supine :- Standing:-
- R/R:

4) Systemic Examination:

- CNS:
- RESPIRATORY:
- PER ABDOMEN:
- CVS:

5) Local Examination of foot:

- Inspection:
- Neurological assessment:
    - Monofilament testing:
    - Tuning fork test:

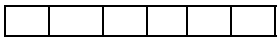
6) Investigations:

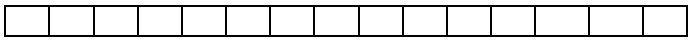
- CBC:
- Sr Creatinine:
- Sr TSH:
- Urine:
  - Routine
  - Microscopy
- HbA1C:
- FBS:
- PPBS:
- Sr Vitamin B12:
- Peripheral Smear:
- Mean Corpuscular Volume:

KEY TO MASTER CHART

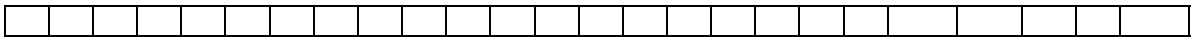
Male	–	1,
Female	–	2
HbA1C 4 to 5.6	–	1, 5.7 to 6.4 – 2, 6.5 and above – 3
MFT Cat	–	Neuropathy present – 1 (Score ≤5), Absent – 2 (Score>5)
SrB12Cat	–	Below Average – 1, Normal level or above – 2
Metformin since	–	0 to 3 years – 1, 4 and above – 2
MCV 80 to 85	–	1, 85 to 90 – 2, 90 – 96 – 3, >96 – 4
Peripheral Smear	–	Normal - N, Dimorphic – D, Macrocytosis - M

					Clinical symptoms							General Physical Examination												
																				Vitals				
																					B/p (mmHg)			
Serial number	In Patient number	Age	Sex	Presenting complaints	History of Presentin illness		Tuberculosis of Bones and joints			Family history	Personal history	Built	Nourishment	Anemia	Jaundice	Cyanosis	Clubbing	Significant lymphadenopathy	Stigmata of Tuber culosis	Pulse rate	Systolic	Dialstlolic	Respiratory rate	Temperature

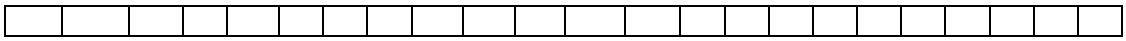




CNS																								
	Cranial nerves												Motor System											
																			Superficial		Corneal		Conjuctiva	
Higher mental functions	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	Nutrition	Tone	Power	Coordination	Abnormal movements	SensorySystem	Right	Left	Right	Left	Right	Left



Reflexes																Sign of Meningeal Irritation						
Abdominal		Plantar		Deep		Biceps		Triceps		Supinator		Knee		Ankle								
Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Neck Rigidity	Kernig" sign	Brudzinski"s Sign	Cerebellar function	Spine and Cranium	Gait	Diagnosis



Serial no.	Patient no.	Sex	Age	Metformin since	Co- morbidities	Monofilament testing	Sr Vit B12	HbA1C	FBS	PPBS	Sr Creatinine	Sr TSH	Hb	WBC	Platelets (lakhs)	HbA1C Cat	MFT Cat	SrB12 Cat	MCV
1	755168	2	32	2	Nil	3	121.6	8	2	2	1	3.2	13.4	7800	3.4	3	2	1	1
2	768061	2	35	7	Nil	6	179	9.4	2	2	0.6	2.6	15.2	9000	4.5	3	2	1	3
3	785216	2	36	1	Nil	6	111.5	11	2	2	0.8	1.5	15	4000	2.2	3	1	2	4
4	714151	1	37	2	Nil	10	301	6.6	1	1	0.9	0.9	14.4	5700	3.8	3	2	1	2
5	4354196	2	37	2	Nil	10	903.9	7.9	2	2	0.8	1.4	13	6800	1.9	3	2	2	3
6	4336568	1	37	5	HTN	10	2000	7.6	2	2	0.8	1.5	14.2	4500	4.3	3	2	2	3
7	826410	1	39	1	Nil	7	281.7	8	2	2	1	2.8	13	10000	3.6	3	2	1	4
8	2476805	2	39	2	HTN	9	506	6.8	1	1	1	1.4	15	7500	2.4	3	1	1	1
9	1621427	2	40	2	HTN	4	50	8.8	2	2	1	2	15.2	4800	4.4	3	2	2	3
10	3304686	2	40	2	Nil	5	73.2	11.2	2	2	1.1	0.8	14.4	8400	3.9	3	2	2	2
11	823989	2	40	2	HTN	6	147.7	8.6	2	2	0.6	1.5	13.2	9500	2.4	3	2	2	4
12	2023817	2	40	3	Nil	10	688.9	6.6	1	1	0.8	2.8	14.5	10700	2.7	2	2	2	4
13	582517	1	41	7	Nil	4	111.5	11	2	2	0.9	1.5	15	6700	3.6	3	2	2	2
14	3422377	1	41	9	HTN	6	147.7	8.6	2	2	0.8	1.5	13.2	9400	1.8	3	2	1	2
15	732201	1	41	2	Nil	9	619.5	7.2	2	2	1	0.9	13	5600	4.1	3	2	2	1
16	792828	2	42	7	Nil	7	121.6	8	2	2	1.1	3.2	13.4	5400	1.6	3	2	2	3
17	722073	2	43	3	Nil	10	2000	6.9	2	2	0.8	1.4	14.8	4100	4	3	2	2	4
18	1998165	2	44	4	Nil	1	50	8.8	2	2	0.9	2	15.2	6600	2.3	3	2	2	1
19	703862	2	46	5	Nil	5	134.6	7	2	2	0.7	1.6	13.2	5000	4.5	3	2	1	2
20	3268371	2	46	8	Nil	6	147.7	8.6	2	2	0.9	1.5	13.2	9200	3.3	3	2	2	1
21	4295441	1	46	4	Nil	8	218	7.1	2	2	1	3.2	14.4	4500	2.9	3	2	2	4
22	3632850	1	46	1	Nil	3	281.7	8	2	2	1	2.8	13	5400	3.4	2	2	2	4
23	897923	2	46	2	Nil	10	838.6	6.5	1	1	0.8	2	15	8500	4.1	3	1	1	3
24	796062	1	48	3	Nil	2	50	8.8	2	2	0.8	2	15.2	8000	2.2	3	2	2	2
25	3148055	1	48	1	HTN	6	179	9.4	2	2	0.8	2.6	15.2	5100	2.9	3	2	1	2
26	623902	2	48	5	Nil	7	281.7	8	2	2	1	2.8	13	8900	3.1	3	2	1	1
27	2432102	1	48	**1**	Nil	9	506	6.8	1	1	1	1.4	15	6200	4.2	3	2	2	4
28	2100114	2	48	4	HTN	10	676.9	7.8	2	2	1	1.2	14.2	7000	2.1	3	2	1	4
29	3790994	1	49	2	Nil	5	73.2	11.2	2	2	0.8	0.8	14.4	10300	2.4	3	2	2	1
30	3910813	2	49	1	Nil	9	235.8	8.9	2	2	0.8	1.2	13.4	8300	4.5	3	2	2	1
31	682418	2	49	1	Nil	9	619.5	7.2	2	2	0.7	0.9	13	7800	3.4	3	2	1	3
32	3213286	2	50	4	Nil	5	73.2	11.2	2	2	0.6	0.8	14.4	5100	2.9	3	1	1	2
33	816682	2	50	1	HTN	9	273.3	6.4	1	1	0.9	2.6	15	4700	3	3	2	2	2
34	694466	2	50	4	Nil	10	301	6.6	1	1	0.8	0.9	14.4	11000	1.7	3	2	2	4
35	1858630	1	50	5	Nil	9	619.5	7.2	2	2	0.7	0.9	13	6100	3.9	3	2	2	2
36	3774463	2	50	1	Nil	10	688.9	6.6	1	1	0.8	2.8	14.5	9900	3.6	2	2	2	1
37	680879	1	50	3	HTN	10	2000	8.6	2	2	0.6	3	13	5500	4.1	3	2	2	2
38	3608528	2	51	5	Nil	7	121.6	8	2	2	0.9	3.2	13.4	6700	2.7	3	2	1	2
39	4336568	1	52	7	Nil	4	111.5	11	2	2	1.1	1.5	15	7900	3.4	3	2	2	1
40	4207500	2	53	4	HTN	6	179	9.4	2	2	0.9	2.6	15.2	4500	4.4	3	2	2	1

Serial no.	Patient no.	Sex	Age	Metformin since	Co- morbidities	Monofilament testing	Sr Vit B12	HbA1C	FBS	PPBS	Sr Creatinine	Sr TSH	Hb	WBC	Platelets (lakhs)	HbA1C Cat	MFT Cat	SrB12 Cat	MCV
41	2042381	2	53	**4**	Nil	8	218	7.1	2	2	0.6	3.2	14.4	8000	2.6	3	2	2	3
42	4024270	2	53	**1**	Nil	10	838.6	6.5	1	1	1	2	15	5400	3.8	3	2	2	4
43	4146301	2	54	14	Nil	6	186.3	9.7	2	2	0.8	2.4	13.4	4300	4.3	3	2	1	4
44	3297044	1	55	3	Nil	9	333.4	10	2	2	1	2.2	14	9800	3.2	3	2	2	3
45	3632850	2	55	5	Nil	10	2000	6.9	2	2	0.7	1.4	14.8	10000	2.8	3	2	2	2
46	3448274	1	56	1	Nil	2	121.6	8	2	2	1.1	3.2	13.4	9400	3.6	2	2	2	2
47	1472597	2	56	5	Nil	6	147.7	8.6	2	2	0.8	1.5	13.2	7100	4.2	3	1	1	3
48	731434	1	56	2	HTN	6	186.3	9.7	2	2	1	2.4	13.4	4400	2.2	3	2	2	4
49	583261	1	57	**6**	Nil	5	134.6	7	2	2	0.9	1.6	13.2	9000	3.9	3	2	1	1
50	597610	1	57	**6**	HTN	6	186.3	9.7	2	2	0.8	2.4	13.4	8200	1.6	3	2	1	3
51	4174467	1	57	1	HTN	9	506	6.8	1	1	0.8	1.4	15	7700	4.5	3	2	2	1
52	3322233	2	57	4	HTN	9	619.5	7.2	2	2	0.8	0.9	13	5600	4.2	3	2	1	2
53	2476805	2	57	2	HTN	10	676.9	7.8	2	2	0.8	1.2	14.2	4000	3.8	3	2	2	2
54	803866	1	57	2	Nil	10	2000	6.9	2	2	1	1.4	14.8	7800	2.3	3	2	2	3
55	981719	2	57	2	Nil	10	2000	6.2	1	1	0.8	2.3	13.6	8600	4.1	3	2	1	4
56	775757	1	58	5	Nil	5	134.6	7	2	2	0.8	1.6	13.2	5100	2.8	3	1	1	3
57	719695	2	58	1	HTN	6	179	9.4	2	2	1	2.6	15.2	10400	3.3	3	2	2	3
58	592849	1	58	8	Nil	6	186.3	9.7	2	2	0.7	2.4	13.4	9900	4.5	3	2	2	4
59	2918718	2	58	3	Nil	10	301	6.6	1	1	0.9	0.9	14.4	6300	1.5	3	2	2	2
60	3855206	1	58	1	HTN	10	2000	7.6	2	2	0.8	1.5	14.2	4500	2.7	2	2	2	4
61	3695518	2	59	5	Nil	9	235.8	8.9	2	2	1	1.2	13.4	6600	3.1	3	2	2	1
62	3205955	1	59	1	Nil	9	273.3	6.4	1	1	1	2.6	15	4700	3	3	2	1	1
63	1621427	1	60	**6**	Nil	5	134.6	7	2	2	0.6	1.6	13.2	4000	2.2	3	2	2	4
64	732077	1	60	1	Nil	6	147.7	8.6	2	2	0.9	1.5	13.2	7700	2.8	3	2	2	4
65	782600	2	60	1	Nil	7	281.7	8	2	2	1	2.8	13	4600	4.4	3	2	2	4
66	3476050	2	60	1	Nil	9	333.4	10	2	2	0.8	2.2	14	8900	3.7	3	2	2	1
67	3262115	2	60	3	Nil	10	688.9	6.6	1	1	1.1	2.8	14.5	7500	4.5	3	2	1	2
68	3323287	2	60	1	Nil	10	2000	6.2	1	1	1	2.3	13.6	5600	2.8	3	2	2	2
69	625734	1	61	1	HTN	6	186.3	9.7	2	2	0.6	2.4	13.4	8600	2.5	3	2	2	3
70	750293	1	61	2	Nil	9	273.3	6.4	1	1	1.1	2.6	15	4500	1.8	2	2	2	4
71	3304686	1	61	**1**	HTN	10	676.9	7.8	2	2	0.8	1.2	14.2	8800	3.7	3	1	1	1
72	755290	2	61	1	Nil	10	2000	8.6	2	2	1	3	13	9000	2.5	3	2	2	1
73	742070	1	62	1	Nil	10	2000	6.9	2	2	0.9	1.4	14.8	6000	3.1	3	2	1	3
74	2863622	1	63	**1**	Nil	10	301	6.6	1	1	0.7	0.9	14.4	7200	2.7	3	2	1	4
75	4166615	2	63	1	Nil	10	903.9	7.9	2	2	1	1.4	13	4100	1.9	3	2	2	1
76	3451044	1	64	**1**	HTN	3	50	8.8	2	2	0.6	2	15.2	9700	3.5	3	2	1	2
77	789112	2	64	2	HTN	10	2000	8.6	2	2	0.9	3	13	6700	4.3	3	2	2	3
78	3892647	2	64	1	Nil	10	2000	6.2	1	1	1.1	2.3	13.6	5500	3.7	3	2	2	2
89	4091075	1	65	**2**	Nil	10	2000	7.6	2	2	0.9	1.5	14.2	6100	4.2	3	2	1	4
80	1378178	1	66	**7**	Nil	4	273.3	6.4	1	1	1	2.6	15	4600	2.3	3	1	1	1

Serial no.	Patient no.	Sex	Age	Metformin since	Co- morbidities	Monofilament testing	Sr Vit B12	HbA1C	FBS	PPBS	Sr Creatinine	Sr TSH	Hb	WBC	Platelets (lakhs)	HbA1C Cat	MFT Cat	SrB12 Cat	MCV
81	2107020	1	66	1	HTN	10	676.9	7.8	2	2	1	1.2	14.2	5000	3.6	3	2	2	1
82	4260485	2	66	1	Nil	10	903.9	7.9	2	2	1.1	1.4	13	4400	4.5	3	2	2	1
83	799462	2	67	1	Nil	8	218	7.1	2	2	0.9	3.2	14.4	9000	2.9	3	2	2	3
84	2579054	1	67	1	Nil	10	2000	6.2	1	1	1	2.3	13.6	6700	1.8	2	2	2	4
85	655957	2	68	**2**	HTN	9	235.8	8.9	2	2	1	1.2	13.4	8800	4,2	3	2	2	2
86	3680644	2	68	4	Nil	9	506	6.8	1	1	1.1	1.4	15	4900	2.2	3	2	1	2
87	4267236	1	68	1	Nil	10	688.9	6.6	1	1	1	2.8	14.5	8800	3.7	3	2	2	4
88	3589824	1	68	**5**	Nil	10	903.9	7.9	2	2	1.1	1.4	13	5400	2.8	3	2	2	3
89	1682689	2	68	10	HTN	10	2000	7.6	2	2	1	1.5	14.2	7000	3.4	3	2	2	4
90	3422377	1	69	3	Nil	3	73.2	11.2	2	2	1.1	0.8	14.4	8900	2.3	3	2	2	1
91	4270672	1	69	2	Nil	8	218	7.1	2	2	1	3.2	14.4	4800	4.2	3	2	1	4
92	4269012	2	69	1	Nil	9	235.8	8.9	2	2	0.8	1.2	13.4	11000	3	3	2	2	4
93	789417	1	69	4	Nil	9	333.4	10	2	2	0.8	2.2	14	6700	1.6	3	2	2	1
94	792828	1	69	1	Nil	10	2000	7.6	2	2	0.8	1.5	14.2	9000	2	2	2	2	1
95	1998165	1	70	8	Nil	7	121.6	8	2	2	1	3.2	13.4	8600	4.1	3	1	1	3
96	2135172	2	72	1	Nil	6	111.5	11	2	2	1	1.5	15	6200	3.3	3	2	2	2
97	732509	1	72	**2**	Nil	9	333.4	10	2	2	0.6	2.2	14	8100	3.1	3	2	1	4
98	6403995	1	73	4	Nil	10	838.6	6.5	1	1	0.9	2	15	4000	2.7	3	2	1	2
99	3340304	1	77	1	Nil	10	838.6	6.5	1	1	1.1	2	15	9900	4.3	3	2	2	2
100	1460559	2	78	1	Nil	10	2000	8.6	2	2	0.6	3	13	5600	2	3	2	1	4

Perpheral Smear
N
D
M
N
N
N
D
N
N
N
M
D
N
N
N
D
N
N
N
M
D
N
N
N
N
N
D
N
N
N
N
N
N

Perpheral Smear
N
M
D
N
N
N
N
D
N
N
N
N
N
N
D
N
D
N
N
D
N
D
D
D
N
N
N
N
D
N
N
N
M
N
N
N
N
D
N

Perpheral Smear
N
N
N
D
N
N
D
N
N
N
D
D
N
N
N
N
N
D