PREVALENCE OF VITAMIN B12 DEFICIENCY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS ON METFORMIN

Dissertation submitted for

MD DEGREE (BRANCH 1) GENERAL MEDICINE

APRIL 2017

THE TAMILNADU DR.M.G.R

MEDICAL UNIVERSITY

CHENNAI- TAMIL NADU

CERTIFICATE FROM THE DEAN

This is to certify that this dissertation entitled **"PREVALENCE OF VITAMIN B12 DEFICIENCY INPATIENTS WITH TYPE 2 DIABETES MELLITUS ON METFORMIN''** is the bonafide work of **Dr .M.SATHYARANGAN** in partial fulfillment of the university regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for M.D General Medicine Branch I examination to be held in April 2017.

Dr.VAIRAMUTHU RAJU MD.

THE DEAN,
Madurai Medical College,
Madurai.

CERTIFICATE FROM THE HOD

This is to certify that this dissertation entitled **"PREVALENCE OF VITAMIN B12 DEFICIENCY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS ON METFORMIN''** is the bonafide work of **Dr. M.SATHYARANGAN** in partial fulfillment of the university regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for M.D General Medicine Branch I examination to be held in April 2017.

DR.V.T.PREM KUMAR,M.D.,

Professor and HOD,
Department Of General Medicine,
Government Rajaji Hospital,
Madurai Medical College,
Madurai.

CERTIFICATE FROM THE GUIDE

This is to certify that this dissertation entitled **"PREVALENCE OF VITAMIN B12 DEFICIENCY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS ON METFORMIN''** is the bonafide work of **Dr. M.SATHYARANGAN** in partial fulfillment of the university regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for M.D General Medicine Branch I examination to be held in April 2017.

DR.M.NATARAJAN, M.D.,

Professor of Medicine ,
Department Of General Medicine,
Government Rajaji Hospital,
Madurai Medical College,
Madurai .

DECLARATION

I **Dr .M.SATHYARANGAN** declare that, I carried out this work on **"PREVALENCE OF VITAMIN B12 DEFICIENCY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS ON METFORMIN''** at the Department of Medicine, Govt. Rajaji Hospital during the period FEB 2016 TO JULY 2016.

I also declare that this bonafide work or a part of this work was not submitted by me or any others for any award, degree or diploma to any other University, Board either in India or abroad.

This dissertation is submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the rules and regulations for the award of M.D Degree General Medicine Branch- I; examination to be held in April 2017.

Place : Madurai

Date : **Dr.M.SATHYARANGAN**

ACKNOWLEDGEMENTS

At the outset, I wish to thank our Dean **Dr.M.R. VAIRAMUTHURAJU M.D.,** for permitting me to use the facilities of Madurai Medical College and Government Rajaji Hospital to conduct this study.

My beloved teacher and Head of the Department of Medicine Prof. **Dr.V.T.PREMKUMAR M.D.,** has always guided me, by example and valuable words of advice and has encouraged innovative thinking and original research work done by post graduates.

I shall remain eternally grateful to my beloved teacher, my guide and my unit chief Prof**. Dr.M.NATARAJAN .M.D** who has given me his moral support and encouragement through the conduct of the study and also during my entire postgraduate course.

I also sincerely thank our beloved **professors Dr. V.T.Premkumar. M.D., Dr.R.Balajinathan.MD.,Dr.G.Bagialakshmi.M.D., Dr.J.Sangumani. M.D., Dr.C.Dharmaraj. M.D.,and Dr.R.Prabhakaran. M.D.,** for their par excellence clinical teaching and constant support.

I offer my heartfelt thanks to my unit Assistant Professors **Dr.P.S.ARULRAJAMURUGAN,M.D.,D.M., Dr.B.PALANIKUMAR.M.D,** for their constant encouragement, timely help and critical suggestions throughout the study and also for making my stay in the unit both informative and pleasurable. I am extremely thankful to Prof**. Dr.MOHANASUNDARAM MD.,** Head of the department of BIOCHEMISTRY & **Prof. Dr.SENTHIL M.D.,**

Head of the department of **DIABETOLOGY** for their constant support, guidance, cooperation and to complete this study

I express my thanks to **Dr.P.THIRUNAVUKARASU, Dr.SRIRAM, Dr.DEEPA, Dr.SHYAM, Dr.RADHAKRISHNAN, Dr.ARUNKUMAR** for their help and support in my dissertation work My patients, who form the most integral part of the work, were always kind and cooperative. I pray to God give them courage and strength to endure their illness, hope all of them go into complete remission.

I thank my friends and family who have stood by me during my times of need. Their help and support have always been invaluable to me. And **last but not the least** I would like thank the Lord Almighty for His grace and blessings without which nothing would have been possible.

INTRODUCTION

1. Diabetic patients are more prone to develop neuropathy.
2. Prolonged vitamin B12 deficiency may result in neuropathy,ranging from paraesthesia and decreased peripheral sensation to altered mental status, subacute combined degeneration of the spinal cord and dementia.
3. Therefore ,it is worthwhile to consider the prevalence of vitamin B12 deficiency among the type 2 DM population.

AIMS AND OBJECTIVE

AIMS :

- Determine the prevalence of vitamin B12 deficiency in patients with T2DM not on metformin and with no history of or treatment for autoimmune diseases.
- Determine the prevalence of vitamin B12 deficiency in patients with T2DM on metformin and if the presence of vitamin B12 deficiency correlates with dose and duration of metformin therapy.
- Determine if metformin induced vitamin B12 deficiency is associated with anemia as measured by Hb and MCV or peripheral neuropathy as measured by the absence of sensation to 10g monofilament**.**

OBJECTIVES:

- This would inform the need for routine annual vitamin B12 measurements in T2DM on metformin.
- We also want to look whether dose and duration of metformin therapy is associated with vitamin B 12 deficiency and whether vitamin B12 deficiency in patients on metformin is associated with clinical complications such as anemia or peripheral neuropathy.

REVIEW OF LITERATURE

ETIOLOGY

Type 2 diabetes is caused by a combination of genetic factors related to impaired insulin secretion and insulin resistance and environmental factors such as obesity, overeating, lack of exercise, and stress, as well as aging. It is typically a multifactorial disease involving multiple genes and environmental factors to varying extents. A fact considered important in pathogenesis is that Japanese show lower insulin secretory capacity after sugar loading, suggesting smaller potential for pancreatic cell function than Western people. It has also been pointed out that Japanese individuals may have many diabetes-sensitive genes including thrifty genes. The number of diabetic patients is increasing rapidly reflecting the changes in lifestyle.

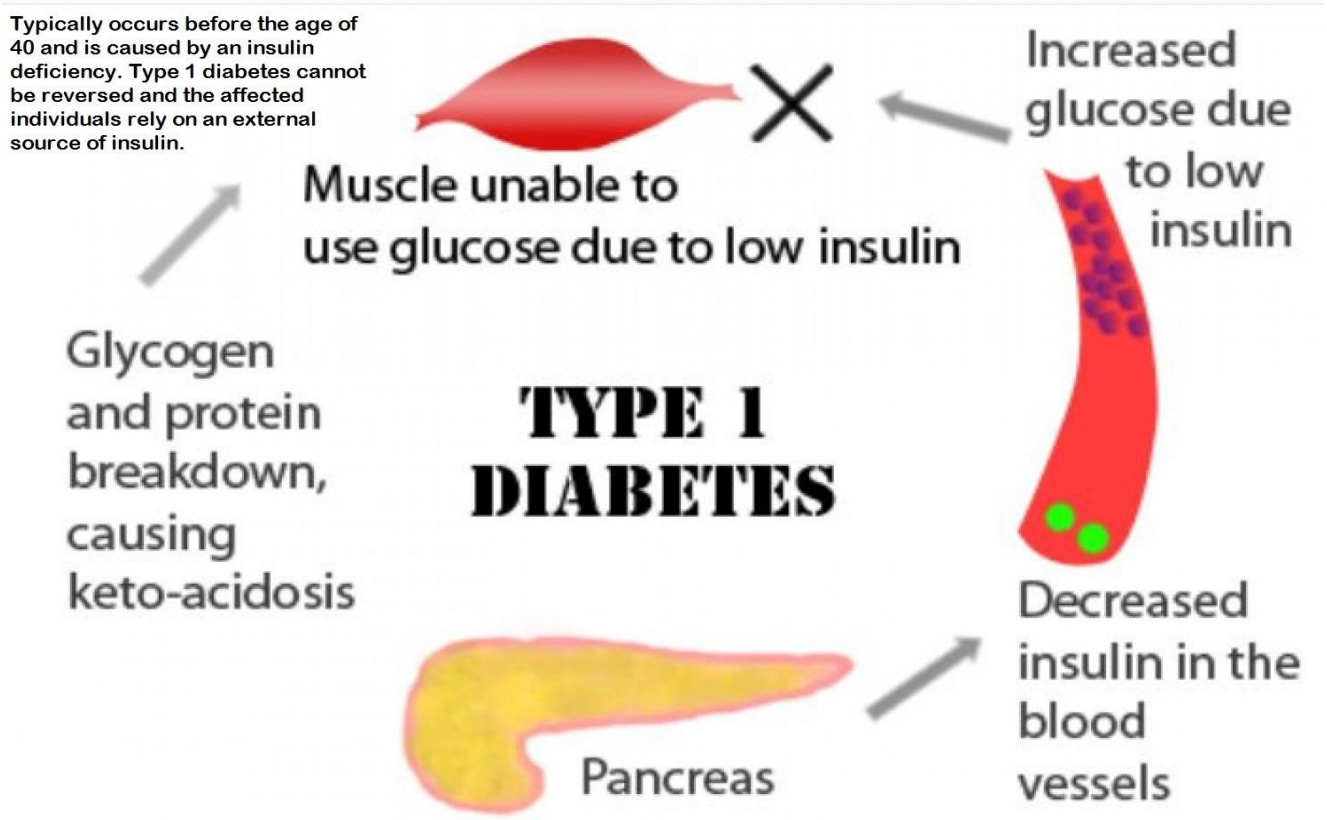
Genetic factors involved in the pathogenesis of diabetes The development of type 2 diabetes is clearly associated with a family history of diabetes. The significantly higher concordance rate between monozygotic twins than between dizygotic twins suggests the considerable involvement of genetic factors.1 The pathogenesis has been assumed to involve genetic abnormality in the molecules related to the regulatory system of glucose metabolism. The analyses of candidate genes targeted at glucose-stimulated insulin secretion of pancreatic cells and the molecules comprising the molecular mechanism for insulin action have identified genetic abnormalities that can be independent causes of pathogenesis, including those in glucokinase genes, mitochondrial genes, and insulin receptor genes. Recently, a genomewide association study (GWAS) has

identified the mutation in the KCNQ1 gene related to insulin secretion abnormality as an important disease-susceptible gene associated with the pathogenesis of diabetes in Asian ethnic groups including the Japanese.2 The genetic abnormalities reported so far, all combined, explain about 30% of the genetic factors for diabetes, and our understanding of genetic factors is expected to be practically complete in the near future.

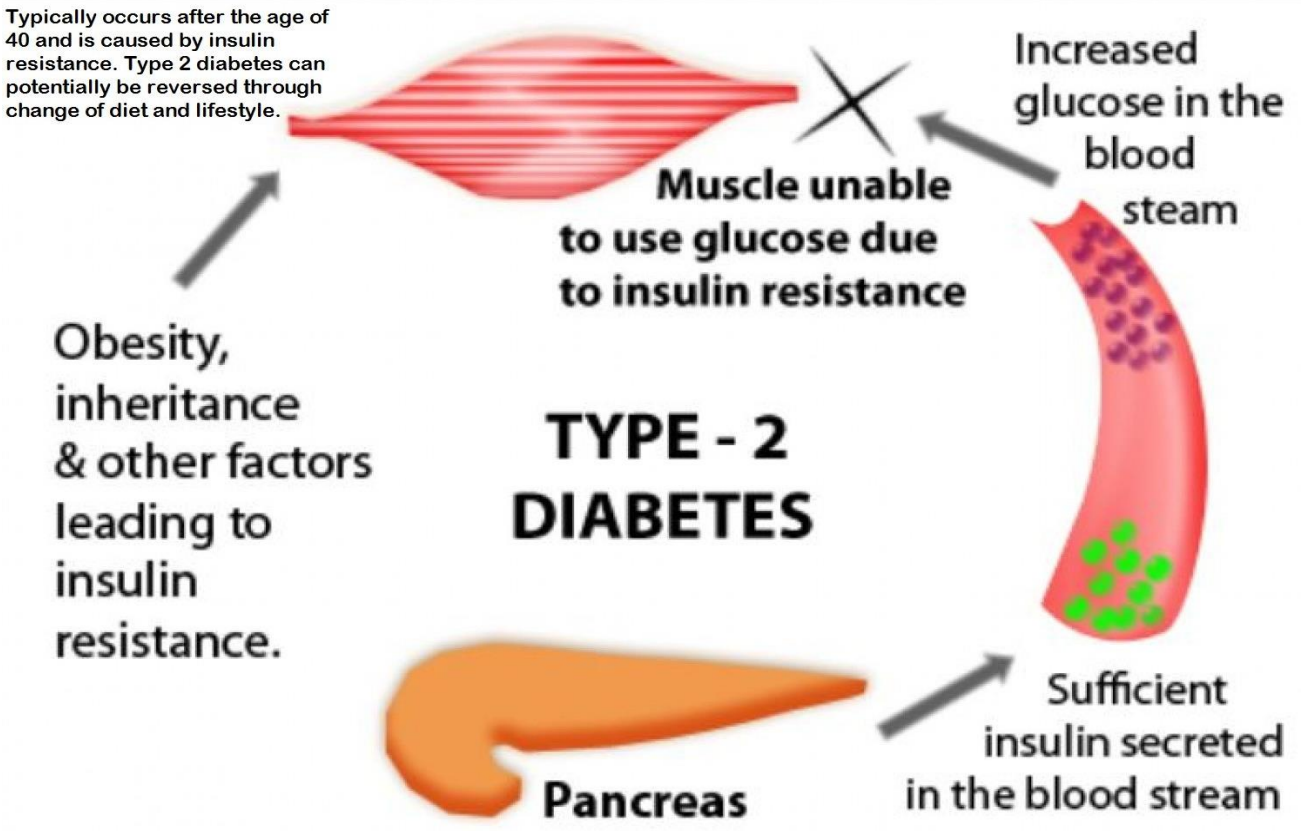
According to the current classification of disease types, diabetic cases with identified genetic abnormality are classified under “those due to other specific mechanisms or diseases.” Roles of environmental factors Aging, obesity, insufficient energy consumption, alcohol drinking, smoking, etc. are independent risk factors of pathogenesis. Obesity (particularly visceral fat obesity) due to a lack of exercise is accompanied by a decrease in muscle mass, induces insulin resistance, and is closely associated with the rapid increase in the number of middle- and high-aged patients.

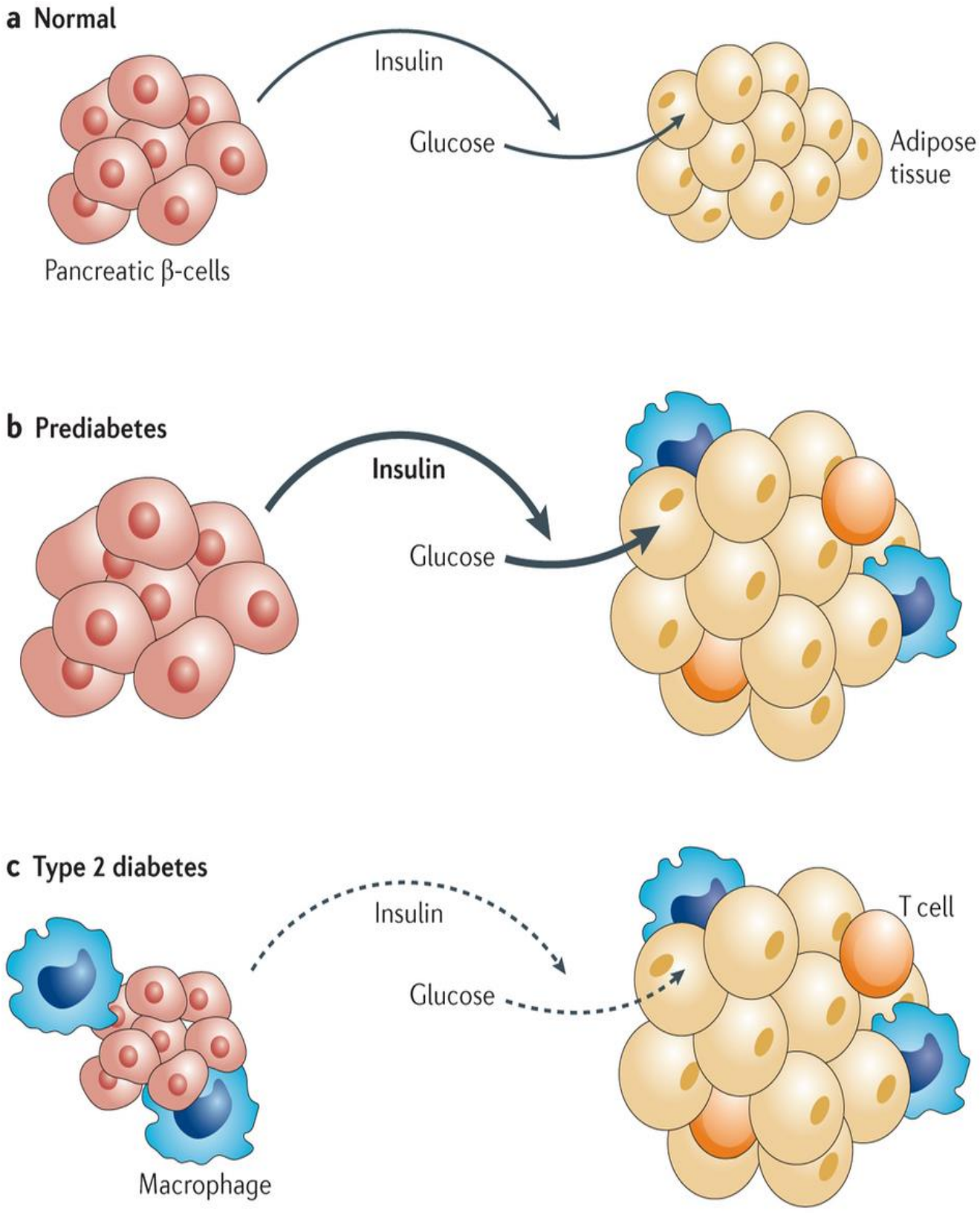
The changes in dietary energy sources, particularly the increase in fat intake, the decrease in starch intake, the increase in the consumption of simple sugars, and the decrease in dietary fiber intake, contribute to obesity and cause deterioration of glucose tolerance. Even mild obesity (BMI 25) causes a 4- to 5-fold increase in the risk of developing diabetes, if accompanied by the increase in visceral fat mass. The Japanese are prone to visceral fat accumulation due to hyperalimentation, and risk factors for diabetes are linked to the accumulation of visceral fat.

Type 1 Diabetes

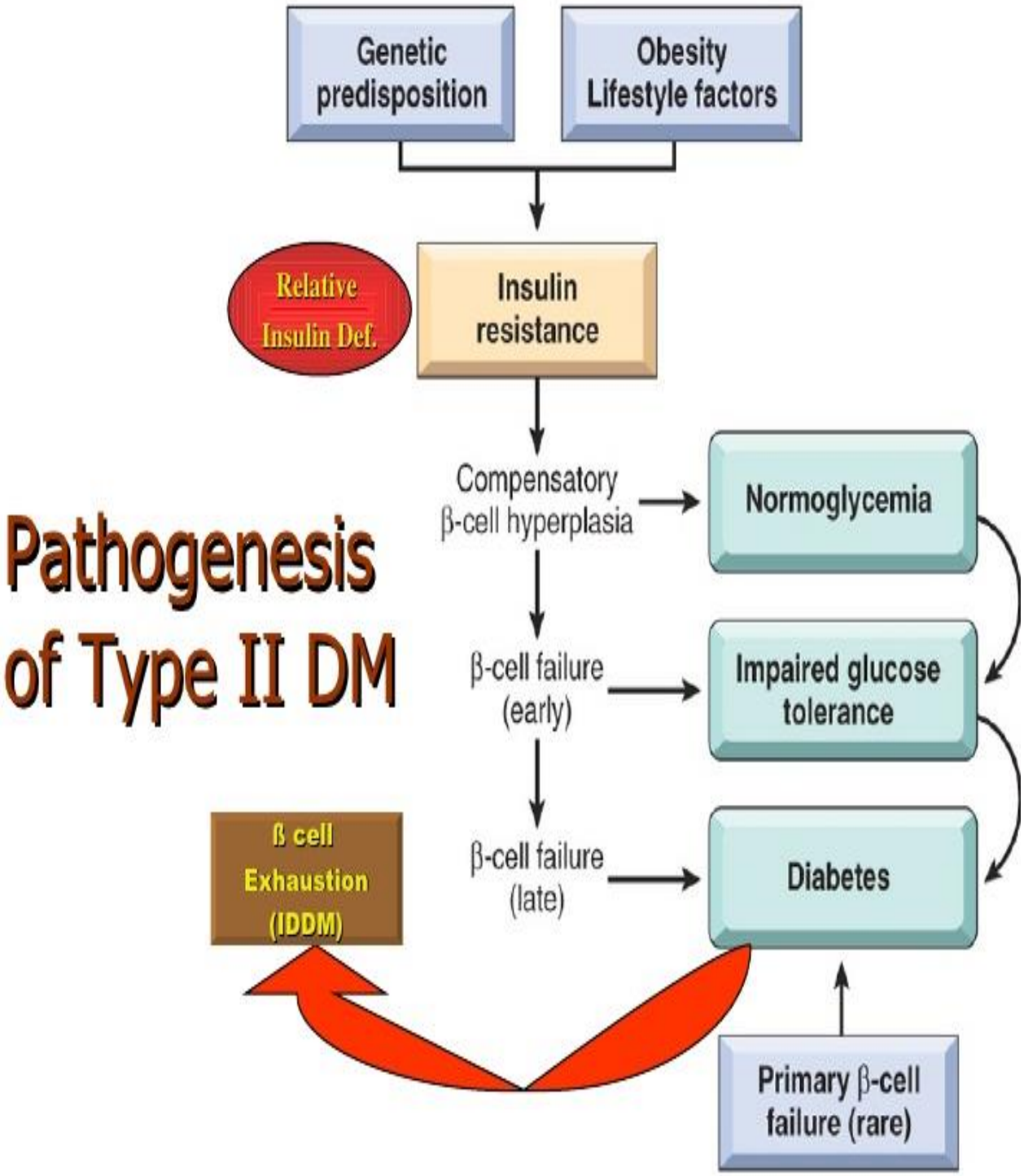


Type 2 Diabetes





Nature Reviews | Drug Discovery


Genetic predisposition
Obesity Lifestyle factors
Relative Insulin Def.
Insulin resistance
Compensatory β-cell hyperplasia
Normoglycemia
Pathogenesis of Type II DM
β-cell failure (early)
Impaired glucose tolerance
ß cell Exhaustion (IDDM)
β-cell failure (late)
Diabetes
Primary β-cell failure (rare)

PATHOPHYSIOLOGY

Impaired insulin secretion and insulin resistance contribute more or less jointly to the development of pathophysiological conditions. Impaired insulin secretion Impaired insulin secretion is a decrease in glucose responsiveness, which is observed before the clinical onset of disease. More specifically, impaired glucose tolerance (IGT) is induced by a decrease in glucose-responsive early-phase insulin secretion, and a decrease in additional insulin secretion after meals causes postprandial hyperglycemia.

An oral glucose tolerance test (OGTT) in IGT cases generally indicates an over-response in Western and Hispanic individuals, who have markedly high insulin resistance. On the other hand, Japanese patients often respond to this test with decreased insulin secretion. Even when an over-response is seen in persons with obesity or other factors, they show a decrease in early-phase secretory response.

The decrease in early-phase secretion is an essential part of this disease, and is extremely important as a basic pathophysiological change during the onset of disease in all ethnic groups.3 Impaired insulin secretion is generally progressive, and its progression involves glucose toxicity and lipo-toxicity. When untreated, these are known to cause a decrease in pancreatic cell mass in animal experiments. The progression of the impairment of pancreatic cell function greatly affects the long-term control of blood glucose. While patients

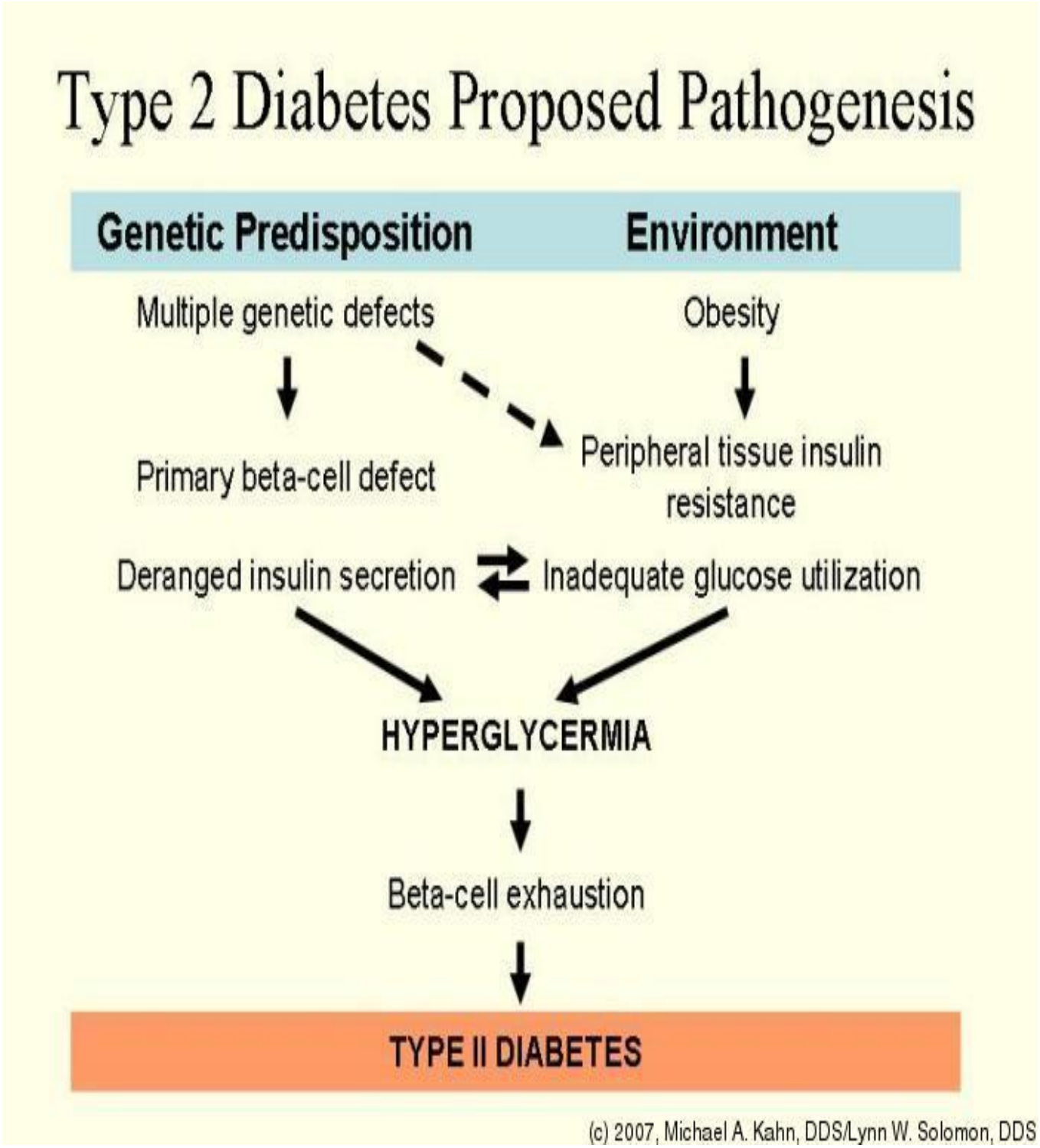
in early stages after disease onset chiefly show an increase in postprandial blood glucose as a result of increased insulin resistance and decreased early-phase secretion, the progression of the deterioration of pancreatic cell function subsequently causes permanent elevation of blood glucose.

Insulin resistance Insulin resistance is a condition in which insulin in the body does not exert sufficient action proportional to its blood concentration. The impairment of insulin action in major target organs such as liver and muscles is a common pathophysiological feature of type 2 diabetes. Insulin resistance develops and expands prior to disease onset. The investigation into the molecular mechanism for insulin action has clarified how insulin resistance is related to genetic factors and environmental factors (hyperglycemia, free fatty acids, inflammatory mechanism, etc.).

Known genetic factors, include not only insulin receptor and insulin receptor substrate (IRS)-1 gene polymorphisms that directly affect insulin signals but also polymorphisms of thrifty genes such as the 3 adrenergic receptor gene and the uncoupling protein (UCP) gene, associated with visceral obesity and promote insulin resistance. Glucolipotoxicity and inflammatory mediators are also important as the mechanisms for impaired insulin secretion and insulin signaling impairment. Recent attention has focused on the involvement of adipocyte-derived bioactive substances (adipokines) in insulin resistance.

While TNF-, leptin, resistin, and free fatty acids act to increase resistance, adiponectin improves resistance. Clinical tests to assess the extent of insulin resistance include homeostasis model assessment for insulin resistance (HOMA-IR), insulin sensitivity test (loading test), steady-state plasma glucose (SSPG), minimal model analysis, and insulin clamp technique. The Matsuda index 4 is now gaining recognition as a relatively simple procedure that can simultaneously evaluate insulin resistance in the liver and muscles.

After performing OGTT, this index is calculated by the formula: Matsuda Index10,000/(FPGFPI)(mean PGmean PI), where FPG is fasting plasma glucose and FPI is fasting plasma insulin. A more convenient way to estimate the degree of resistance is to check for the presence of high fasting blood insulin, visceral obesity, hypertriglyceridemia, etc.


Type 2 Diabetes Proposed Pathogenesis
Genetic Predisposition
Environment
Multiple genetic defects
Obesity
Primary beta-cell defect
Peripheral tissue insulin resistance
Deranged insulin secretion
Inadequate glucose utilization
HYPERGLYCERMIA
Beta-cell exhaustion
TYPE II DIABETES
(c) 2007, Michael A. Kahn, DDS/Lynn W. Solomon, DDS

SIGNS AND SYMPTOMS

Signs and symptoms of type 2 diabetes often develop slowly. In fact, you can have type 2 diabetes for years and not know it. Look for:

- **Increased thirst and frequent urination.** Excess sugar building up in your bloodstream causes fluid to be pulled from the tissues. This may leave you thirsty. As a result, you may drink — and urinate — more than usual.

- **Increased hunger.** Without enough insulin to move sugar into your cells, your muscles and organs become depleted of energy. This triggers intense hunger.

- **Weight loss.** Despite eating more than usual to relieve hunger, you may lose weight. Without the ability to metabolize glucose, the body uses alternative fuels stored in muscle and fat. Calories are lost as excess glucose is released in the urine.

- **Fatigue.** If your cells are deprived of sugar, you may become tired and irritable.

- **Blurred vision.** If your blood sugar is too high, fluid may be pulled from the lenses of your eyes. This may affect your ability to focus.

- **Slow-healing sores or frequent infections.** Type 2 diabetes affects your ability to heal and resist infections.

- **Areas of darkened skin.** Some people with type 2 diabetes have patches of dark, velvety skin in the folds and creases of their bodies — usually in the armpits and neck. This condition, called acanthosisnigricans, may be a sign of insulin resistance.


1. Very thirsty
2. Very tired
3. Losing weight
160
4. Urinating more than usual
5. Sores that do not get well.
6. Blurred vision
6. Eating a lot of food.

DIAGNOSTIC CRITERIA FOR DIABETES:

- Symptoms of diabetes plus random venous blood glucose concentration more than or equal to 200mg/dl.

Or

- Fasting plasma glucose more than or equal to 126mg/dl.

Or

- Two hour plasma glucose more than or equal to 200 mg/dl during an oral glucose tolerance test.

A large number of individuals who meet the current criteria for diabetes are unaware that they have the disorder and equally a good number refuse the diagnosis. Epidemiologic studies suggest that type 2 diabetes mellitus may be present for upto a decade before diagnosis.

SCREENING

The expert committee suggests screening of all individual of more than 45years every 3 years and screening asymptomatic individuals with additional risk factors at an earlier age.

The best screening test for diabetes, the fasting plasma glucose (FPG), is also a component of diagnostic testing. The FPG test and the 75-g oral glucose tolerance test (OGTT) are both suitable tests for diabetes; however, the FPG test is preferred in clinical settings because it is easier and faster to perform, more convenient and acceptable to patients, and less expensive. An FPG ≥126 mg/dl (7.0 mmol/l) is an indication for retesting, which should be repeated on a different day to confirm a diagnosis. If the FPG is <126 mg/dl (7.0 mmol/l) and there is a high suspicion for diabetes, an OGTT should be performed. A 2-h postload value in the OGTT ≥200 mg/dl (11.1 mmol/l) is a positive test for diabetes and should be confirmed on an alternate day. Fasting is defined as no consumption of food or beverage other than water for at least 8 h before testing.

Nondiabetic individuals with an FPG ≥110 mg/dl (6.1 mmol/l) but <126 mg/dl (7.0 mmol/l) are considered to have IFG, and those with 2-h values in the OGTT ≥140 mg/dl (7.8 mmol/l) but <200 mg/dl (11.1 mmol/l) are defined as having IGT. Both IFG and IGT are risk factors for future diabetes. Normoglycemia is defined as plasma glucose levels <110 mg/dl (6.1 mmol/l) in the FPG test and a 2-h postload value <140 mg/dl (7.8 mmol/l) in the OGTT.

If necessary, plasma glucose testing may be performed on individuals who have taken food or drink shortly before testing. Such tests are referred to as casual plasma glucose measurements and are given without regard to time of last meal. A casual plasma glucose level ≥200 mg/dl (11.1 mmol/l) with symptoms of diabetes is considered diagnostic of diabetes. A confirmatory FPG test or OGTT should be completed on a different day if the clinical condition of the patient permits.

Laboratory measurement of plasma glucose concentration is performed on venous samples with enzymatic assay techniques, and the above-mentioned values are based on the use of such methods. The A1C test values remain a valuable tool for monitoring glycemia, but it is not currently recommended for the screening or diagnosis of diabetes. Pencil and paper tests, such as the American Diabetes Association's risk test, may be useful for educational purposes but do not perform well as stand-alone tests. Capillary blood glucose testing using a reflectance blood glucose meter has also been used but because of the imprecision of this method, it is better used for self-monitoring rather than as a screening tool.

OTHER CONSIDERATIONS

In screening for disease, it is crucial that an interpretation of the screening test results be provided to the patient and that follow-up evaluation and treatment are made available. Also, it is important to consider that certain drugs, including glucocorticoids and nicotinic acid, may produce hyperglycemia.

ACUTE AND CHRONIC COMPLICATIONS

ACUTE

- Diabetic ketoacidosis(DKA)
- Hyperglycemichyperosmolarsyndrome (HHS)
- hypoglycemia
- metformin associatedlactic acidosis, MALT

Chronic

- nephropathy
- retinopathy
- neuropathy
- Macrovascular diseases(CHD, peripheralvascular disease,stroke)

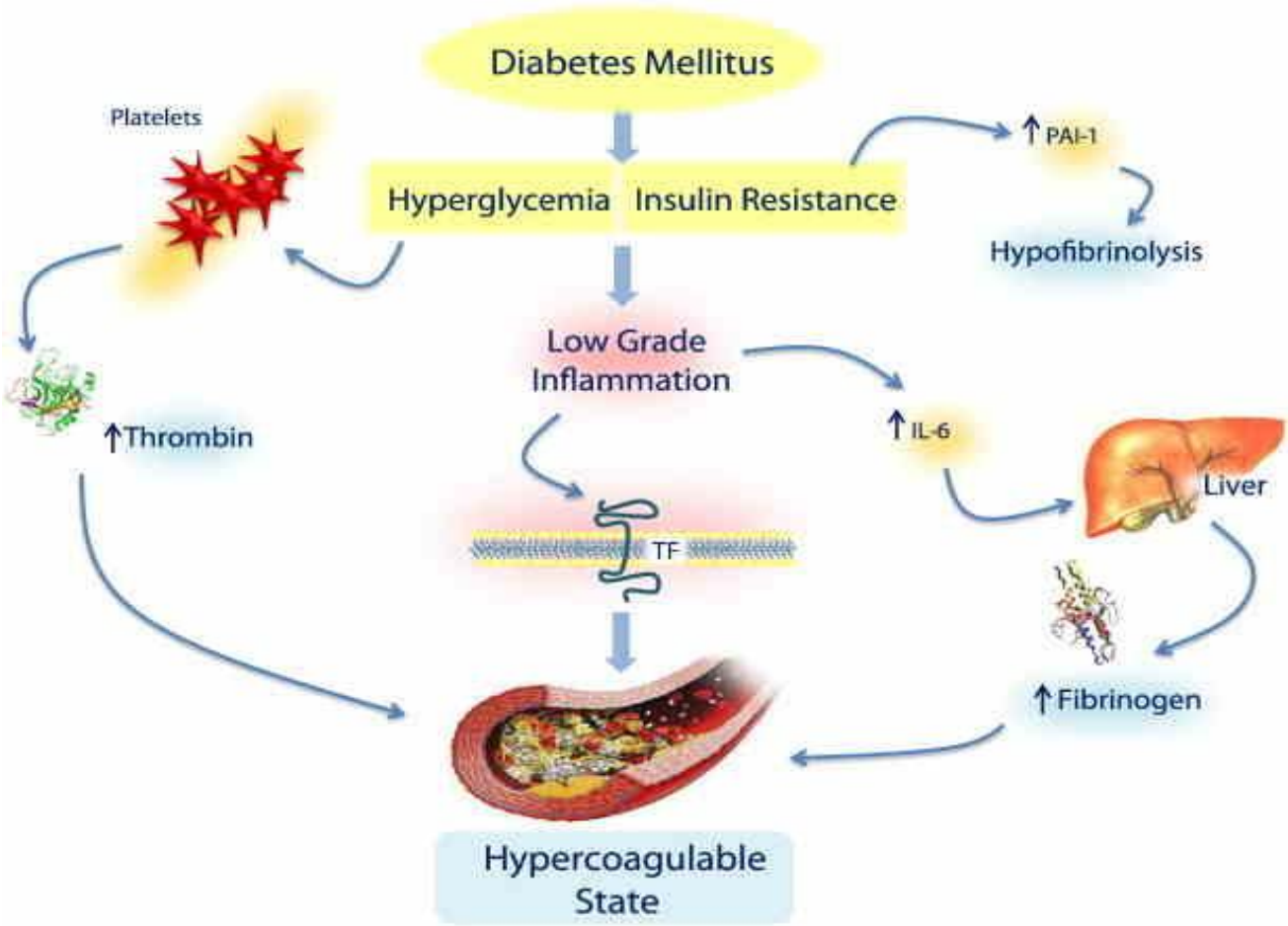
Hyperglycemia causes acute reversible and cumulative irreversible changes Acute, reversible intracellular metabolic changes • Cumulative, irreversible effects on stabile macromolecules Metabolic changes caused by hyperglycemia Acute, reversible intracellular metabolic changes

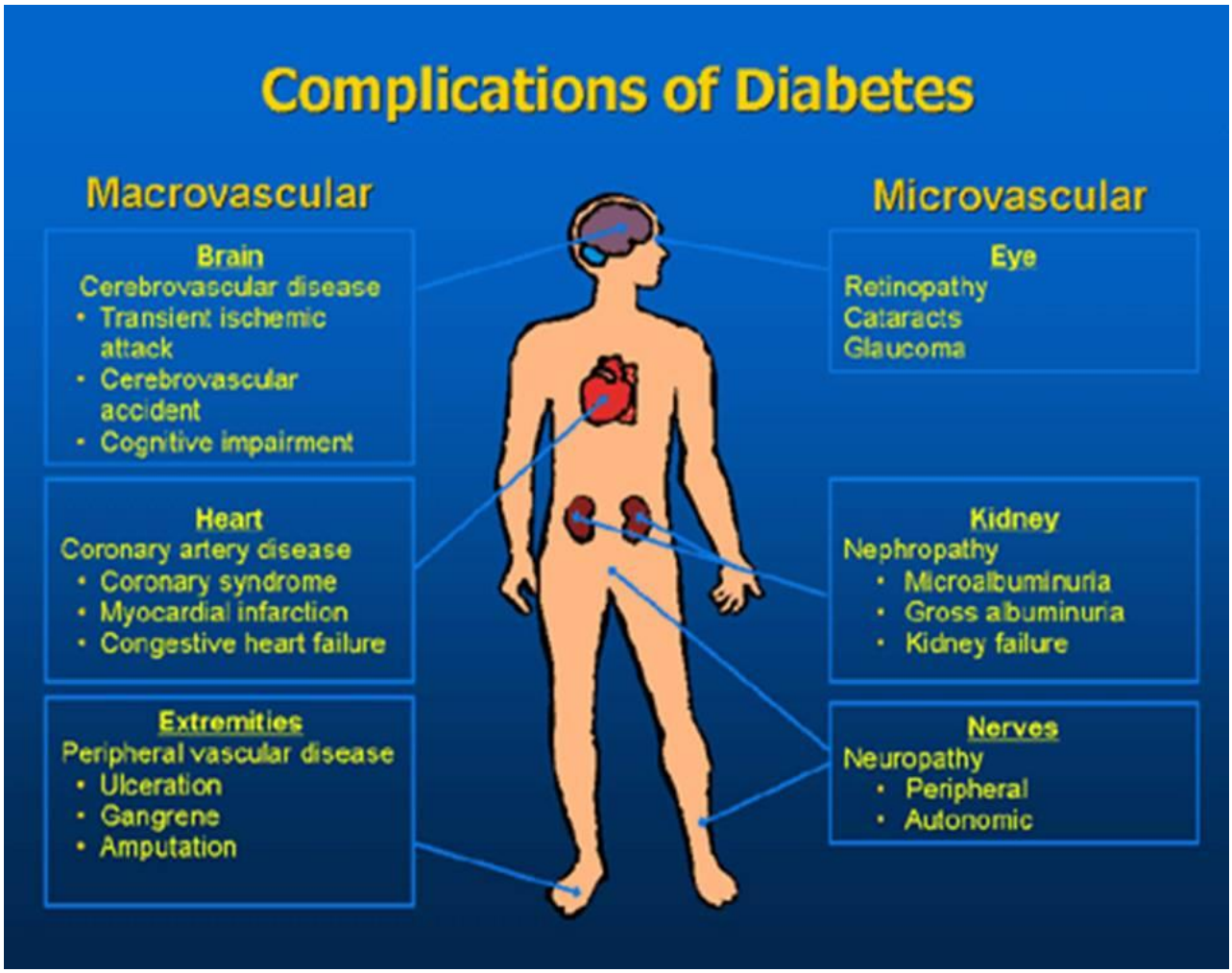
- Increased activity of polyol pathway
- Modified protein kinase C activity
- Early glycation products
- Increased production of free radicals

Effects of advanced glycation end products (AGE)

- Crosslinking of extracellular proteins
- Interactions with specific AGE receptors
- Crosslinking with intracellular DNA
- Cells having AGE-receptors
- Monocyte, macrophage


Thoroughly inspect your feet daily, and keep them clean and dry
ADAM.


Diabetes Mellitus
Platelets
↑PAI-1
Hyperglycemia
Insulin Resistance
Hypofibrinolysis
Low Grade
Inflammation
↑Thrombin
↑IL-6
Liver
TF
↑Fibrinogen
Hypercoagulable
State


Complications of Diabetes
Macrovascular
Brain
Cerebrovascular disease
• Transient ischemic attack
• Cerebrovascular accident
• Cognitive impairment
Heart
Coronary artery disease
• Coronary syndrome
• Myocardial infarction
• Congestive heart failure
Extremities
Peripheral vascular disease
• Ulceration
• Gangrene
• Amputation
Microvascular
Eye
Retinopathy
Cataracts
Glaucoma
Kidney
Nephropathy
• Microalbuminuria
• Gross albuminuria
• Kidney failure
Nerves
Neuropathy
• Peripheral
• Autonomic

• Endothelium

• Pericyte

• Podocyte

• Astrocyte

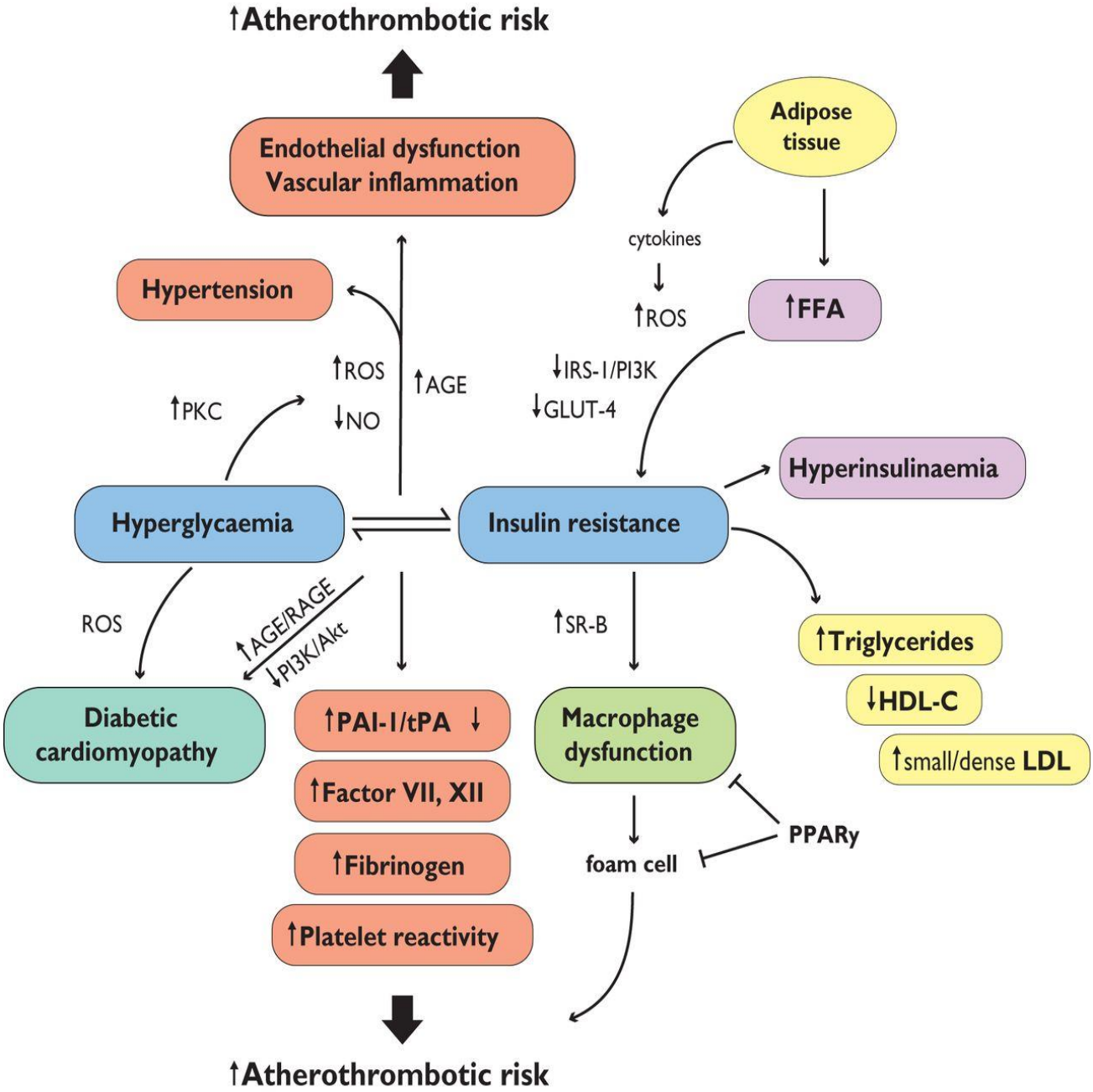
• Microglia

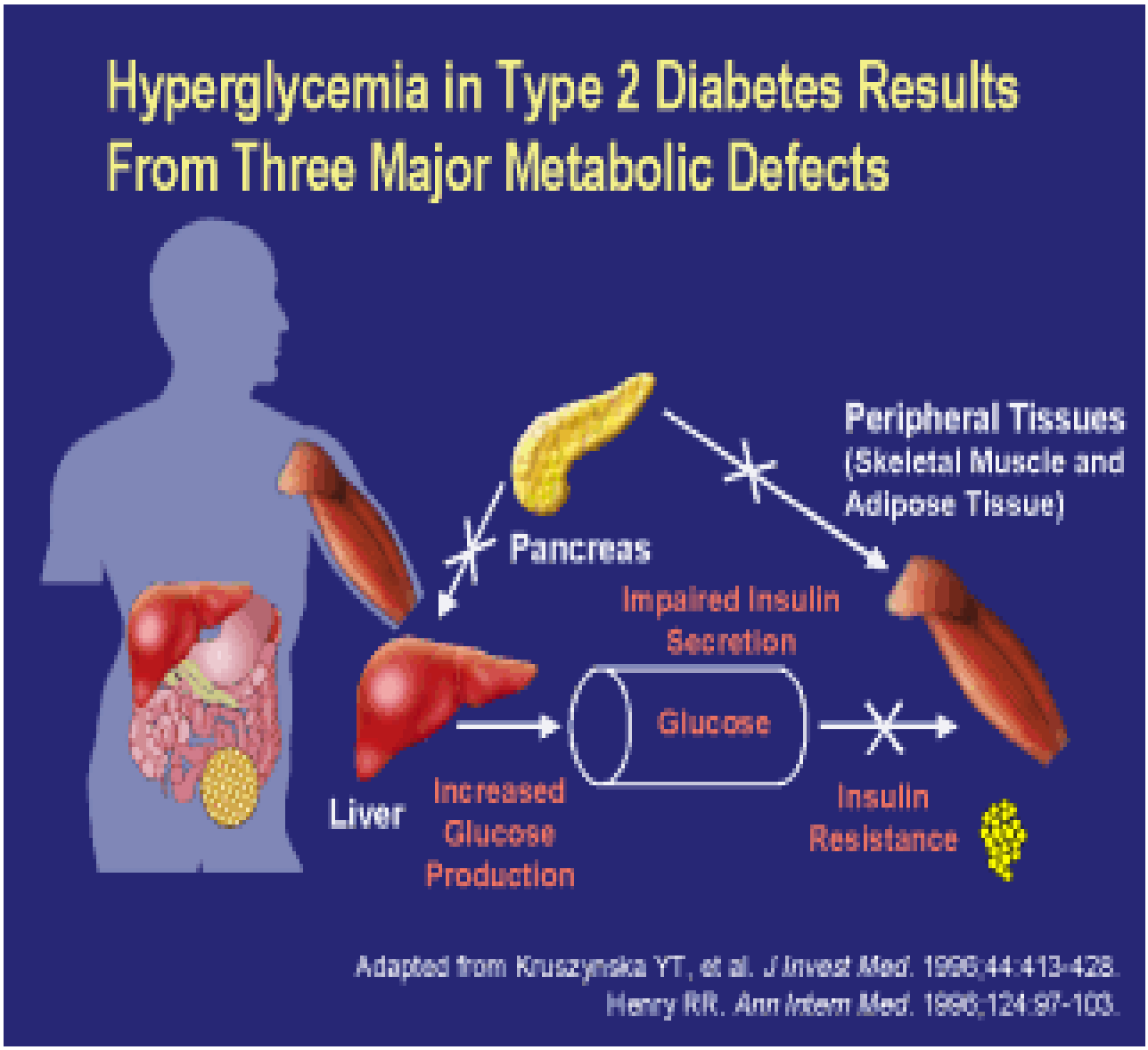
Hemodynamic disturbances in diabetes

- Increased blood flow.
- Increased permeability.
- Hemorrheological and coagulation abnormalities.
- increased plasma viscosity.
- decreased red-cell deformability.
- increased platelet aggregability.

Structural abnormalities in diabetes

- Leakage of glycated plasma proteins
- Extracellular matrix is increased - BM is thickened - mesangial matrix is expanded - collagen is increased
- Hypertrophy and hyperplasia of endothelial, mesangial and arterial smooth muscle cells


↑Atherothrombotic risk
Endothelial dysfunction
Vascular inflammation
Adipose tissue
cytokines
↑ROS
↑FFA
Hypertension
↑ROS
↓NO
↑AGE
↑PKC
↓IRS-1/PI3K
↓GLUT-4
Hyperinsulinaemia
Hyperglycaemia
Insulin resistance
ROS
↑AGE/RAGE
↓PI3K/Akt
↑SR-B
↑Triglycerides
↓HDL-C
↑small/dense LDL
Diabetic cardiomyopathy
↑PAI-1/tPA ↓
↑Factor VII, XII
↑Fibrinogen
↑Platelet reactivity
Macrophage dysfunction
PPARγ
foam cell
↑Atherothrombotic risk


Hyperglycemia in Type 2 Diabetes Results From Three Major Metabolic Defects
Peripheral Tissues (Skeletal Muscle and Adipose Tissue)
Pancreas
Impaired Insulin Secretion
Glucose
Liver
Increased Glucose Production
Insulin Resistance
Adapted from Kruszynska YT, et al. J Invest Med. 1996;44:413-428.
Henry RR. Ann Intern Med. 1996;124:97-103.

Nephropathia Stages of nephropathy in T1DM V. insuff. renalis ↓ Diagnosis and treatment of microalbuminuria

- Screening once a year in T1DM (at least), at diagnosis in T2DM
- Urinary albumin excretion 30-300 (299) mg / 24 h
- 2 positive out of 3 samples (collected urine) (fever, urinary tract infection, heart failure etc.)
- ACE-inhibitors (ARB), good metabolic control • DM + albuminuria increases the CVD mortality with 20 x
- NOT characteristic for diabetic nephropathy
- Rapid progression (rapid development of nephrotic syndrome)
- Considerable hematuria, red-cell casts
- Absence of retinopathy
- Short disease duration (T1DM)

Diabetic Eye Disease- Retinopathy

Stages of diabetic retinopathy

Non-proliferative retinopathy

- mild non-proliferative (background): microaneurysms, scattered exsudates, haemorrhages (no complains) macular oedema macular ischaemia

- severe non-proliferative (preproliferative): multiple previous abnormalities, cotton-wool spots, intraretinalmicrovascular abnormalities (IRMA) through the whole retina

Proliferative retinopathy

- Impaired vision, blindness
- New vessels, fibrous proliferation, hemorrhages (preretinal vitreous), retinal detachment

Screening

- Screening at least once a year
- DR no + good metabolic control 1x a year mild DR + good metabolic control 6 months RD no + bad metabolic control 3-6 months

dilated pupil

glaucoma

Visus, pressure, fundus!

- Laser photocoagulation!! (FLAG, OCT)

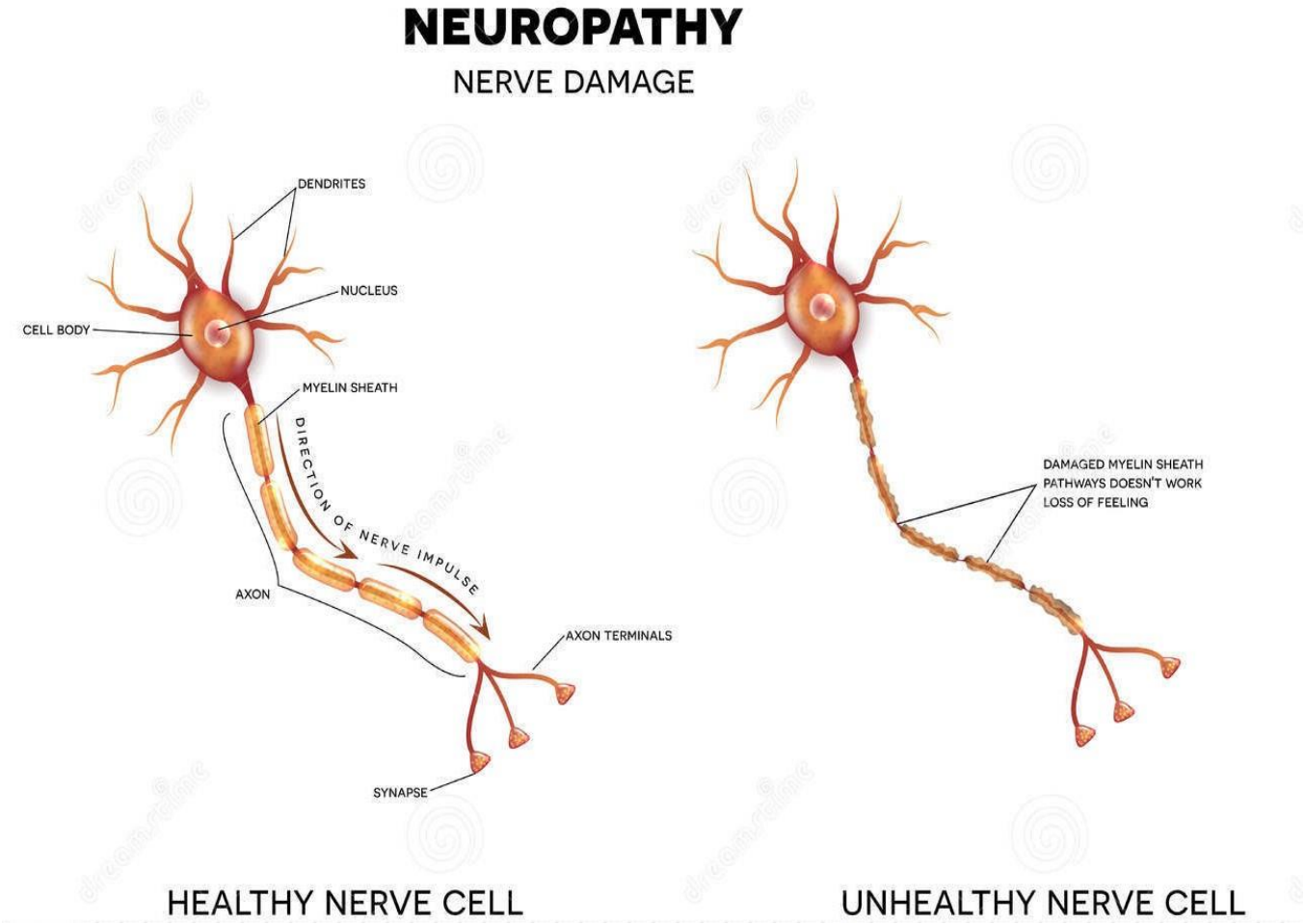
Diabetic Neuropathies

Classification of diabetic neuropathy

- Diffuse neuropathy

  - somaticnp.: sensorimotor

  - autonomicnp.: cardiovascular, gastrointestinal, genitourinary, pupil


NEUROPATHY
NERVE DAMAGE
DENDRITES
NUCLEUS
CELL BODY
MYELIN SHEATH
DIRECTION OF NERVE IMPULSE
AXON
AXON TERMINALS
SYNAPSE
DAMAGED MYELIN SHEATH
PATHWAYS DOESN'T WORK
LOSS OF FEELING
HEALTHY NERVE CELL
UNHEALTHY NERVE CELL

- Focal syndromes -

focalnp.: mononeuritis, entrapment syndr.

- multifocalnp.: proximal neuropathies

- Subclinical neuropathy -

abnormalelectrodiagnostic tests -

abnormal quantitative sensory tests -

abnormal autonomic function tests

Quantitative sensory tests

- Tuning fork (vibration perception)
- Monofilament (touch sensation, predict foot ulceration)
- Pain and thermal sensation
- Tendon reflexes (Achilles)
- Neurometer (áramérzetküszöb)
- Classification of diabetic foot ulcer (Meggitt-Wagner Ulcer Classification
- Grade 0: No ulcer, but high-risk foot (bony prominences, callus, deformities, previous ulcer)

• Grade 1: Superficial, full-thickness ulcer

• Grade 2: Deep ulcer, may involve tendons, but without bone involvement

• Grade 3: Deep ulcer with osteomyelitis

• Grade 4: Local gangrene

• Grade 5: Gangrene of whole foot

University Texas Wound Classification System

• Grade 0: Pre- or postulcerativelesion, completely epithelialized • Grade 1: Superficial wound not involving tendon, capsule or bone

• Grade 2: Wound penetrating to tendon or capsule

• Grade 3: Wound penetrating to bone or joint

• Stage A: without infection or ischemia

• Stage B: with infection

• Stage C: with ischemia

• Stage D: with infection and ischemia

Treatment of diabetic foot ulcer

• Removing necrotic tissue

• Removing the pressure (casts, total contact casts)

• Antibiotic treatment (1-12 weeks): clidamycin, ciprofloxacin, cephalexin, amoxicillin-clavulanate, impenem,

Cardiovascular tests

Quantitative autonomic function tests

Parasympathic function,

heart rate Variability:

• Valsalva'smaneuver

• Deep breathing

• Supine vs. standing

Sympathic function (RR):

• Orthostatic hypotension

Autonomic neuropathy increases the five-year mortality with 3 times!

Macrovascular complications

Cardiovascular risk in diabetes

• Peripheral arterial disease 2-4x ↑ (risk of amputation 16x ↑)

• CHD: risk of AMI 2-3x ↑, heart failure 5x ↑

• Stroke 2-4 x ↑

• Protection of female gender is disappeared

• The macrovascular risk is 10 x ↑ in the presence of microvascular complication Survival

Hypertension/blood pressure control

• Should be measured at

every visit

• Repeat RR ≥ 130/80 Hgmm confirms the diagnosis of hypertension

• Therapeutic goal: RR < 130/80 Hgmm

• 130-139/80-89 Hgmm lifestyle for 3 months

• RR ≥ 140/90 Hgmm drug therapy

• ACE-I or ARB

Dyslipidemia/lipid management

• At least annually measurement (low risk 2 years)

• Therapeutic goal:

LDL-chol.< 2.6 mmol/l (no CVD)

LDL-chol.< 1.8 mmol/l (with CVD)

TG < 1.7 mmol/l

HDL-chol.> 1.0 (male); > 1.3 mmol/l (female)

Dyslipidemia/lipid management

• Lifestyle modification

• Statin regardless of basal lipid levels!!!! If - DM + overt CVD > 40 years of age, + risk faktor(s) for CVD

• < 40 years of age, LDL > 2.6 mmol/l or multiple CVD risk factors

Contraindicated in pregnancy

CHD screening in diabetes (ESC and EASD guideline 2007) • Resting ECG (1x a year) •

EchocardiographY •

Exercise testing ECg

↓ Diabetes and infections

• Infections are more frequent: pneumonia, urinary tract, skin and mucosal infections 1.5-2 x ↑

• Infections are more severe, mortality rate is increased 2-3x ↑.

• Provokes hyperglycemic crisis.

• Rare, life threatening infections.

• **Immunization:** annually influenza vaccine, pneumococcal polysaccharid vaccine > 2 years (repeat > 64 years of age, renal disease, transplantation)

Rare, life threatening infections.in diabetes

• Mucormycosis (rhinocerebralis)

• Malign otitis externa (Ps. aeruginosa)

• Psoas abscessus (St. aureus)

• Emphysematosuscholecystitis (E. coli, Cl. Perfringens)

• Emphysematosusurocystitis, pyelonephritis (E. coli, K. pneumoniae)

• Fasciitis necrotisans (polymicrobe)

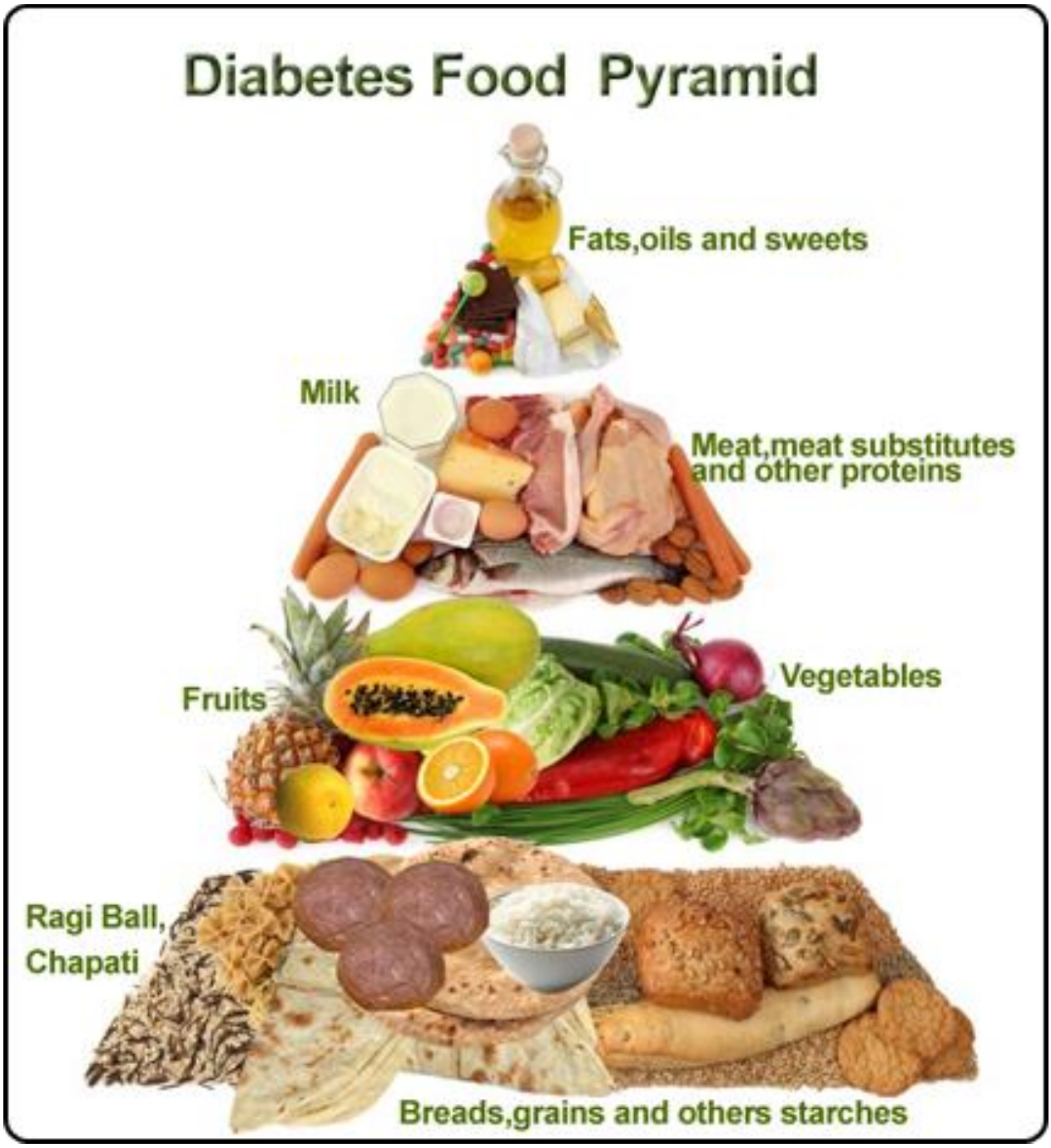
TREATMENT STRATEGIES:

LIFE STYLE MODIFICATION:

Lifestyle changes are often advised for people at higher risk of diabetes and those who are newly diagnosed with type 2, to help manage their diabetes.

The recommended lifestyle interventions include:

- Taking two and a half hours each week of moderate intensity physical activity or one hour and 15 minutes of high intensity exercise.
- Losing weight gradually to achieve a healthybody mass index
- Replacing refined carbohydrates withwholegrain foods and increase intake of vegetables and other foods high in dietary fibre
- Reducing the amount of saturated fat in the diet


Diabetes Food Pyramid
Fats,oils and sweets
Milk
Meat,meat substitutes and other proteins
Fruits
Vegetables
Ragi Ball,
Chapati
Breads,grains and others starches

Physical activity

NICE recommend taking either 2 ½ hours of moderate intensity physical activity or 1 ¼ hours of intense exercise.

Moderate intensity physical activity includes:

- Brisk walking
- Cycling on relatively flat terrain
- Water aerobics
- Hiking
- Rollerblading
- Using a manual lawnmower

Vigorous physical activity may include:

- Jogging
- Swimming lengths
- Cycling either rapidly or over steep terrain
- Football
- Gymnastics
- Skipping

Some people may be able to be referred for structured or supervised exercise sessions.

WEIGHT LOSS

Guideline issued by NICE recommend those that are overweight aim to lose weight gradually until a healthy BMI is achieved.

A healthy BMI range is:

- Between 18.5 and 24.9
- Or between 18.5 and 22.9 for people of South Asian descent

For those with a BMI above the healthy range, NICE recommends aiming to achieve weight loss gradually, with a target to reduce weight by 5 to 10% over a period of a year.

Weight loss can help to reduce the risk of developing diabetes and can enable people with existing pre-diabetes or type 2 diabetes to better control blood glucose levels.

If you have a BMI of over 30, your GP may refer you to take part in a structured weight loss programme. People unable to achieve weight loss via lifestyle changes may be prescribed a weight loss pill called orlistat.

1) Defect in insulin sensitivity:

- Exercise – aerobic
- Weight reduction – drugs ,diet
- Thiazolidinediones-Glitazones.
- Metformin.

2)Defect in insulin secretion:

- Beta cell stimulation- sulfonylurease,repaglinide.
- Insulin exogenous supplementation.

3)Increased hepatic glucose output:

- Metformin >Glitazones.
- Insulin supplementation, SU.

4)Carbohydrate absorption:

(post prandial hyperglycemia)

- Acarbose.

Often the defects are multiple and hence the need for combination of the above strategies.

METFORMIN

History:

1.In early medieval periods,in Europe ,the biguanides which used was leguminosaGalegaofficinalis.

2.By 1918- the active glucose reducing compound was discovered as GUANIDINE.

3.Between 1957 & 1960,three biguanides were used medical purposes.They are

1. PHENFORMIN
2. METFORMIN
3. BUFORMIN.
4. Since chance for lactic acidosis is very high in phenformin and buformin,they were withdrawn.

ACTIONS OF METFORMIN:

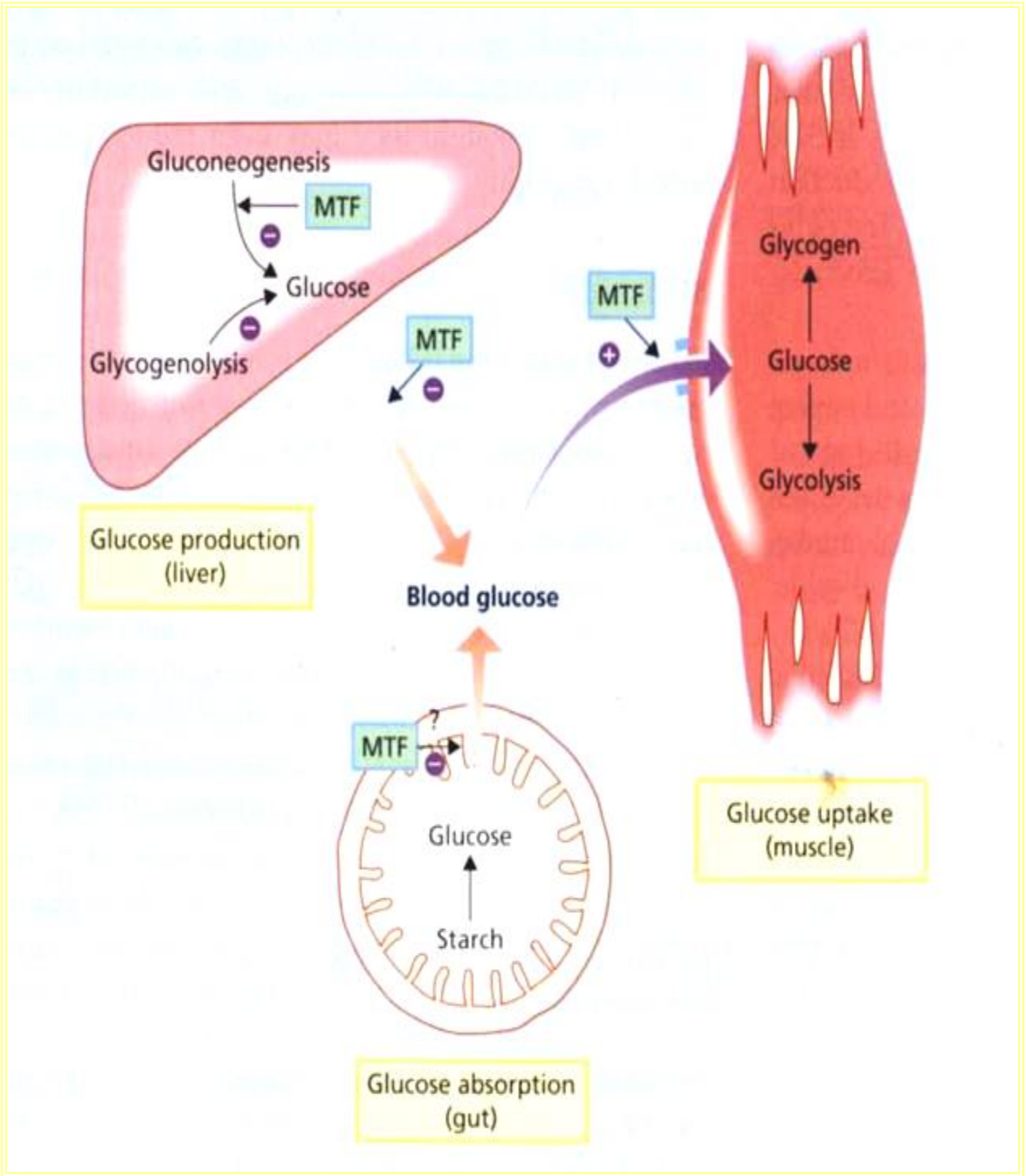
1. Metabolic actions
2. Cellular actions
3. Additional actions.

METABOLIC ACTIONS:

1. Reduction of excessive Hepatic glucose output,ie ,they suppresses hepatic gluconeogenesis.
2. Stimulation of insulin- mediated muscle glucose uptake-glycogen synthesis is increased.
3. Inhibition of lipolysis and FFA availability.

CELLULAR ACTIONS:

1. Increased insulin binmding.
2. Stimulation of insulin receptor tyrosine kinase activity.
3. Enhanced glucose transport (GLUT 4)
4. Increased glycogen synthase.
5. Doesn’t cause hypoglycemia.


Gluconeogenesis
MTF
Glucose
Glycogenolysis
Glucose production (liver)
MTF
MTF
Glycogen
Glucose
Glycolysis
Blood glucose
MTF
?
Glucose
Starch
Glucose absorption (gut)
Glucose uptake (muscle)

ADDITIONAL ACTIONS:

1.Favorable lipid effects.

2.Weight loss.

3.Increased fibrinolytic activity

4.Decreases the platelet aggregability

5.Favourable effects on hypertension.

Preferable choice in:

1.Obeses diabetics.

2.Diabetics with hypertension

3.Diabetics with prominent Dyslipidemia.

4.Patients with IGT.

Pharmacokinetics:

Bio-availability(% of dose) - 50 to 60%

C max(mcg/ml) - 1.0 to 1.5

t max (in hours) - 1.9 10 3.0

Plasma half life - 2.0 to 5.4

Renal clearance(ml/min) - 400 to 600

Total clearance (ml/min) - 1,300

Side effects:

1.nausea, vomiting, distension

2.Loss of appetite,diarrhea

3.Skin rashes

4.Urticaria

5.Increase in liver enzymes.

6.Lactic acidosis

7.Vitamin B12 deficiency.

CONTRAINDICATIONS:

1.Patient with type 1 diabetes.

2.Patient with hepatic and renal impairment.

3.Alcoholic liver disease.

4. Chronic obstructive airway disease.

5.Congestive heart failure.

6.Myocardial infarction

7.Pregnancy

8.Lactation.

9.Peripheral vascular disease.

10.Any condition associated with hypoxia.

11.Patients with more than 70 years of age.

12.Care while using diuretics concomitantly.

METFORMIN IN COMBINATION WITH GLYBURIDE:

Initial combination treatment with glyburide &methformin tablets produces good results in glycaemic control than either glyburide or methformin alone.

The superiority of initial therapy with glyburide+metformin tablets may arise from simultaneous treatment of both pathophysiological defects of type 2 diabetes.

METFORMIN IN COMBINATION WITH PIOGLITAZONE:

- Very effective tolerability.
- No hepatotoxicity seen.
- Fall in HbA1c and FPG noted.

METFORMIN IN COMBINATION WITH SECONDARY OHA FAILURE:

Metformin plays an important role in the success of the combination therapy.In case of people who were having secondary drug failure,the rational prescription of methformin with other drugs is suitable for the metabolic control.

METFORMIN AND PCOD:

Metformin administration during pregnancy reduces 1st trimester pregnancy losses in women with polycystic ovary syndrome.

It treats the root culprit of PCOS and rectifies metabolic and endocrine functions ,thus improving fertility.It acts as an insulin sensitizer.

Besides reducing the level of insulin,methformin also help in reduction of total and free testosterone and elevates the sex hormone binding globulin.

Ovulation can occur in 70-80% and chance for pregnancy is 30-40%.

METFORMIN IN OBESITY:

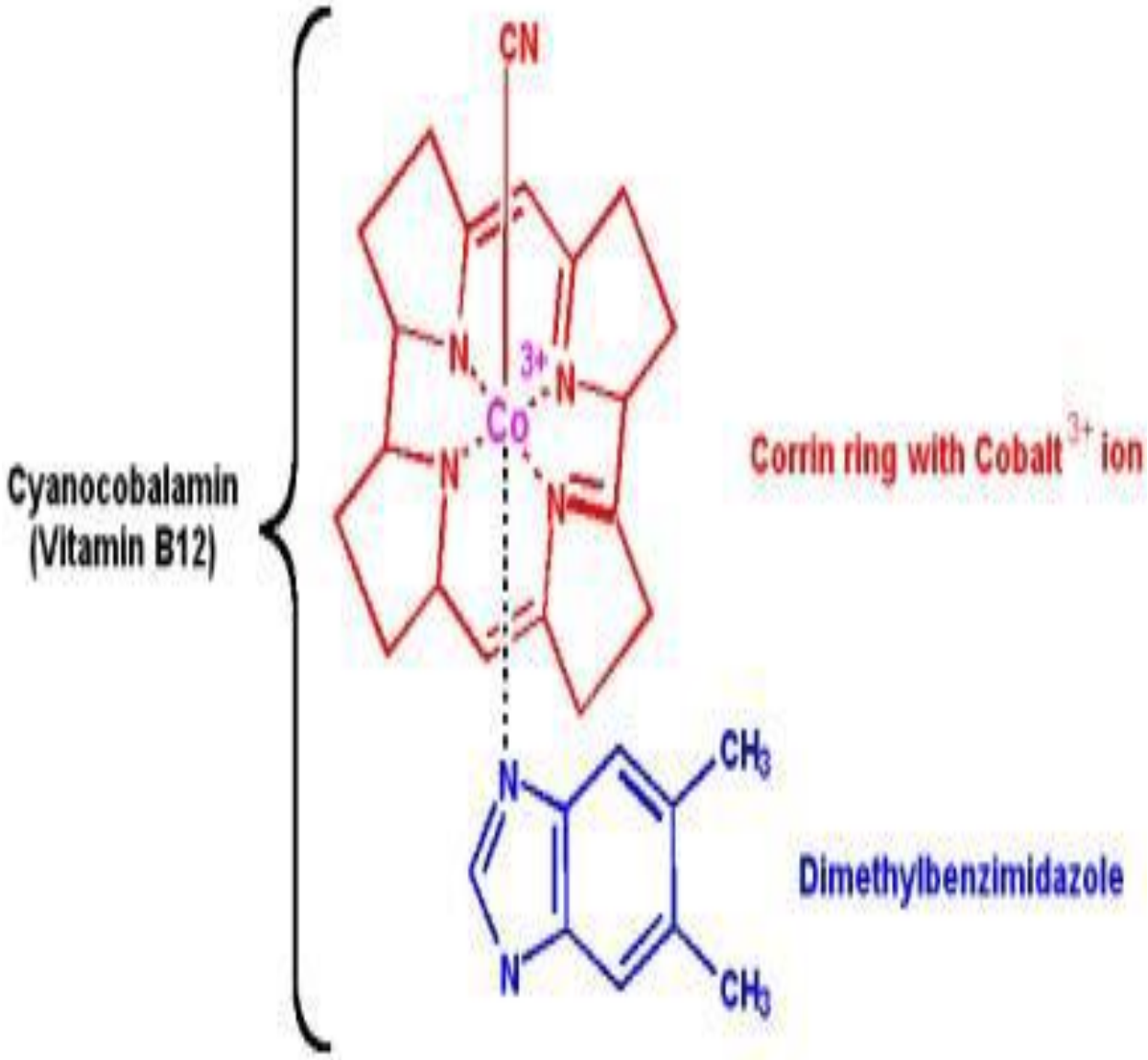
Its action is interference of glucose absorption in the intestine through ANOREXIO-GENIC ACTION.

No effects on normal blood sugar;nonhypoglycemic (only anti hyperglycemic)

VITAMIN B12(COBALAMINE)

1. It is a water soluble vitamin.
2. It plays a key role in the normal physiological functioning of the brain and the nervous system and also for the hemopoeisis.
3. It acts as a coenzymes for enzymes which transfer methyl groups and produces red blood cells.

COMPOSITION:



VITAMIN B12 DERIVATIVES:

- Cyanocobalamine (digested form)
- Adenosylcobalamine
- Chlorocobalamine
- Hydroxycobalamine
- Methylcobalamine
- 5'deoxyadenosylcobalamine.

SOURCES OF VITAMIN B12:

1)Natural forms

- produced by the microorganisms (bacteria/fungi)may inhabit in gut.

- plant don't produce or contain Vit b12.

2)Food sources rich in Vit b12

-Liver,kidney,Muscle

-Egg,Milk,Cheese and other diary products.

-Sea foods.

-Foods fortified with B12 are also sources of the vitamin B12

VITAMIN B12 Stores:

1. Normal body stores of vitamin B12 about 3-4 mg,primarily in liver.
2. This would be sufficient for 3 years if dietary intake is ceased or if the ability to absorb the vitamin was lost.

REQUIREMENT:

- Recommended daily dietary allowance is 3mcg per day.
- Pregnancy and lactation – 6mcg per day.

BIOCHEMICAL FUNCTIONS:

Plays essential role in one carbon transfer metabolism

– DNA synthesis

– Fatty acid synthesis

– Energy production.

– One carbon transfer reactions are required in the biosynthesis of:

– Amino Acids

– Serine,

– Methionine

– Glycine,

– Purine nucleotides

Enzymes that require vitamin B12 as cofactor

1) Methylmalonyl-coamutase:

– Isomerization of methyl malonyl CoA from odd C. numbered fatty acids.

– Above reaction is an essential step for:

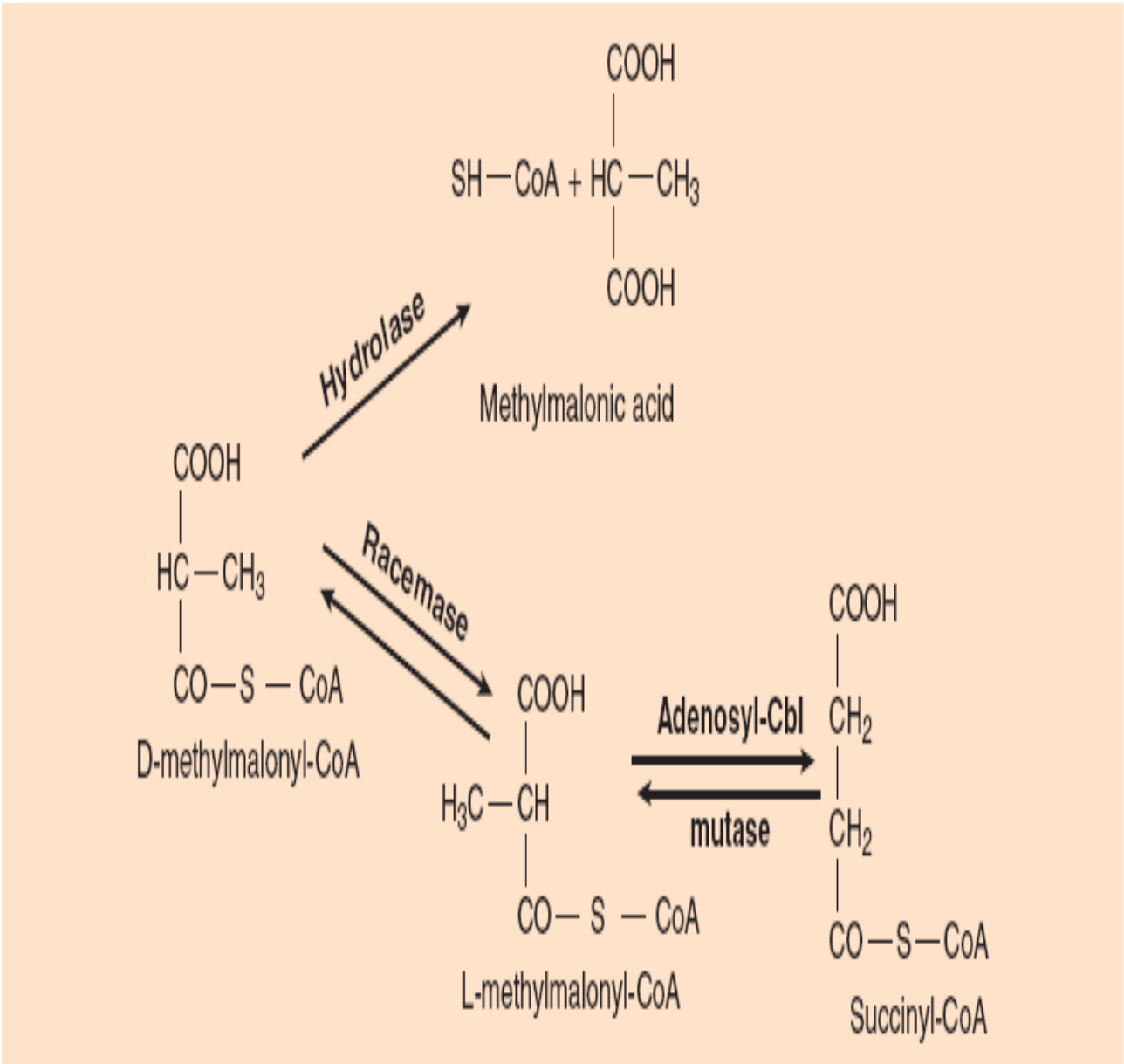
• Catabolism of fatty acids with an odd number of carbon atoms.

• Amino acids (Valine, Isoleucine and Threonine).

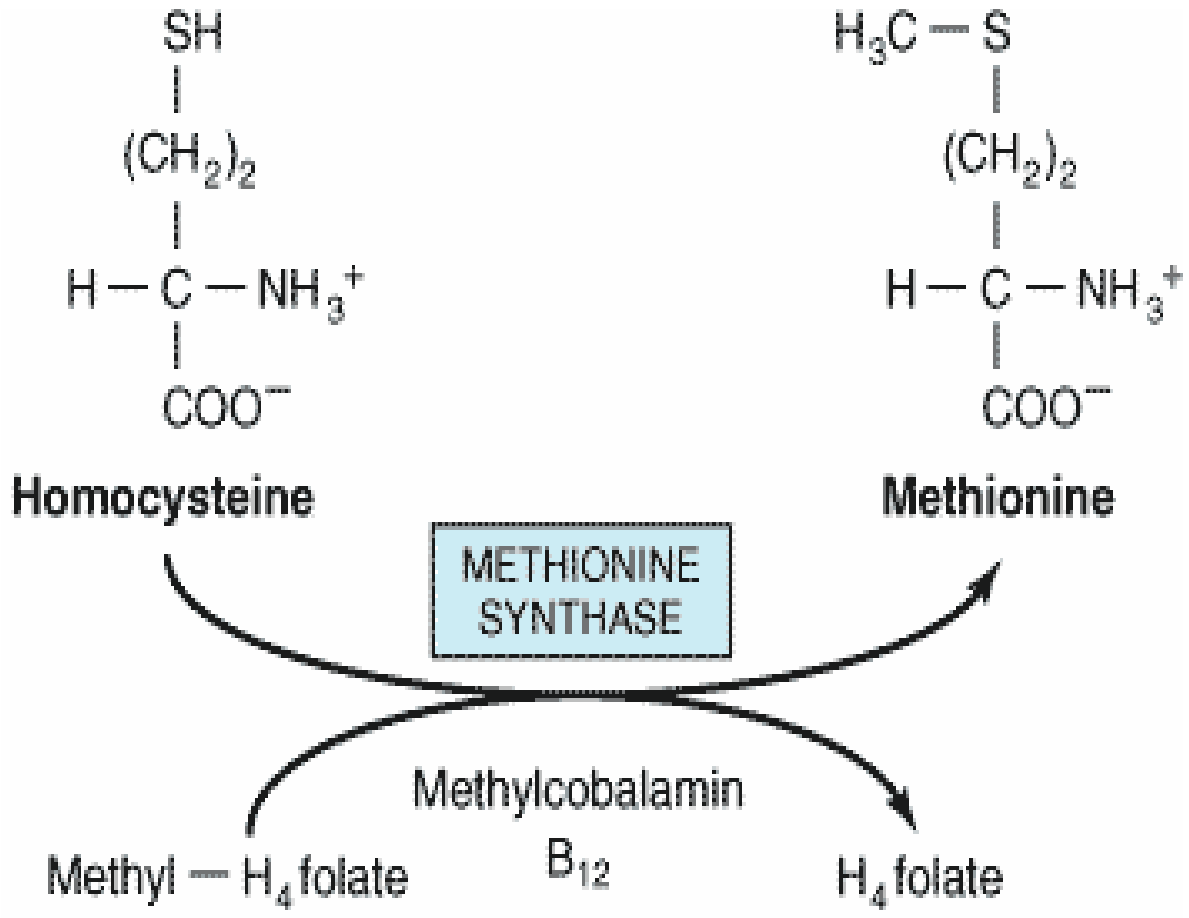
• When B12 is deficient odd C. numbered fatty acids accumulate in cell membrane of C.N.S Causing Neurologic symptoms.

2) Methionine synthase:

– Synthesis of Methionine from Homocysteine


COOH
SH—CoA + HC—CH3
COOH
Hydrolase
Methylmalonic acid
COOH
HC—CH3
CO—S—CoA
D-methylmalonyl-CoA
Racemase
COOH
H3C—CH
CO—S—CoA
L-methylmalonyl-CoA
Adenosyl-Cbl
mutase
COOH
CH2
CH2
CO—S—CoA
Succinyl-CoA

ENZYME METHIONINE SYNTHASE REQUIRES VITAMiN B12 AS A COFACTOR



Absorption of vitamin B12:

1.The preliminary step in the metabolism of b12 involves its release from animal source,a process mediated by the action of pepsin and gastric acid. 2.After the release,dietary vitamin B12 binds to the R-protein secreted by the salivary glands.In the duodenum,in the presence of an alkaline medium and pancreatic proteases, the R-protein is hydrolysed to release vitamin b12 which later binds with the intrinsic factor secreted by the gastric parietal cells. 3.The vitamin b12 –IF complex is resistant to the proteolyticdegradation.The complex attaches at its specific receptors on the mucosa of the terminal ileum, a site where its absorption occurs.This stage of vitamin B12 absorption is calcium mediated.

4.The intracellular B12 is released following the IF degradation.This free vitamin b12 attaches to another protein carrier,transcobalamine-II and is later released into the circulation.This vitamin B12-TC-II complex,also referred to as holo TC-II is then actively taken up by the liver, bone marrow and all other vital cells.The liver serves as a principal storage site of upto 90% of the body's total vitamin B12.

Vitamin B12 works together with folate in the synthesis of DNA and red blood cells. It's also involved in the production of the myelin sheath around the nerves, and the conduction of nerve impulses. You can think of the brain and the nervous system as a big tangle of wires. Myelin is the insulation that protects those wires and helps them to conduct messages.

Severe B12 deficiency in conditions like pernicious anemia (an autoimmune condition where the body destroys intrinsic factor, a protein necessary for the absorption of B12) used to be fatal until scientists figured out death could be prevented by feeding patients raw liver (which contains high amounts of B12). But anemia is the final stage of B12 deficiency. Long before anemia sets in, B12 deficiency causes several other problems, including fatigue, lethargy, weakness, memory loss and neurological and psychiatric problems

B12 deficiency occurs in four stages, beginning with declining blood levels of the vitamin (stage I), progressing to low cellular concentrations of the vitamin (stage II), an increased blood level of homocysteine and a decreased rate of DNA synthesis (stage III), and finally, macrocytic anemia (stage IV).

B12 deficiency: a silent epidemic with serious consequence

- Alzheimer's, dementia, cognitive decline and memory loss (collectively referred to as "aging")
- Multiple sclerosis (MS) and other neurological disorders
- Mental illness (depression, anxiety, bipolar disorder, psychosis)
- Cardiovascular disease
- Learning or developmental disorders in kids
- Autism spectrum disorder
- Autoimmune disease and immune dysregulation
- Cancer
- Male and female infertility

B12 DEFICIENCY:

An invisible epidemicB12 deficiency isn't a bizarre, mysterious disease. It's written about in every medical textbook and its causes and effects are well-established in the scientific literature.

However, B12 deficiency is far more common than most health care practitioners and the general public realize. Data from the Tufts University Framingham Offspring Study suggest that 40 percent of people between the ages of 26 and 83 have plasma B12 levels in the low normal range – a range at which many experience neurological symptoms. 9 percent had outright deficiency, and 16 percent exhibited "near deficiency". Most surprising to the

researchers was the fact that low B12 levels were as common in younger people as they were in the elderly.

That said, B12 deficiency has been estimated to affect about 40% of people over 60 years of age. It's entirely possible that at least some of the symptoms we attribute to "normal" aging – such as memory loss, cognitive decline, decreased mobility, etc. – are at least in part caused by B12 deficiency.

Why is B12 deficiency so under-diagnosed?

B12 deficiency is often missed for two reasons. First, it's not routinely tested by most physicians. Second, the low end of the laboratory reference range is too low. This is why most studies underestimate true levels of deficiency. Many B12 deficient people have so-called "normal" levels of B12.

Yet it is well-established in the scientific literature that people with B12 levels between 200 pg/mL and 350 pg/mL – levels considered "normal" in the U.S. – haveclear B12 deficiency symptoms. Experts who specialize in the diagnosis and treatment of B12 deficiency, like Sally Pacholok R.N. and Jeffery Stewart D.O., suggest treating all patients that are symptomatic and have B12 levels less than 450 pg/mL. They also recommend treating patients with normal B12, but elevated urinary methylmalonic acid (MMA), homocysteine and/or holotranscobalamin (other markers of B12 deficiency).

In Japan and Europe, the lower limit for B12 is between 500-550 pg/mL, the level associated with psychological and behavioral manifestations such as cognitive decline, dementia and memory loss. Some experts have speculated that the acceptance of higher levels as normal in Japan and the willingness to treat levels considered "normal" in the U.S. explain the low rates of Alzheimer's and dementia in that country.

VITAMIN B12 DEFICIENCY AMONG PATIENTS WITH TYPE 2 DIABETESMELLITUS

There is increased frequency of vitamin b12 deficiency among type 2 DM patients.

Metformin use has been unequivocally demonstrated as the first factor associated with vitamin B12 deficiency among the patients with type 2 DM.

The prevalence ranges from about 5.8% to 33% to define vitamin B12 deficiency,the serum B12 concentration must be less than <200pg/ml or elevated serum methylmalonic acid of more than 243 nmol/L or homocysteine concentrations of more than 11.9nmol/Li if serum vitamin B12 concentration were between 100 to 350 pg/ml.

In the absence of contraindications like renal and hepatic dysfunction,metformin is used as the first line glucose lowering agent concurrently with life style modification.

Despite its very superior glycemiccontrol,methformin has been shown to decrease vitamin B12.

The risk of developing methformin associated vitamin B12 deficiency is greatly influenced by increasing age,methformin dose and duration of use.

Decrease in vitamin b12 absorption and levels following metformin use typically starts as early as the 4thmonth.Clinically overt features of vitamin B12 deficiency manifest by 5-10 years owing to the large body stores in the liver mainly that are not quickly depleted.

The proposed mechanism to explain methformin induced vitamin B12 deficiency among patients with T2DM include:

alteration in small bowel motility which stimulates bacterial overgrowth and consequential vitamin B12 deficiency,competitive inhibition in inactivation of vitamin B12 absorption,alteration in intrinsic factor levels and interaction with the cubulinendocytic receptor.

Metformin has also been shown to inhibit the calcium dependent absorption of the vitamin B12-IF complex at the terminal ileum.This inhibitory effect is reversed with calcium supplementation.

SCREENING APPROACH FOR VITAMIN B12 DEFICIENCY AMONG PATIENTS WITH T2DM:

Currently there are no guidelines advocating for routine screening for vitamin B12 deficiecy among patients with T2DM.

However among type 2 diabetic patients ,it is clinical plausible to screen for vitamin B12 deficiency prior to initiation of metformin and later annually among elderly patients with history of long term use of metformin,use of high doses of metformin, clinically worsening diabetic distal polyneuropathy in the presence or absence of the hematological abnormalities.

The screening approach for vitamin B12 deficiency among diabetic patients and the general population is similar.Measurement of the serum vitamin B12 concentration should be the preliminary screening step for vitamin B12 deficiency among patients with T2DM.Concentration <200 pg/ml are usually diagnostic of diagnostic of vitamin B12 deficiency while concentrations >400 pg/ml confirm absence of vitamin B12 deficiency.

Measurement of serum MMA or homocysteine concentrations is a more sensitive and specific approach for screening especially among type 2 diabetes patients with borderline serum vitamin B12 concentration of 200-400 pg/ml and subtle hematologicalmanifestations.Serumhomocysteine and MMA concentrations of 5-15 mcgmol/l and 0.28 mcgmol/l are considered within the normal range respectively.

TREATMENT OF VITAMIN B12 DEFICIENCY AMONG DIABETIC PATIENTS

Treatment of vitamin B12 deficiency doesnot differ regardless of the aetiology. All patients deficit of vitamin B12 should receive must be treated with either oral or parenteral vitamin B12. Both formulations have been demonstrated to induce comparable desirable hematological and neurological improvements regardless of the etiology of the deficiency.

THERAPEUTIC BENEFITS OF VITAMIN B12 REPLACEMENT AMONG T2DM PATIENTS WITH DIABETIC NEUROPATHY

Vitamin B12 deficiency and the accompanying hyperhomocysteinemia and elevated MMA levels have been documented to cause a distinct sensory polyneuropathy which closely mimics diabetic neuropathy.

Worsening of diabetic neuropathy is also noted among patients with coexisting vitamin b12 deficiency.

Vitamin B12 repalcement has been shown to cause symptomatic improvement among patients with severe diabetic neuropathy. Either alone or in combination with B complex, there was a significant improvement in the somatic symptoms like pain and parasthesia.

VITAMIN B12 SUPPLEMENTATION AMONG PATIENTS WITH DM:

Administration of oral vitamin B12 among type 2 DM patients on long term use of metformin was ineffective in correcting biochemical vitamin B12 deficiency.The doses used in combination with B complex tablets were inadequate to correct vitamin B12 deficiency.

To overt vitamin B12 deficiency especially among adult type 2 diabetic patients on long term use of metformin .it is plausible to adopt a simple and cost effective supplementation approach in diabetic care.

"A 1000mcg dose of vitamin B12 given annually would be sufficient to replenish the body's vitamin B12 stores among this category of patients".

MATERIALS & METHODS

SETTING:

Department of diabetology&Medicine,GovtRajajihospital,MaduraiMedical College,Madurai.

INCLUSION CRITERIA:

Study group:Type 2 diabetic not on methformin for more than 18 months.

Control group:Type2 diabetic not on methformin for more than 18 months.

EXCLUSION CRITERIA:

1.Parenteral Vitamin b12 supplementation

2.Malabsorption(celiac diseases,inflammatory bowel disease,gastro intestinal surgery)

3.malnutrition (pure veg, anorexia nervosa)

4.Chronic alcoholism.

DESIGN OF STUDY: Prospective analytical study.

Period of study:6 months

PARTICIPANTS:

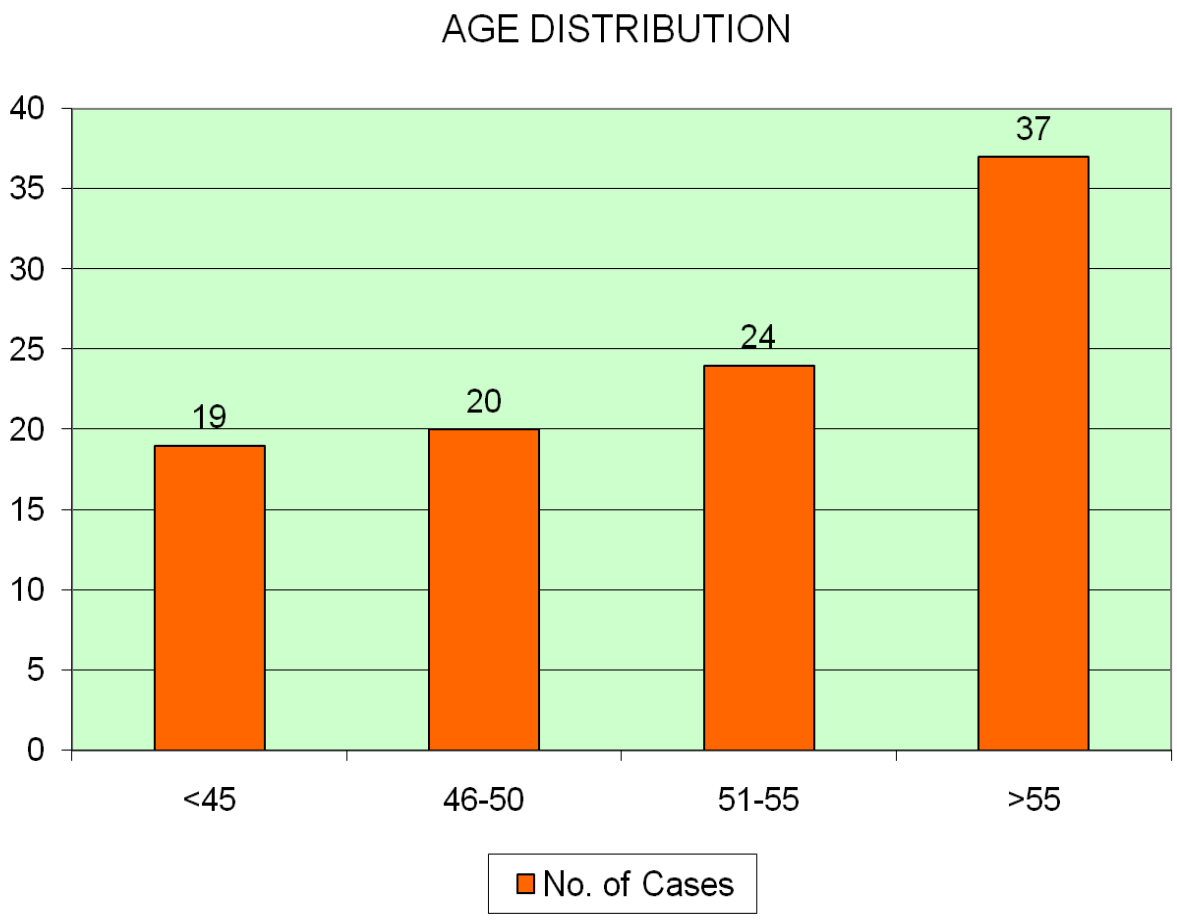
Patients with diabetes mellitus diagnosed according to World Health Organisation criteria and onset of diabetes after 30 years and duration more than or equal to 5 years in General medicine wards or attending Diabetology OPD of Government Rajajihospital,Madurai from Febrarury 2016 to july 2016.

The study will be conducted on 100 patients from General Medicine ward and diabetology OPD of Government rajaji Hospital Madurai in whom serum B12 assay by

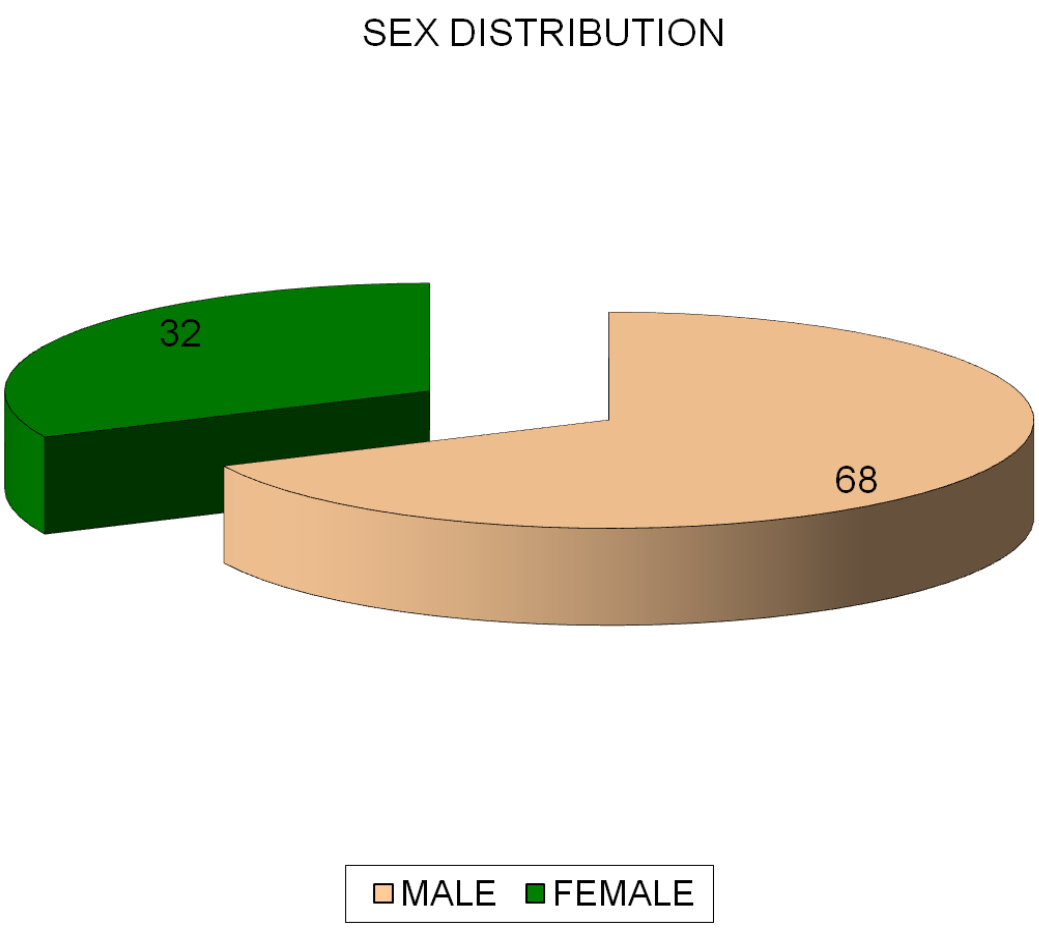
Hundred healthy controls will be selected randomly from by standersattendind the hospital .Significant medical illness will be ruled out by history ,physical examination and investigations .Comparisons among various groups and controls would be made by statistical tests.

OBSERVATION AND RESULTS

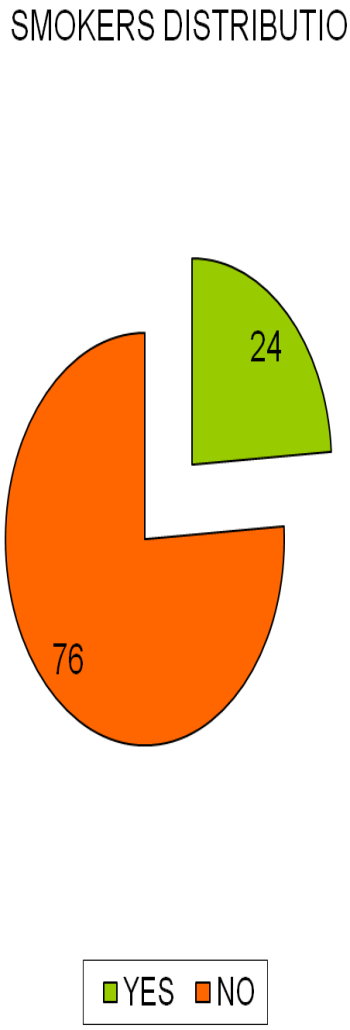
AGE	No. of Cases
<45	19
46-50	20
51-55	24
>55	37
Total	100
Mean	51.88
SD	6.037



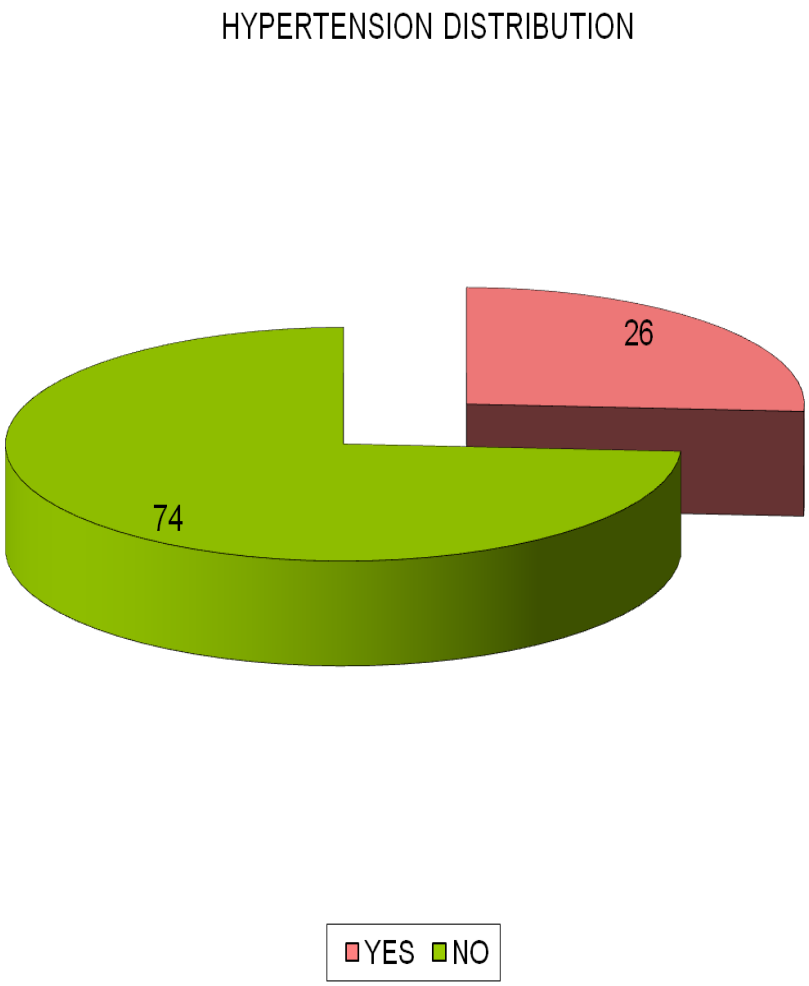
SEX	No. of Cases
MALE	68
FEMALE	32
Total	100
P'Value	0.005



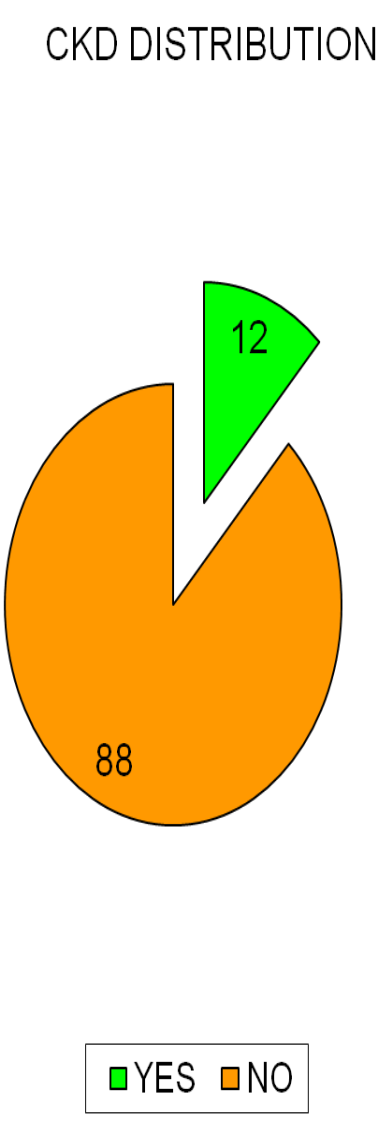
SMOKERS	No. of Cases
YES	24
NO	76
Total	100

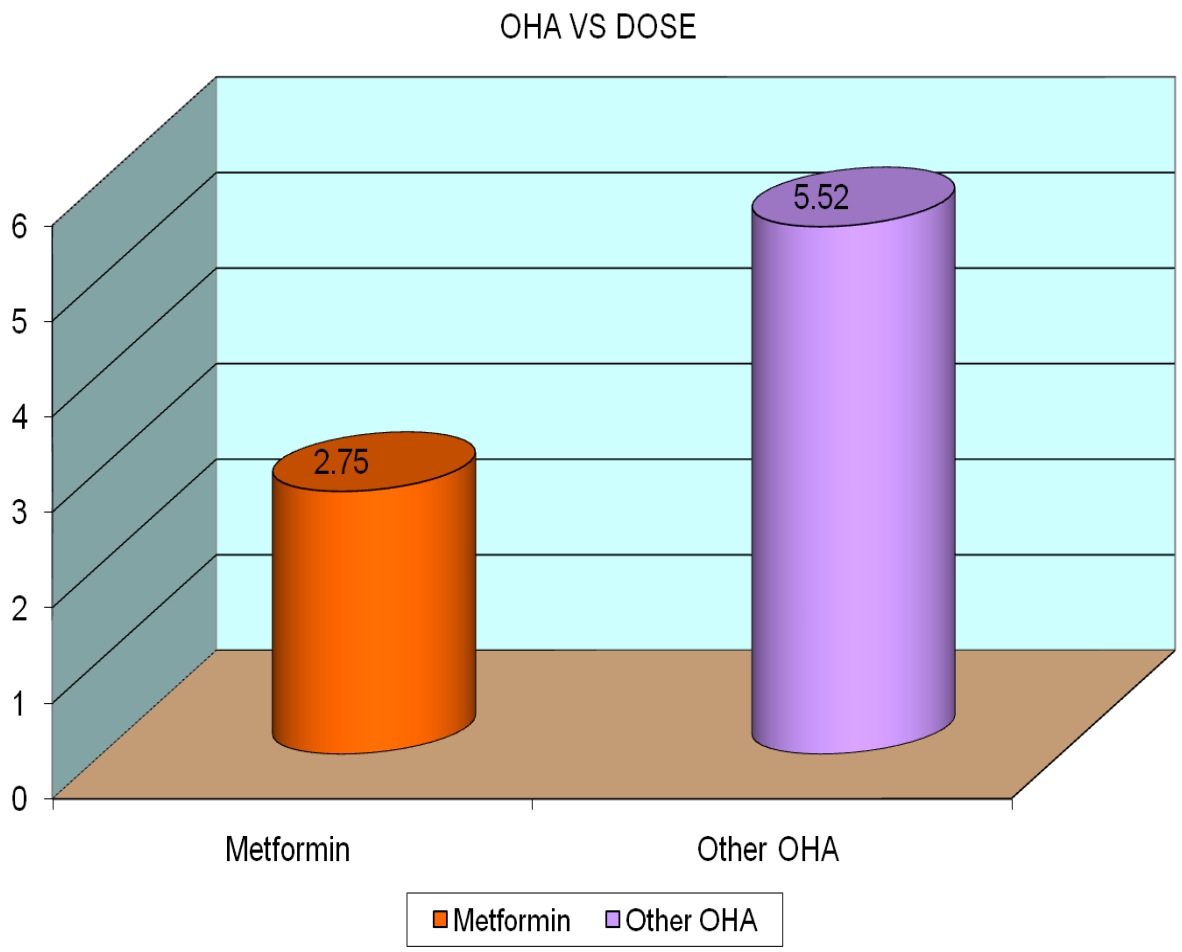


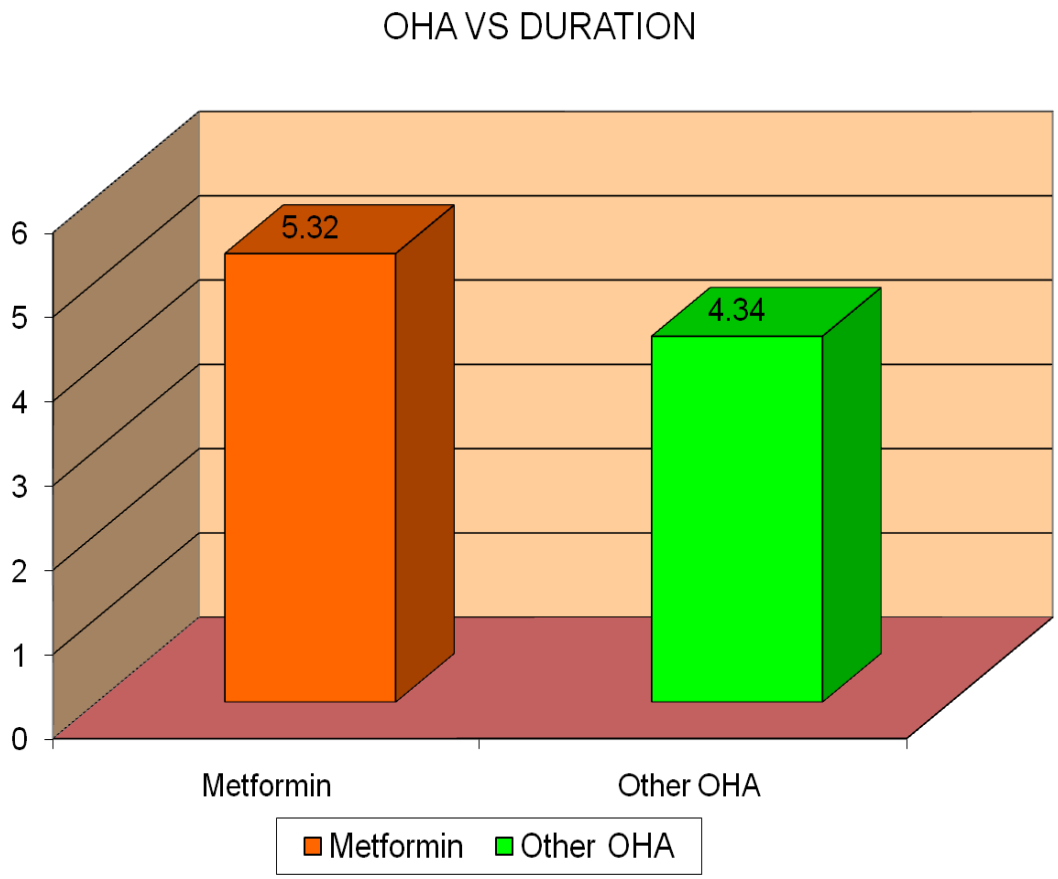
HTN	No. of Cases
YES	26
NO	74
Total	100



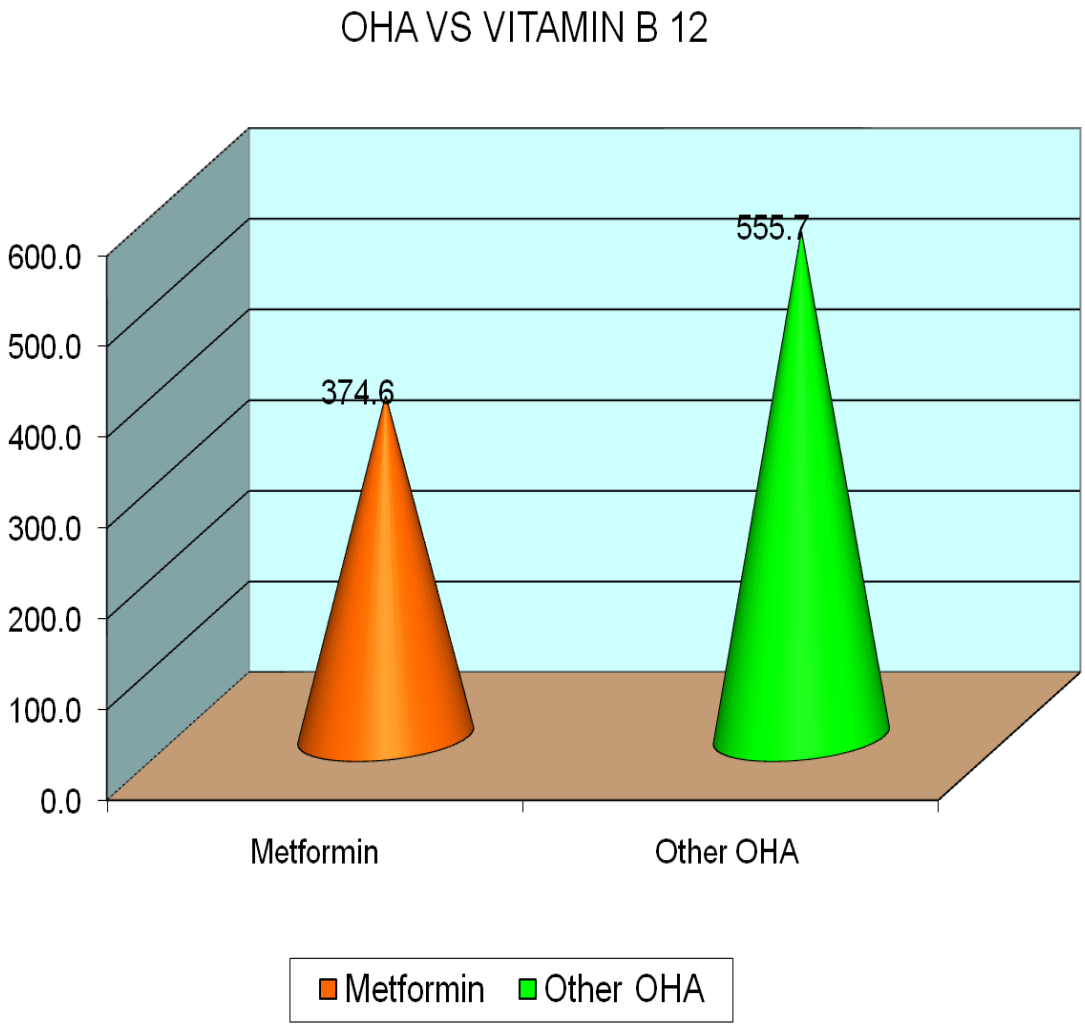
CKD	No. of Cases
YES	12
NO	88
Total	100




OHA VS DOSE
6
5
4
3
2
1
0
2.75
5.52
Metformin
Other OHA
Metformin
Other OHA


OHA VS DURATION
6
5
4
3
2
1
0
5.32
4.34
Metformin
Other OHA
Metformin
Other OHA

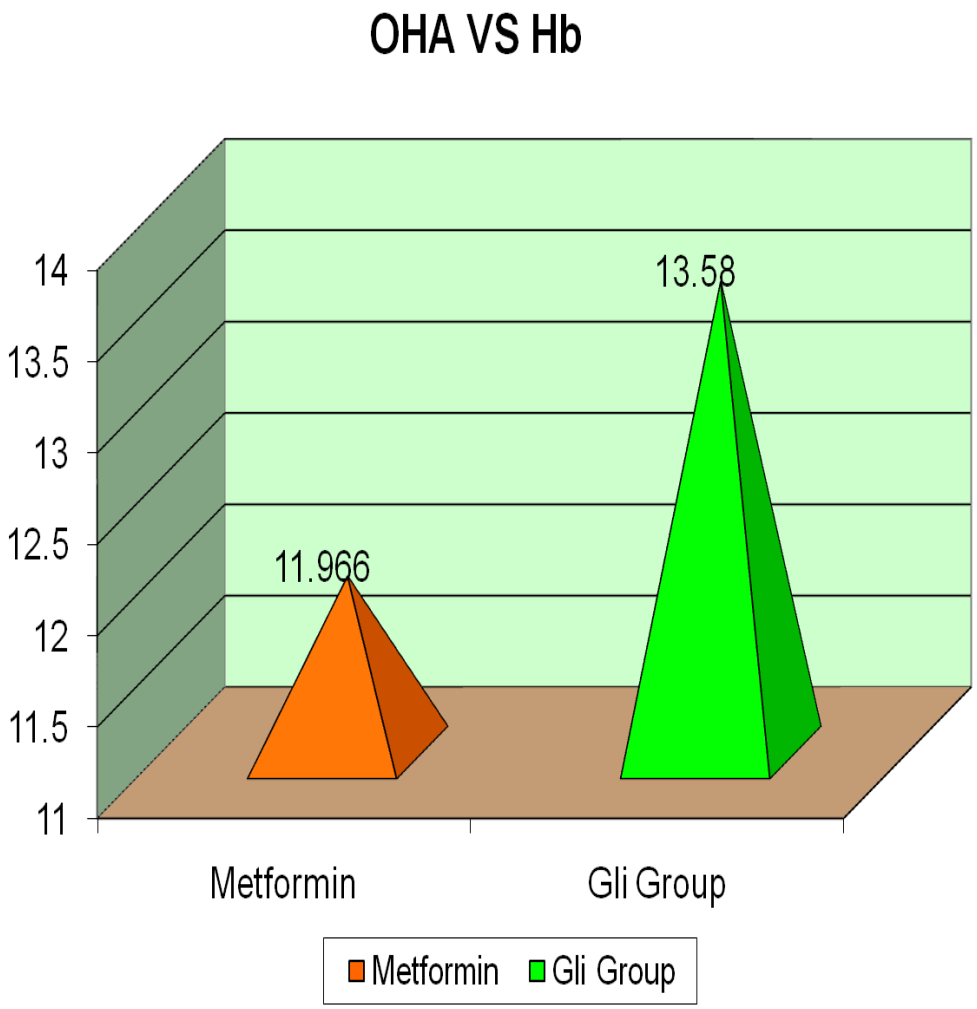
Metformin(OHA) vsVit B12		
Metformin	**Mean**	**SD**
< 1	476.154	151.550
> 1	338.649	191.977
P'Value	0.024	Significant


OHA VS VITAMIN B 12
600.0
500.0
400.0
300.0
200.0
100.0
0.0
374.6
555.7
Metformin
Other OHA
Metformin
Other OHA

OHA vs MCV		
OHA	**MCV**	
	Mean	**SD**
Metformin	100.18	11.102
Gli Group	95.6	3.785
P'Value	0.007	significant

OHA vsNurological Deficit			Total
OHA	**YES**	**NO**	
Metformin	15	35	50
Gli Group	1	49	50
Total	16	84	100
p.Value	0.031		

OHA vsHb		
OHA	**Hb**	
	Mean	**SD**
Metformin	11.966	3.002
Gli Group	13.58	1.851
P'Value	0.002	significant


OHA VS Hb
14
13.5
13
12.5
12
11.5
11
11.966
13.58
Metformin
Gli Group
Metformin
Gli Group

DISCUSSION

In a total of 100 patients studied; (68 male, 32 female)

19 people < 45 years

20 people between 45 to 50 years

24 people between 50 to 55 years

37 people above 55 years

Out of the 100 persons

24 were smokers

76 were non smokers

Other risk factors like hypertension and CKD were present.

26 persons had hypertension

12 persons had CKD

In this study, we are comparing type 2 Diabetes mellitus taking OHA other than Metformin and those who are taking metformin.

In those patients taking metformin-Hb value mean was found to be 11.9; And in those taking OHA taking other than metformin, mean Hb found to be 13.58; found to be statistically significant.

In those patients taking metformin ,neurological deficits seen in 15 persons and other OHA – one person presented with neurological deficit; -statistically significant

In those patients taking metformin for less than 1 year-

B12 level- 476.154

In those taking metformin for morethan 1 year

B12 level-338.649

Thus found to be statistically significant.

Duration and dose of metformin and other OHAs also plays a significant role.

SUMMARY:

- In those patients taking metformin-Hb value mean was found to be 11.9; And in those taking OHA taking other than metformin, mean Hb found to be 13.58; found to be statistically significant.
- In those patients taking metformin ,neurological deficits seen in 15 persons and other OHA – one person presented with neurological deficit; -statistically significant
- In those patients taking metformin for less than 1 year-

  B12 level- 476.154
- In those taking metformin for morethan 1 year

  B12 level-338.649
- Thus found to be statistically significant.
- Duration and dose of metformin and other OHAs also plays a significant role.
- Therefore, there is a significant prevalence of Vitamin B12 deficiency in Type 2 diabetic patients on Metformin therapy which showed a positive correlation to the dose & duration of therapy since Diabetic patients are more prone to develop neuropathy,Prolonged vitamin B12 deficiency may result in neuropathy

CONCLUSION

In this study we come to a conclusion that there is a statistical significant prevalence of Vitamin B12 in Type 2 diabetic patients on Metformin therapy which showed a positive correlation to the dose & duration of therapy since Diabetic patients are more prone to develop neuropathy,Prolonged vitamin B12 deficiency may result in neuropathy, ranging from paraesthesia and decreased peripheral sensation to altered mental status ,subacute combined degeneration of the spinal cord and dementia,hencePeriodic monitoring of serum B12 values in these patients is warrented to avoid serious neurological problems

BIBLIOGRAPHY

1.American Diabetes association. Standard of medical care in diabetes - 2009.care.2009;32:s13-61(PMCID;PMC2613589)[pub Med:1911886]

2. WHO;2009. World health organization. WHO model list ofEssential medicines p.24 available at http;//www.who.int/medicines

3.Liu KW,Dai DL, HO W Lau E,Woo j. metformin –associated vitamin B12 deficiency in the elderly. Asian j GerontolGeriator 2011;6:82-7

4.Diabetes federation of Ireland[home page on the internet].Tablets for type2 DM. Updated 2009 .cited February 14,2010.

5.Pflipsen MC , Oh RC, Saguil A, Seehusen DA, Topolski R. the prevalence of vitamin B12 deficiency in patients with type2DM;a cross sectional study. j am Board Fam Med.2009;22(5);58-34.

6.Filioussi K, Bonovas s, Katsaros T. should we screen diabetic patients using Biguanides for megaloblasticanemiaAustFam Physician 2003;32:383-4

7.Andres E, Noel E , Goichot B. Metformin-associated vitamin B12 deficiency Arch Intern Med 2002;162;2251-2.

8.Kirpichnikov D, McFarlane SI,Sowers JR. Metformin; an update. Ann intern Med 2002;137;25-33

9.UK prospective Diabetes study(UKPDS) group . Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS34)Lancet1998;352;854-65.

10.Matthew C. Pflipsen Robert C.oh ,Aaron S, Dean A.Seehusen, and Richard Topolski . The Prevalence of vitamin B12 Deficiency in patients with type 2DM;A cross sectional study.the journal of the American board of family medicine 2009 ;22;528-534.

LIST OF ABBREVATIONS

DM- Diabetes mellitus

OHA- Oral Hypoglycemis agents

MF- Metformin

VIT B12- Vitamin B12

HTN-Hypertension

IF- Intrinsic Factor

PROFORMA

Name: **Age / Sex:**

IP no: **Occupation:**

Presenting complaints:

Past History:

Personal history

alcoholic/ non alcoholic

smoker/ nonsmoker

Clinical Examination:

General Examination:Consciousness, orientation,febrile/afebrile, Pallor, jaundice, Clubbing, Lymphadenopathy, pedal edema.

Vitals:

PR

Bp

RR

SPO2

Systemic examination:

CVS:

RS:

ABDOMEN:

CNS:

Laboratory investigations:

Diagnosis

MADURAI MEDICAL COLLEGE
MADURAI, TAMILNADU, INDIA -625 020
(Affiliated to The Tamilnadu Dr.MGR Medical University, Chennai, Tamil Nadu)

ETHICS COMMITTEE CERTIFICATE

Name of the Candidate	:	Dr.Sathyarangan.M
Course	:	PG in MD., General Medicine
Period of Study	:	2014-2017
College	:	MADURAI MEDICAL COLLEGE
Research Topic	:	A prevalence study of vitamin B12 deficiency in patients with type 2 diabetes mellitus on Metformin
Ethical Committee as on	:	27.07.2016

The Ethics Committee, Madurai Medical College has decided to inform that your Research proposal is accepted.

Member Secretary Chairman Dean / Convenor

DEAN
Madurai Medical College
Madurai-20

06 SEP 2016

Sno	Age	Sex	Smoker	HTN	CKD	OHA	Dose of OHA	Duration (years)	Vit B 12 pg/ml	Hb	MCV	Neurological deficit
1	50	M	Yes	Yes	No	Metformin	1	1.5	340	12	92	No
2	45	M	Yes	Yes	No	Glipizide	10	6	540	16	94	No
3	56	M	No	No	No	Metformin	1.5	2	460	14.5	93	No
4	60	F	No	Yes	Yes	Metformin	1	3	280	9.5	98	No
5	58	F	No	No	No	Metformin	1.5	2	670	14.1	97	No
6	47	M	No	No	No	Glipizide	10	5	670	13.8	94	No
7	58	M	Yes	No	No	Glimepride	2	3	455	14.5	96	No
8	59	M	No	No	No	Metformin	3	6	190	15.2	110	Yes
-9	43	F	No	Yes	Yes	Metformin	2	2	185	8.6	114	yes
10	49	M	No	No	No	Glimepride	2	5	780	11.8	92	No
11	60	M	Yes	No	No	Metformin	1	5	570	15.5	94	No
12	58	M	No	No	No	Glimepride	2	5	800	16.8	92	No
13	42	F	No	No	No	Glipizide	10	5	630	13.4	90	No
14	58	M	No	No	No	Metformin	1.5	2	710	14.6	92	No
15	60	M	No	No	No	Glimepride	2	4	375	11.3	94	No
16	46	M	Yes	Yes	No	Metformin	1	2.5	350	13.5	95	No
17	57	M	No	No	No	Glimepride	2	5	770	12.8	93	No
18	53	F	No	Yes	Yes	Metformin	3	10	140	7.9	120	Yes
19	54	M	Yes	No	No	Metformin	1.5	3	460	13.5	90	No
20	48	M	No	No	No	Glipizide	10	3	530	12.8	94	No
21	53	M	No	No	No	Metformin	10	3	290	14.4	92	No
22	57	F	No	Yes	No	Metformin	1	4	540	12.7	93	No
23	60	F	No	No	No	Glimepride	2	5	765	14	94	No
24	49	M	Yes	No	No	Glipizide	10	3	680	15.3	95	No
25	57	M	No	No	No	Metformin	1.5	4.5	430	12.8	92	No
26	54	M	No	Yes	Yes	Glipizide	10	5	345	15.6	94	No
27	48	F	No	No	No	Metformin	3	10	165	7.3	112	Yes
28	43	M	No	No	No	Metformin	1	7	570	11.3	94	No
29	57	F	No	No	No	Metformin	1.5	9	360	12.9	96	No
30	54	M	Yes	No	No	Glimepride	2	3	780	15.7	93	No
31	48	M	No	Yes	No	Glimepride	2	4	475	14.5	98	No
32	43	M	Yes	No	No	Metformin	10	2	190	10.1	110	Yes
33	56	F	No	Yes	Yes	Metformin	3	12	170	6.5	118	Yes
34	57	M	No	No	No	Glimepride	2	4	530	16.5	98	No
35	54	M	No	No	No	Glimepride	2	5	790	14.3	94	No
36	53	F	No	No	No	Glipizide	10	5	365	12.9	92	No
37	54	F	No	No	No	Metformin	1	3	315	11.5	94	No
38	56	F	No	No	No	Metformin	1.5	2	420	10.9	90	No

39	43	M	Yes	No	No	Metformin	3	12	130	12	116	No
40	47	M	No	Yes	No	Glimepride	2	3	550	13	94	No
41	56	F	No	No	No	Glipizide	10	4	685	10	96	No
42	52	M	No	Yes	Yes	Metformin	3	10	155	8.4	118	yes
43	49	M	No	No	No	Metformin	2	5	345	14.6	94	No
44	56	M	No	No	No	Glipizide	10	4	165	9.6	118	Yes
45	60	M	Yes	No	No	Glipizide	10	5	465	11.4	96	No
46	41	F	No	No	No	Metformin	1.5	2	800	13	97	No
47	53	M	Yes	No	No	Glimepride	2	5	565	11.3	95	No
48	52	M	Yes	No	No	Metformin	1.5	1.5	780	17.8	94	No
49	47	M	No	Yes	No	Metformin	3	9	160	7.5	120	Yes
50	51	F	No	No	No	Metformin	2	6	235	12.3	102	No
51	56	M	No	No	No	Glimepride	2	5	340	11.9	94	No
52	48	M	No	Yes	No	Glipizide	10	4	450	12.5	96	No
53	58	M	No	No	No	Metformin	1	8	645	8.2	116	Yes
54	60	M	No	No	No	Glimepride	2	2	560	13.3	94	No
55	57	M	Yes	No	No	Glipizide	10	3	705	16	96	No
56	53	M	No	No	No	Metformin	1.5	7	175	7.1	116	yes
57	42	F	No	Yes	Yes	Metformin	2	5	345	13	98	No
58	47	F	No	No	No	Glipizide	10	4	670	17.7	92	No
59	52	M	No	No	No	Metformin	1	4	560	12.6	94	No
60	43	M	No	No	No	Glimepride	2	5	325	11.1	96	No
61	48	F	No	No	No	Glimepride	2	4	430	13.9	94	No
62	53	M	Yes	No	No	Metformin	10	7	185	12.7	118	yes
63	60	M	No	Yes	No	Metformin	1.5	8	260	15.9	98	No
64	46	F	No	No	No	Glipizide	10	5	710	14.3	96	No
65	53	M	No	No	No	Glimepride	2	3	235	14	98	No
66	54	M	No	No	No	Glimepride	2	5	460	12.6	94	No
67	59	F	No	Yes	Yes	Metformin	3	9	195	6.8	100	yes
68	60	M	Yes	No	No	Metformin	2	4	310	16.8	97	No
69	52	M	No	No	No	Metformin	1	5	345	11.6	96	No
70	42	F	No	No	No	Glimepride	2	3	220	10.9	98	No
71	41	M	No	Yes	Yes	Metformin	10	5	145	9.5	120	Yes
72	56	M	Yes	No	No	Glipizide	10	4	800	14.8	98	No
73	55	M	No	No	No	Metformin	1.5	4.5	660	13.2	96	No
74	44	F	No	No	No	Glimepride	2	5	740	16.8	97	No
75	60	M	No	No	No	Glipizide	10	3	345	12.9	94	No
76	57	M	Yes	No	No	Glimepride	2	4	680	15.3	98	No
77	54	F	No	Yes	Yes	Metformin	1	13	560	6.6	120	Yes
78	44	F	No	No	No	Glipizide	10	3	580	13.3	98	No
79	41	M	No	No	No	Glipizide	10	6	670	12.9	96	No

80	48	M	Yes	No	No	Metformin	2	5	335	15.6	95	No
81	54	M	No	No	No	Glimepride	2	5	680	14.5	98	No
82	46	M	No	Yes	No	Glipizide	10	7	465	11.6	97	No
83	58	M	No	No	No	Glimepride	2	3	800	13.8	96	No
84	55	F	No	No	No	Metformin	1.5	3.5	470	14.3	93	No
85	59	M	Yes	No	No	Metformin	1	4	355	16	98	No
86	60	M	No	Yes	No	Glimepride	2	4	290	14.5	97	No
87	43	M	No	No	No	Glipizide	10	6	485	12.1	94	No
88	45	F	No	Yes	Yes	Metformin	10	5	355	13	96	No
89	46	M	Yes	No	No	Glimepride	2	6	740	11.5	94	No
90	56	F	No	No	No	Metformin	3	8	190	8.9	82	No
91	47	M	No	Yes	No	Glimepride	2	7	440	16	98	No
92	42	M	No	No	No	Glimepride	2	2	255	14.6	97	No
93	46	F	No	No	No	Glipizide	10	4	665	11.8	95	No
94	56	M	Yes	No	No	Metformin	1.5	6	410	12.9	96	No
95	60	M	No	No	No	Glimepride	2	4	790	13.7	95	No
96	44	M	Yes	Yes	No	Glipizide	10	5	545	13.4	94	No
97	55	F	No	No	No	Metformin	1	2	760	12.9	90	No
98	60	M	Yes	Yes	No	Metformin	1.5	2	550	15.7	96	No
99	41	F	No	No	No	Metformin	10	3	335	12.5	93	No
100	51	F	No	Yes	Yes	Metformin	3	10	165	7.6	74	Yes

4 **PREVALENCE OF VITAMIN B12 DEFICIENCY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS ON METFORMIN**

Dissertation submitted for

MD DEGREE (BRANCH 1) GENERAL MEDICINE

APRIL 2017

THE TAMILNADU DR.M.G.R
MEDICAL UNIVERSITY
CHENNAI.

INTRODUCTION

1. Diabetic patients are more prone to develop neuropathy.

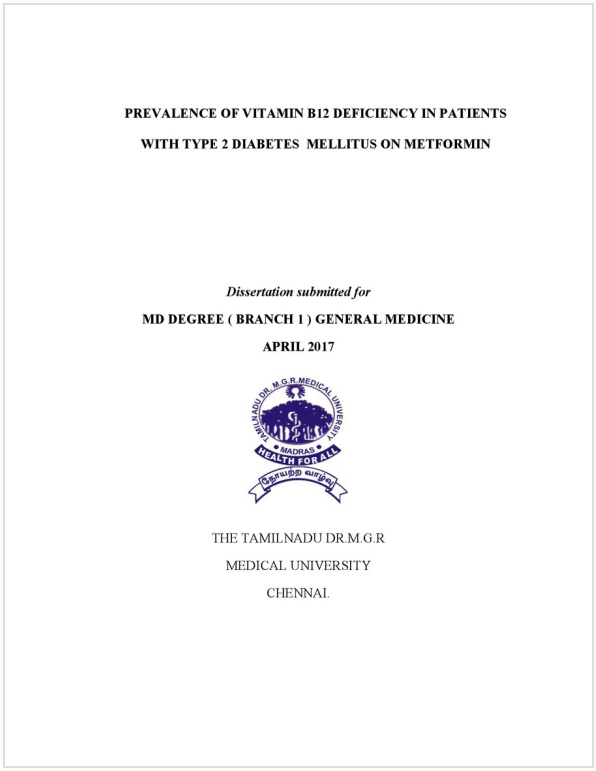
2".Prolonged vitamin B12 deficiency may result in neuropathy ,ranging from paraesthesia and decreased peripheral sensation to altered mental

Digital Receipt

This receipt acknowledges that Turnitin received your paper. Below you will find the receipt information regarding your submission.

The first page of your submissions is displayed below.

Submission author:	201411114 Md Gen Med M.SATHY…
Assignment title:	2015-2015 plagiarism
Submission title:	PREVALENCE OF VITAMIN B12 DE…
File name:	sathya_plagirism.docx
File size:	2.32M
Page count:	90
Word count:	6,637
Character count:	39,123
Submission date:	28-Sep-2016 02:12AM
Submission ID:	711275907



PREVALENCE OF VITAMIN B12 DEFICIENCY IN PATIENTS

WITH TYPE 2 DIABETES MELLITUS ON METFORMIN

Dissertation submitted for

MD DEGREE (BRANCH 1) GENERAL MEDICINE

APRIL 2017

THE TAMILNADU DR.M.G.R

MEDICAL UNIVERSITY

CHENNAI.