C-REACTIVE PROTEIN AND GLYCEMIC CONTROL IN ADULTS WITH TYPE 2 DIABETES MELLITUS

Dissertation submitted to

THE TAMIL NADU DR. M.G.R MEDICAL UNIVERSITY, CHENNAI

In fulfilment of the regulations for the award of the degree of

Doctor of Medicine in General Medicine

DEPARTMENT OF GENERAL MEDICINE

P.S.G INSTITUTE OF MEDICAL SCIENCES & RESEARCH

THE TAMIL NADU DR. M.G.R MEDICAL UNIVERSITY,

CHENNAI, TAMIL NADU

APRIL 2016

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The Tamil Nadu Dr. M.G.R Medical University, Chennai

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Doctor of Medicine in General Medicine

Under the guidance of

PROFESSOR. SUJAYA MENON, M.D.,

DEPARTMENT OF GENERAL MEDICINE

P.S.G INSTITUTE OF MEDICAL SCIENCES & RESEARCH, COIMBATORE

THE TAMIL NADU DR. M.G.R MEDICAL UNIVERSITY,

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APRIL 2016

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This is to certify that the dissertation entitled, **"C-REACTIVE PROTEIN AND GLYCEMIC CONTROL IN ADULTS WITH TYPE 2 DIABETES MELLITUS"** is the bonafide original work of **Dr. NANUBALA SIVA KRISHNA** in fulfilment of the requirements for the degree of Doctor of Medicine in General Medicine.

Signature of the guide

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I hereby declare that this dissertation entitled **"C-REACTIVE PROTEIN AND GLYCEMIC CONTROL IN ADULTS WITH TYPE 2 DIABETES MELLITUS"** is a bonafide and genuine research work carried out by me under the guidance of **Dr. SUJAYA MENON, M.D.,** Professor of Medicine, PSG IMS&R, Coimbatore.

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August 25, 2014

To
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Postgraduate
Department of General Medicine
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The Institutional Human Ethics Committee, PSG IMS & R, Coimbatore -4, has reviewed your proposal on 30th May, 2014 in its expedited review meeting held at IHEC Secretariat, PSG IMS&R, between 10.00 am and 11.00 am, and discussed your study proposal entitled:

"C-reactive protein and glycemic control in adults with type 2 diabetes mellitus admitted in a tertiary care hospital""

The following documents were received for review:

1. Duly filled application form
2. Proposal
3. Informed Consent Forms
4. Data collection tool
5. Permission letter from concerned Head of the department
6. CV
7. Budget

After due consideration, the Committee has decided to approve the study.

The members who attended the meeting at which your study proposal was discussed are as follows:

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Dr P Sathyan	DO, DNB	Clinician, Chairperson	Male	No	Yes
Dr S Bhuvaneshwari	M.D	Clinical Pharmacologist Member - Secretary	Female	Yes	Yes
Dr Sudha Ramalingam	M.D	Epidemiologist Alt. Member - Secretary	Female	Yes	Yes
Dr Y S Sivan	Ph D	Member –Social Scientist	Male	Yes	Yes
Dr D Vijaya	Ph D	Member – Basic Scientist	Female	Yes	Yes

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We request you to intimate the date of initiation of the study to IHEC, PSG IMS&R and also, after completion of the project, please submit completion report to IHEC.

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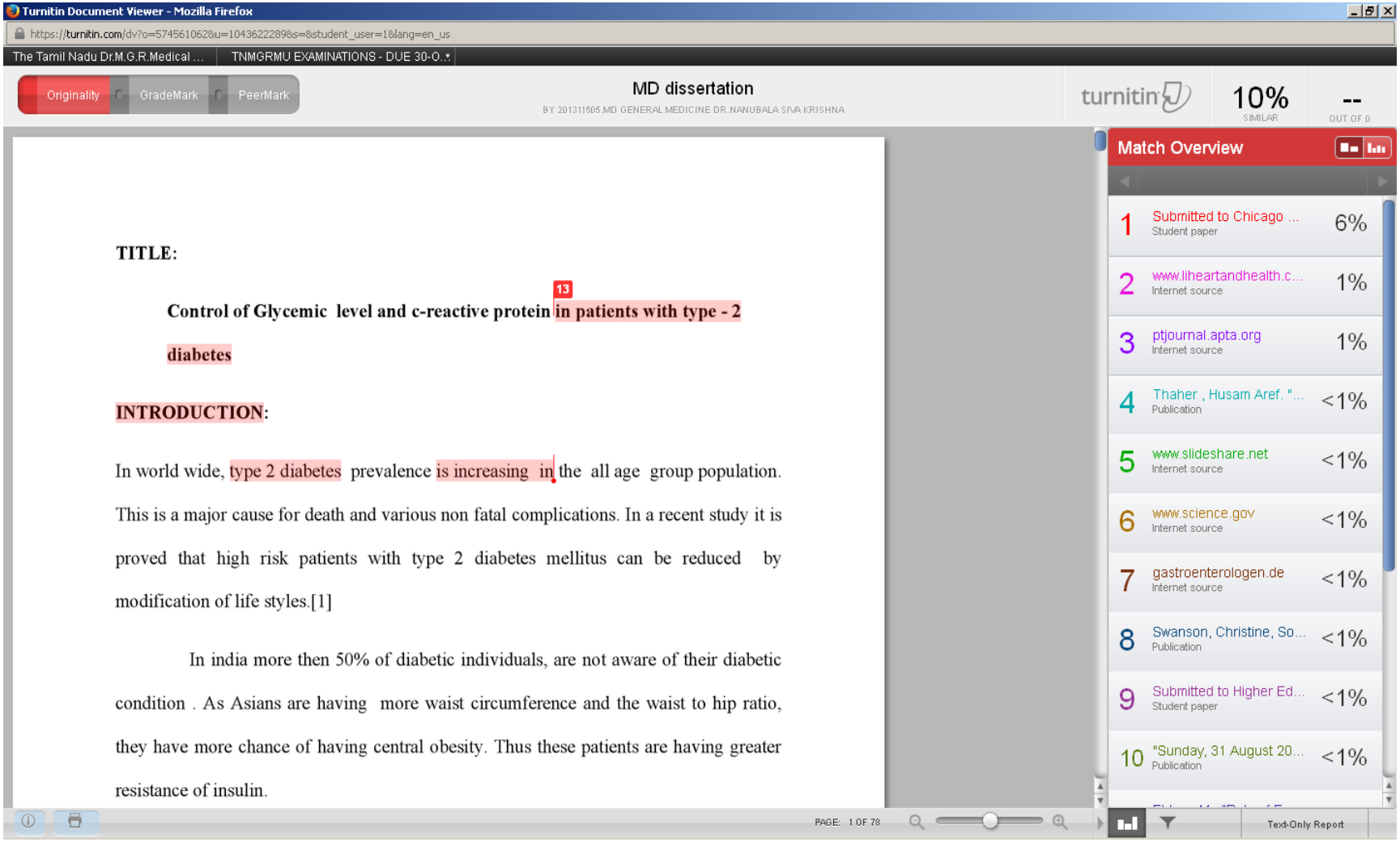
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Control of Glycemic level and c-reactive protein in patients with type - 2 diabetes
INTRODUCTION:
In world wide, type 2 diabetes prevalence is increasing in the all age group population. This is a major cause for death and various non fatal complications. In a recent study it is proved that high risk patients with type 2 diabetes mellitus can be reduced by modification of life styles.[1]
In india more then 50% of diabetic individuals, are not aware of their diabetic condition . As Asians are having more waist circumference and the waist to hip ratio, they have more chance of having central obesity. Thus these patients are having greater resistance of insulin.
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CONTENTS

TITLE

C-REACTIVE PROTEIN AND GLYCEMIC CONTROL IN ADULTS WITH TYPE 2 DIABETES MELLITUS

INTRODUCTION

In worldwide, type 2 diabetes prevalence is increasing in the all age group population. This is a major cause for death and various non fatal complications. In a recent study it is proved that high risk patients with type 2 diabetes mellitus can be reduced by modification of life styles.[1]

In india more then 50% of diabetic individuals, are not aware of their diabetic condition . As Asians are having more waist circumference and the waist to hip ratio, they have more chance of having central obesity. Thus these patients are having greater resistance of insulin.

In type 2 diabetes mellitus individuals, the development coronary disease is more common. More over, these cardiovascular events are more common in diabetic individuals than those without diabetics. [44]

C-reactive protein is synthesized in liver. Once tissue damage or inflammation occurs, CRP activates complement classical pathway, as C-reactive protein is a acute phase reactant. C-reactive protein is largely regulated by circulating levels of interleukin-6 predicts coronary heart disease incidence in healthy subjects.[4]

After myocardial infarction and stroke, CRP levels rises significantly in the serum.[2] These increase is observed within 6hours of inflammation and the level may be up to 2000 times normal.

High sensitive CRP is a measurement of CRP of lower concentration. It is a quantitative assay of CRP in plasma and it gives a new method for identification of rupture of plaque in high risk individuals.[5]

For the diagnosis of future myocardial infarction and stroke in a healthy men and women ,HSCRP plays an important independent predictor. It also has a role in primary prevention of cardiovascular disease.[6,7]

For the development of cardiovascular disease, CRP and glycosylated hemoglobin are having an important increased risk factors. HSCRP indicates inflammation and Hba1c indicates hyperglycemia. Both together establishes cardiac risks in individual with atherosclerosis.

In diabetic patients, there will be development of macrovascular changes, when there is a poor control of glycemic level. CRP is a significant risk factor for the development of cardiovascular diasease. Increase levels of c-reactive protein ia also linked in increase risk for development of diabetes in later stages.

Hence the study has been taken up to know the relation between the Hba1c and CRP in type 2 diabetes mellitus.

AIMS AND OBJECTIVES

- Correlation of glycaemic control as estimated by Hba1c with C-Reactive protein in type-2 diabetic patients.
- To determine if better control of Hba1c reduces CRP levels.

METHODOLOGY

Prospective observational study.

Duration of study: 12months.

Study locale: PSG Institute of Medical Sciences and Research.

Sample size: 30 subjects

Inclusion criteria:

- Patients with fasting venous blood glucose value equal or more than 126mg/dl and post prandial glucose more than 200mg/dl.

Exclusion criteria:

- Patients with established coronary artery disease.
- Patients on statins, and anti inflammatory drugs which are known to reduce CRP levels are excluded from the study.
- Patients with hemolytic anemias

REVIEW OF LITERATURE

CLASSIFICATION OF DIABETES:

- Type 1 diabetes: absolute deficiency of insulin secretion
- Type 2diabetes: combination of insulin resistance and relative insulin deficiency
- Diabetes can also results from- genetic beta cell dysfunction, and exocrine pancreatic diseases or intake of certain drugs

DIAGNOSIS OF DIABETES MELLITUS:

HBA1c > 6.5 %.

OR

Fasting >126 mg/dl. Fasting means individual should not take any food at least for eight hours

OR

2-hrs blood glucose >200mg/dl .The test is performed, using a glucose load containing 75 g of glucose mixed in water

OR

Features of hyperglycemia and a blood glucose >200mg/dl. Symptoms of hyper glycemia include polyuria, polydipsea ,weight loss

RECOMMENDATIONS FOR ADULT WITH DIABETES:

GLYCEMIC CONTROL TARGETS:

Hba1c	<6.5%
Fasting glucose	70 -120 mg/dl
Post prandial	>160 mg/dl
Blood pressure	<130/80 mmhg

LIPIDS:

LDL	<100 mg/dl (less than 70 in patients with established cardiovascular disease)
Triglycerides	<150 mg/dl
HDL	in men > 40 mg/dl, in women >50 mg/dl

FOLLOW-UP OF PATIENTS AND FREQUENCY OF TESTING

TESTS	TIME TO VISIT
Blood glucose	-controlled (Hba1c<7%)-every 3 months -uncontrolled every 2 weeks until target sugars Reached
Hba1c	-controlled (Hba1c<7%)-6months to 1 year -uncontrolled every 3 months
Tests for neuropathy Monofilament	-Annual

Biothesiometer Foot examination	-Annual -once in 3 months
Test for retinopathy Fundus examination	 Annually
Tests for nephropathy Urinary micro albumin s.creatinine	 Annual Annual
Miscellaneous test: Ecg Lipid profile	Annual Annual

HSCRP

History:

CRP is a substance in the patients serum with active inflammation, it reacts with pneumococcal c-polysaccharides.

In 1930 HSCRP was invented by Tillett and Francis. initially CRP was thought that it is a pathogenic secrection, as it is increased in various diseases, later it is found that it is native protein.

Structure:

The CRP gene is situated on the 1q21-q23 chromosome. It belongs to pentraxins family. CRP contains 224 aminoacids [3] has annular penta meric shape.

Function:

CRP attaches to phosphocholine which expressed on dead and dying cell surface and also on few bacteria. It activates the complement pathway which promotes

phagocytosis with help of macrophages[4] it removes necrotic and apoptotic cells.

CRP is a acute phase reactant occurs as a result of increase in IL 6 concentration ,which is secreted by macrophages, in response to bacterial, viral and fungal infection with other inflammatory disease and tissue injury.

CRP has a role in innate- immunity, as an early defense mechanism against infections.

CRP rises significantly within early hours of onset of inflammation and it reaches its peak at 48hours. It has a half life of 18hours. It levels are estimated by production rate. Thus CRP is a inflammatory marker for screening diseases.

Clinical importance and uses:

CRP is basically implicated as a inflammatory marker.

Measuring CRP is helpful in assessing disease progress and efficacy of treatment. CRP is measured by ELISA, rapid immune diffusion and visual agglutination

High- sensitive CRP measures low levels of CRP with help of laser nephlelometry. In 25 minutes it gives result with a good sensitivity.

The American heart associations have defined risk of developing cardiovascular disease as below [5]

- ✓ Low :less than 1.0 mg/dl
- ✓ Intermediate :between 1.0 and 3 mg/dl
- ✓ High: more than 3.0 mg/dl

Hs-CRP should not be indicated alone and it should be used along with increased cholesterol levels, triglycerides and glycemic levels.

HsCRP is a significant association for assessment of risk in primary prevention of cardiac diseases.

In atherosclerosis, inflammation plays an important role and measuring HsCRP gives new method in detecting a person at risk for rupture of plaque.

In a study that demonstrate to diagnose future myocardial infarction and stroke in normal healthy men and women HsCRP plays a good independent marker for prediction.[6,7]

HBA1C

INTRODUCTION:

In 1958 using a chromatographic column, by Hluisman and Meyering, Hba1c was separated from other forms of hemoglobin. In 1968 it was first identified as a glycoprotein by Bookchin and Gallop. In 1969 by Samuel Rahbar, found that Hba1c is increased in DM. In 1975 by Bunn and his colleagues found that the reaction lead on to its formation.

In 1976 by Anthony Ceremi, Ronald Koenig and colleagues proposed that the use of HbA1c in monitoring the control of metabolism of glucose in DM individuals.

Principle:

Hemoglobin a non-enzymatic reaction which happens between sugars and N-end of the betachain. It forms a Schiff base, which converts to 1-deoxy fructose. When plasma glucose levels are more, these glucose substances attaches to HB in RBC. The higher the glucose content in blood, the more glucose attaches to the HB in the RBC and thus HBa1c is increases. Over the past 4weeks to 3 months, The Hba1c value is proportional to plasma concentration of glucose [8]

Measurement of HBA1c:

There are various methods for measuring HBA1c

These are

- High- performance liquid chromatography(HPLC)
- Enzymatic testing
- Electrophoresis Capillary testing
- Bronate affinity chromatography testing

Introduction and use:

Hba1c test is done for both measuring the plasma glucose control in pre-diabetics and monitoring plasma glucose control in patients with high levels.[9]

In a patients with diabetes, Hba1c test is done at least twice in a year which is recommended by American diabetic association.

When Hba1c is measured by ion-exchange chromatography , both in diabetic patients and renal failure patients Hba1c are increased.

As when Hba1c is measured by The Thio barbituric acid method,even a patient with renal dysfunction will have Hba1c which is similar to normal individuals

The levels of Hba1c is undetermined In autoimmune hemolytic anemia,. But by adding prednisolone Hba1c could be detected[10] .The fructosamine test is also

helpful in these situations. During pregnancy to diagnose diabetes,Hba1c is not necessary but require fasting blood sugars and glucose tolerance test.

PATHOGENESIS — Type 2 diabetes mellitus is characterized by high blood glucose levels and resistance of insulin.

In a study it showed that before making diagnosis of type 2 diabetes mellitus in adults, 80% of beta cell function of pancreas is lost [11,12].

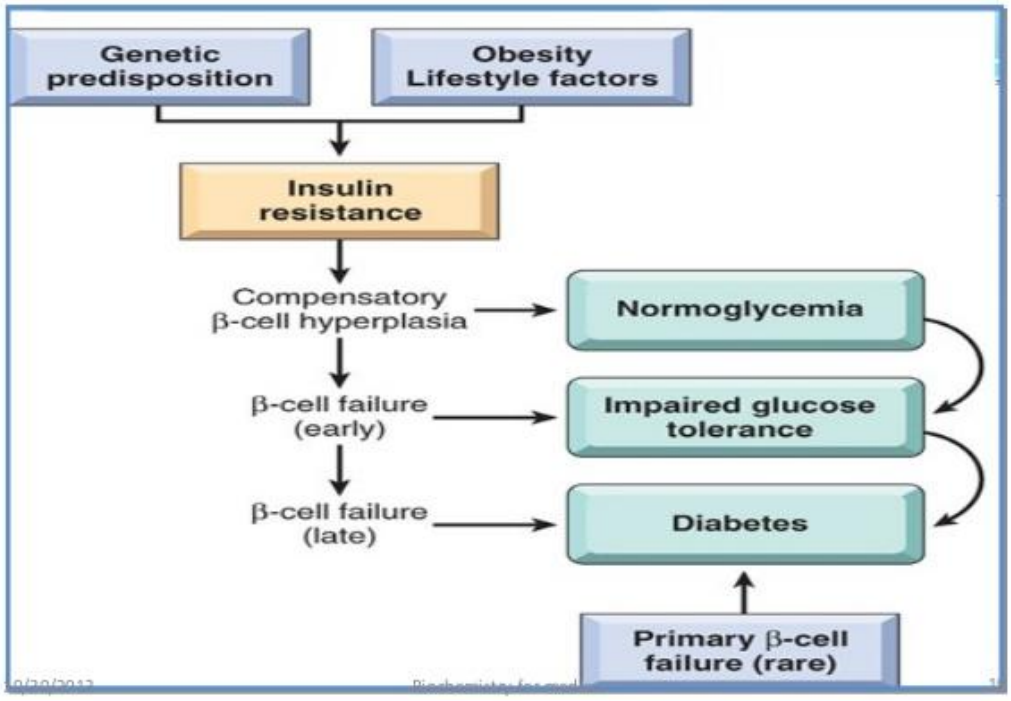

FIGURE 1: PATHOPHYSIOLOGY OF TYPE 2 DM

Unlike type 2 DM, type 1 DM is characterized by absolute deficiency of insulin, this deficiency is mediated by T-cell immune destruction of beta cells of pancreas, and it is marked by autoantibodies of pancreas.

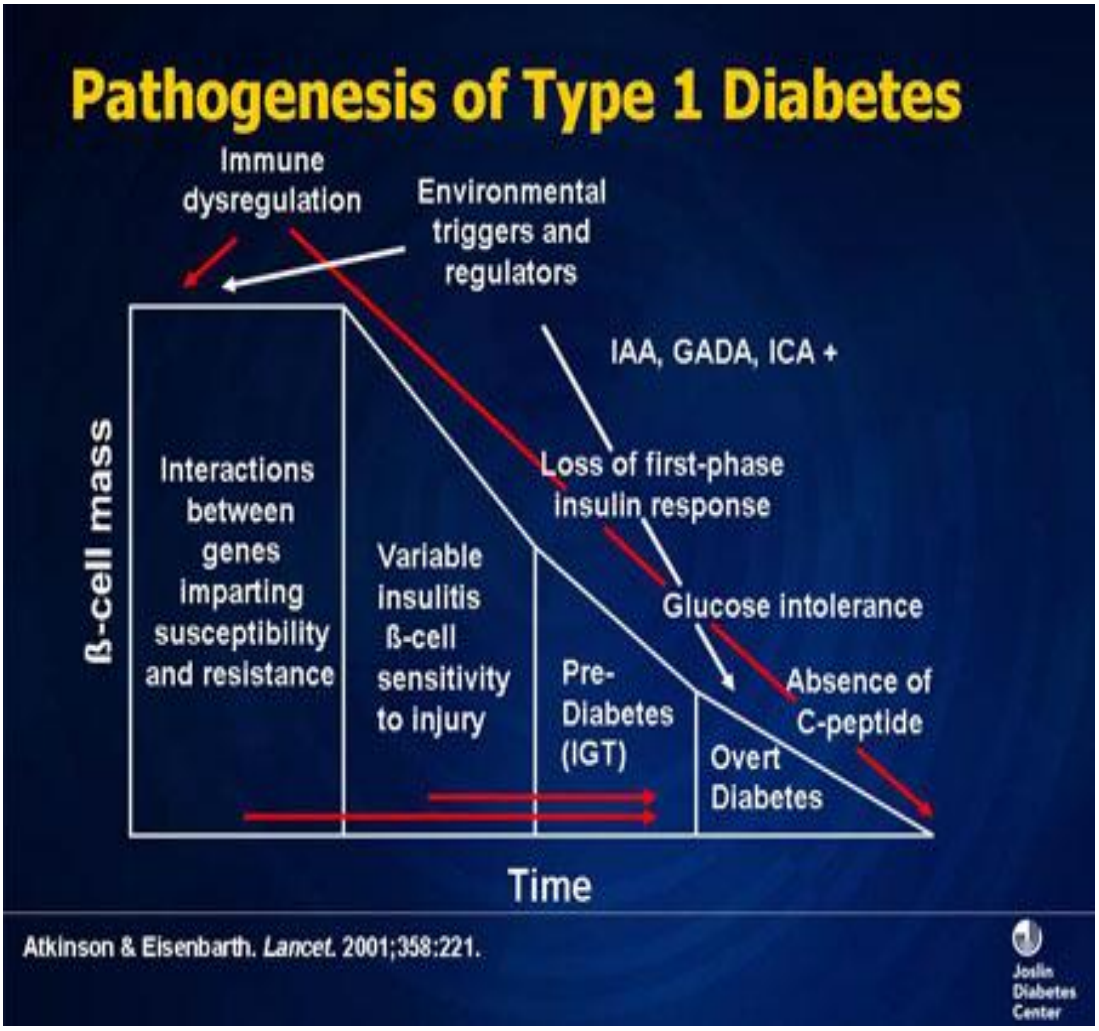

FIGURE 2

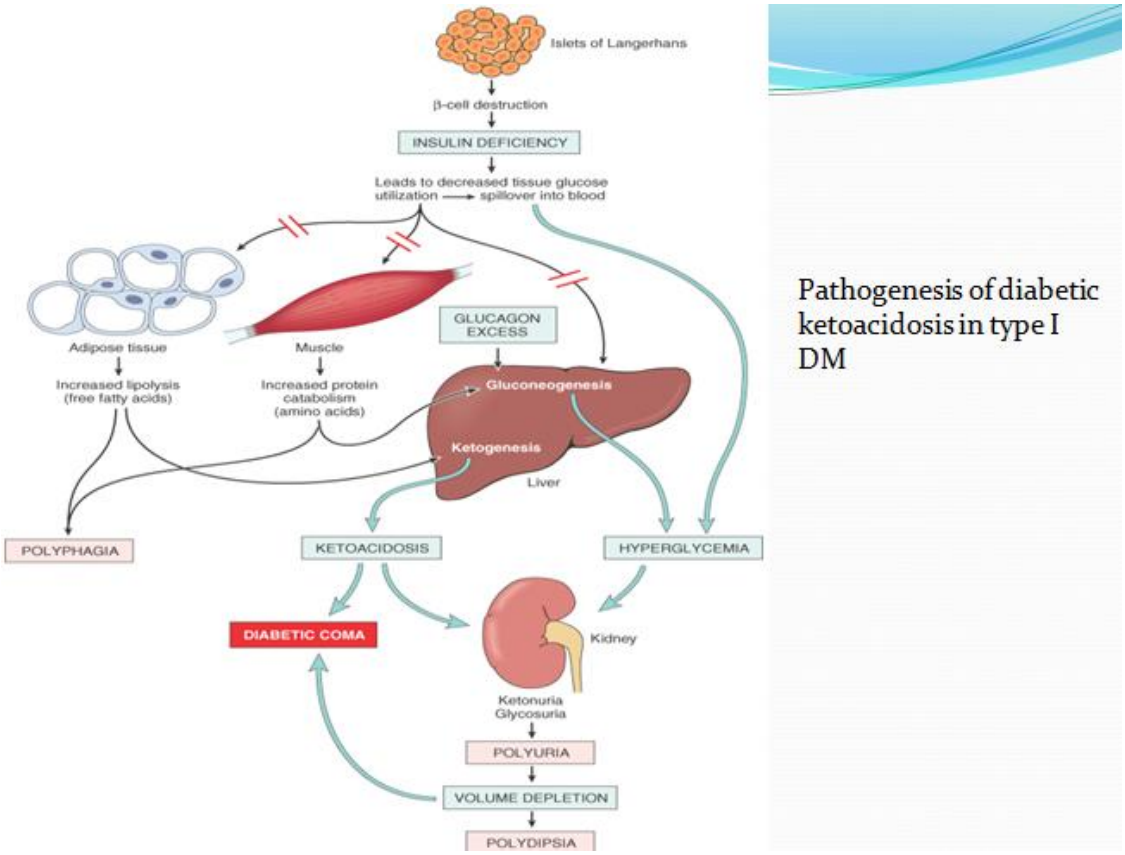

FIGURE 3

CLINICAL PRESENTATION — Childhood type 2 diabetes mellitus (T2DM) can present in many ways [14]:

- Asymptomatic – Approximately 40 percent [13]
- Symptomatic (eg, polydipsia and polyuria) without ketonuria – 57 to 70 percent [26]

- Diabetic ketoacidosis (DKA) -hyperglycemia, ketonuria, and acidosis – 5 to 13 percent [13,15,16)]

- Hyperglycemic hyperosmolar state (HHS) – Uncommon but serious [17-21]DKA is more common with type-1 diabetes than individual with type-2 diabetecs.Hyperosmolar hyperglycemic state — Adolescents with T2DM may present with HHS, it is presented high plasma glucose levels and serum osmolality and severe dehydration and little or no urine ketones [17].

HHS diagnosing is very important as it is characterized by very severe dehydration than typical DKA, thus has more morbidity as well as mortality if does not treat properly.

- ✓ Indications — The American Diabetes Association (ADA) recommends testing asymptomatic children for T2DM if they meet the following screening criteria:

    - Overweight or obese body mass index [BMI] ≥85th percentile have 2 or more of risk factors described below [22].

    - T2DM mellitus in a first- or second-degree relative

- High risk racial or ethnic group: local American, African American, Latino.

- Having insulin resistance signs, diseases associated with resistance of insulin-includes- hypertension, dyslipidemia, polycystic ovary syndrome (PCOS), or low birth weight babies.

- History of gestational diabetes mellitus,maternal history

Screening tests-Fasting plasma glucose

Oral glucose tolerance test — OGTT is done , especially when diabetes suspicion is high despite a FPG or A1C that is non-diagnostic.

The FPG is less sensitive, when compare with that of OGTT. Because FPG does not detects diabetes early in establishment of their disease [23]

The standard glucose load used for the OGTT is with adose of 75 g can be given and results are interpreted as follows:

- Blood glucose ≥200 mg/dL observed 2 hours after the sugar load is diagnostic in diabetes individual

- Blood glucose ≥ 140 to 199 mg/dL observed 2 hours after sugar load demonstrates impaired glucose tolerance (IGT), and indicates increased risk for diabetes,

PREDIABETES: It is diagnosed if any of following are there

- Impaired fasting glucose (IFG) – Fasting plasma sugars ≥100 to 125 mg/dL.
- IGT – blood glucose ≥140 to 199 mg/dL measured two hours after a glucose load
- Hemoglobin A1C level is between 5.7 and 6.4 % (39 to 46 mmol/mol) have also been considered to indicate risk for diabetes and have been viewed as prediabetes in adults;

Diabetes related microvascular and macrovascular complication:

In type 2 diabetes mellitus the vascular disease are caused by hyperglycemia, insulin resistence, dyslipidemia and hypertension and obesity as well.

The Mechanism of these vascular diseases include glycation of end product accumulation , dysfunction of smooth muscle cell , over production of endothelial derived growth-factors, long term inflammation, fibrinolytic dysfunction , enhancement of aggregation of platelets.

Both microvascular and macrovascular complications are more common with DM which includes retinopathy, nephropathy, neuropathy and IHD ,peripheral vascular diseases and cerebrovascular diseases respectively, which in turn result in damage of both tissues and organs.

Microvascular changes of DM :

Diabetic- retinopathy:(DR)

Diabetic- retinopathy is the leading cause of blindness in the middle aged people .The exact mechanism by which diabetes causes retinopathy remains to be unclear[44,45]

Signs and symptoms:

Initially these patients are generally asymptomatic, and in the advance stage of the disease they may expirence blurred vision , distorsion and progressive loss of visual acquity.

Signs include

- Microaneurysms: these are earliest sign of diabetic retinopathy. occurs secondary to capillary wall outpouching because of pericyte loss. seen in superficial retinal layer

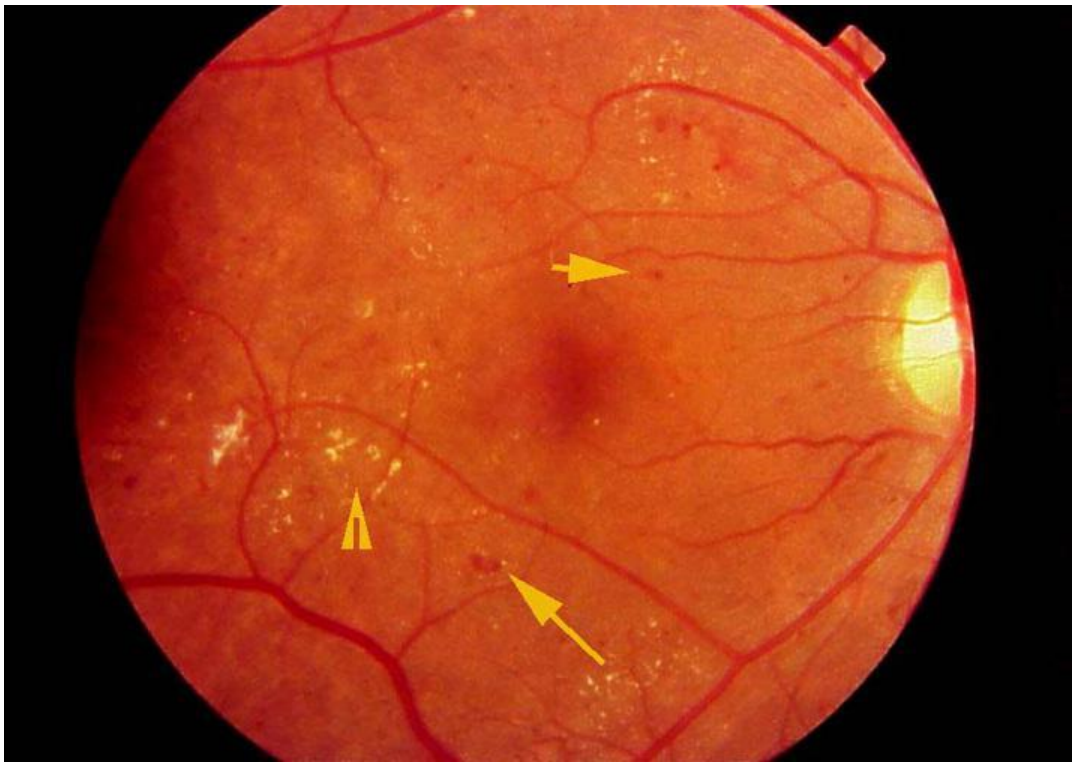

FIGURE 4

Long arrow indicate blot hemorrhages, short arrow-microaneurysms, arrow head-hard exudates

- Dot and blot hemorrhages
- Flame-shaped hemorrhage
- Retinal edema and hard exudates
- Macular edema

Diagnosis:

- Fluorescein angiography
- B-scan ultrasonography

Management:

- ✓ Glucose control
- ✓ Laser photocoagulation
- ✓ Vitrectomy
- ✓ Cryotherapy

Diabetic- neuropathy:

- ➢ Neuropathy is one of the important complication of DM
- ➢ Most of the diabetic individual has neuropathy in form of diabetic polyneuropathy ,mono neuropathy and also the autonomic neuropathy.

Clinical features :

In type 1 diabetes mellitus symptoms of neuropathy occurs later stages of disease, where as in type 2 diabetic individuals neuropathic symptoms occurs early stages of diabetes.[46]

These symptoms include:

- Sensory symptoms occurs in form of glove and stocking involvement in the distal parts.
- Motor involvement occurs in the proximal and also distal parts.
- Autonomic features which includes- cardiovascular,genitourinary systems and gastrointestinal

Diagnosistic tests: these are

- Fasting plasma glucose
- HBA1C
- CBC, fasting B-12 and folate levels, and TFT

Other diagnostic tests include:

- Nerve conduction studies
- Electro physiologic tests

Management:

- Foot care includes –regular follow up and patient education
- Tight glycemic control
- Pain management by pregabalin, gabapentin, sodium valprovate

- Treatment of diabetic gastroparesis which include metoclopramide, cisapride, erythromycin and polyethylene glycol[47]

Surgical treatment include:

- Aggressive debridement for foot necrosisor infection
- Jejunostomy in case of recurrent gastroparesis

Diabetic nephropathy:

In both type 1 and type 2 Diabetes mellitus, it is serious complication .The earliest finding would be micro albumi nuria (300mg/d) which develops to overt albumi nuria which finally leads to renal dysfunction and this lead on to cause end stage kindey disease.

Another important features of DN are glomerular basement membrane thickening & hyperfiltration lead on to expansion of mesangial extracellular matrix and which ultimately progression to renal failure.

The factors causing DN are hyperglycemia, diabetes duration, , dyslipidemia, SHT and also obesity.

Management include

- Good glycemic control
- Control of hypertension by ACE and ARB inhibitors
- Renal replacement therapy with end - stage renal disease

Macro-vascular changes of diabetes:

Main mechanism in the macrovascular changes is the formation of atherosclerosis, and this lead on to stenosis of arterial wall in whole body.

The genesis of atherosclerosis is due to injury to coronary as well as peripheral vessels and also due to chronic inflammation.

Apart from occurrence of atheroma, there will be a significant platelets adhesion and also hyper-coagulability in these type- 2 diabetic individual.

Diabetes increases the risk of developing cardiovascular disease but exact mechanism by which it occurs is not known, patients with type- 1 or type -2 DM cerebrovascular disease is the major factor for death. [48,49]

Of all macrovascular complication of diabetes, Coronary artery disease has significant association with DM,Framingham study.[50].

Type 2 diabetes itself is a risk factor in developing cerebrovascular disease, myocardial infarction and death [51] . In individuals with type 2 DM, women are at risk in developing coronary artery disease than men population. [52]

In a patient with type-2 DM, treating hypertensive individuals and achieving good glycemic levels can reduce the macrovascular events and also mortality efficiently.

In a study showed that,treating the hypertensive individuals can significantly reduces the macro vascular events in patient with diabetes. [53,54]

ACE and ARBs acts by inhibiting the rennin angiotensin system , and there by reduces the cardiovascular events significantly when compared with other antihypertensive agents.[55,56]

In diabetic patients,the use of statins can also reduces the macrovascular complications significantly.

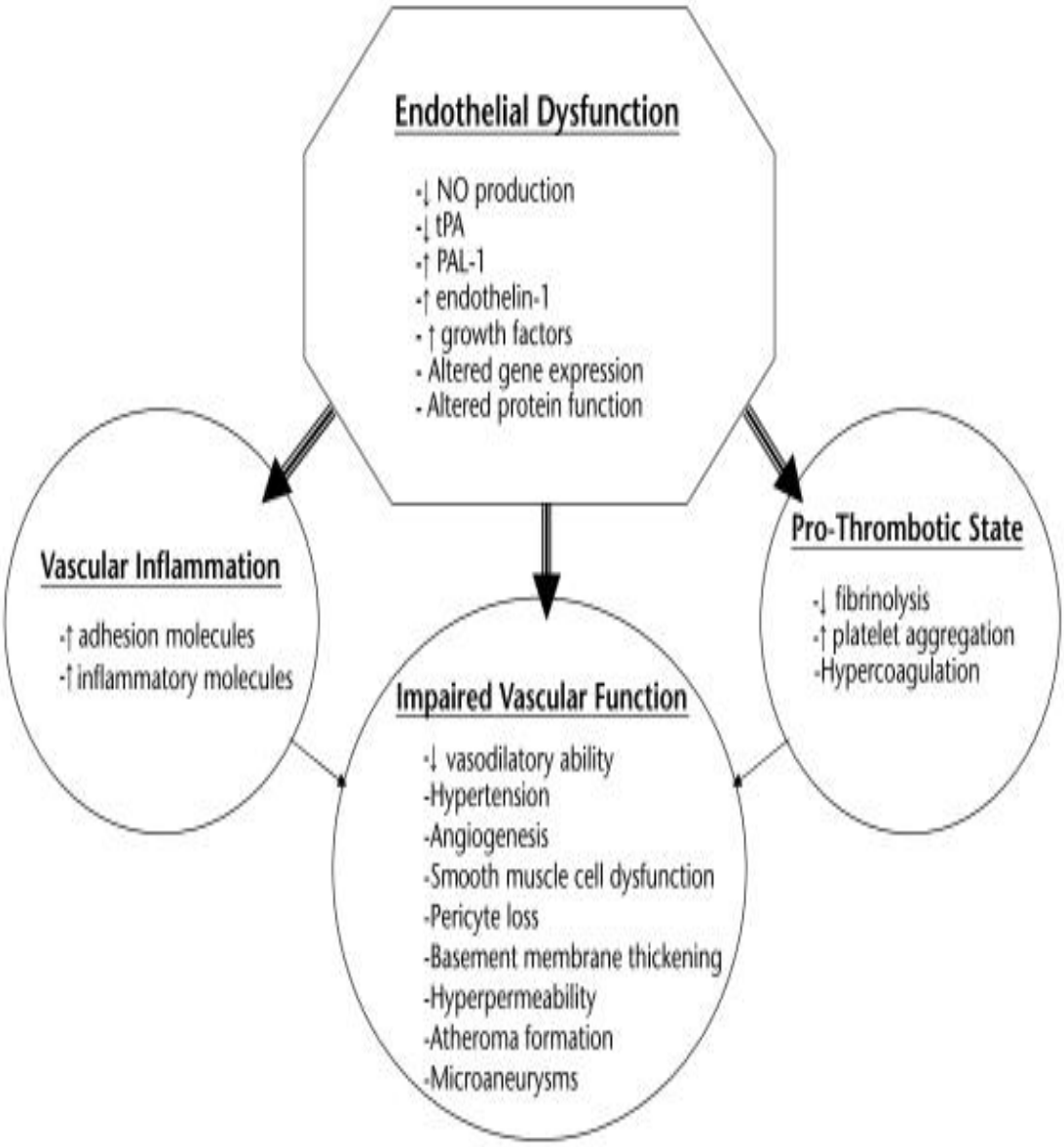

FIGURE 5

NO- Nitric oxide, tPA - Tissue plasminogen activator-1, PAI-1-plasminogen activate or inhibitor

Cardiovascular disease in patients with diabetes:

- ✓ In finish cohort study ,among subjects with type 2 DM without prior CHD the risk of MI was high as those without diabetes with previous MI i.e diabetic patient without prior CHD have the same event rate compared to nondiabetics with prior vascular disease
- ✓ Coronary artery disease is 3 to 4 times more common in patients with diabetes
- ✓ Sudden death is 50% greater in males and 100% greater risk in female compared to non diabetic patients
- ✓ There is loss of premenopausal protection in females
- ✓ Unexplained cardiac failure, fatal arrhythmias, hyperglycemia complicate the acute coronary syndrome
- ✓ Atypical presentation delays prompt treatment. diabetic autonomic neuropathy may mask symptoms and episodes of silent ischemia may occur
- ✓ Associated diabetic cardiomyopathy may worsens the outcome
- ✓ Revascularization procedure have less favorable outcome and restenosis is more common
- ✓ CHD is the commonest cause of mortality in diabetes with renal failure

PATHOGENESIS OF CHD:

CHD risk factors like hypertension, dyslipidemia , obesity, Insulin resistence, aggregate in patients with diabetes .These atherosclerosis occurs due to atherogenic factors in diabetes :

Hyperglycemia and other metabolic abnormalities: The excess risk found in diabetes which cannot be attributed to interaction between other risk factors is supposed to be mediated by hyperglycemia per se.

Insulin resistance and hyperinsulinemia: It is an underlying link between hyperglycemia and CHD.These patients have increased proinflammayory markers.

Obesity: intra-abdominal obesity is associated with insulin resistance .this is associated with an increased influx of free fatty acids to liver.

Atherogenic dyslipidemia of diabetes: It is best characterized risk factor.the decreased HDL levels and infective HDL in diabetes also worsens atherosclerosis.[44]

Hypertension: More than half of the patients with diabetes have hypertension even at the time of diagnosis.

Endothelial dysfunction: Decreased nitric oxide availability and impaired endothelial vasorelaxation increased response to endothelian-1 and altered permeability are found more in diabetic patients.

Low grade inflammation and fibrosis: increased CRP and cytokines like TNF-alpha activate and sustain atheroma formation.

CLINICAL MANIFESTATIONS:

- ✓ Angia or acute coronary syndrome
- ✓ Silent ischemia in the presence or even absence of cardiac autonomic neuropathy
- ✓ Atypical ischemic symptoms like dyspnea, hypotension, sweating, syncope and vomiting and fatigue
- ✓ Cardiac failure
- ✓ Complications following MI like shock, conduction disturbances, cardiac failure and ketoacidosis
- ✓ Fatal or non fatal dysrhythmias

A high index of suspicion is always necessary in patients with diabetes

SCREENING FOR CORONARY ARTERY DISEASE IN DIABETES:

The goal of screening in these individuals with Coronary artery disease is to identify people with more cardiac risk, and their outcome could be improved with life style modification or with recanalisation of the CAD.

Indications for testing of CAD:

1) Those with atypical symptoms

2) Baseline ECG indicative of either ischemia or infarction

Cardiac testing:

- ✓ Resting ECG-low sensitivity
- ✓ Holter monitoring –has usefulness to detect arrhythmias ,as it is usually done for 24 or 48 hours period
- ✓ Stress ECG-exclude triple vessel disease but not single or double disease
- ✓ Stress echocardiography: It is done using dobutamine .induced regional wall motion abnormalities during stress echo is sensitive marker for ischemia. It is cost effective and reliable but more operator-dependent.
- ✓ Angiography: It is currently gold standard in evaluation of coronary artery disease .The introduction of newer methods includes- intravascular ultrasound (IVUS) and flow wire to check coronary fractional flow reserve (FFR) in patients with CAD.
- ✓ Magnetic resonance imaging for heart (MRI):It is another rapidly emerging technology for imaging the heart including the coronaries.

- ✓ Positron emission tomography(PET-CT)-PET allows quantification of absolute myocardial perfusion and also gives information of myocardial metabolism using radioactive metabolic markers.

MANAGEMENT:

Differences in management strategies and outcome are due to:

- ✓ Atypical symptoms
- ✓ Requirement of repeated interventions and longer hospital stay
- ✓ Higher incidence of postintervention and complications

Lifestyle modification: Regular exercises –walking, jogging cycling or swimming

- Limitation of fat and total energy intake
- Cessation of smoking

Glycemic control: Even the base line HbA1c at the time of diagnosis of diabetes has been shown (UKPDS 66) to predict the future cardiovascular outcome.

- ✓ For every increase in HbA1c by 1 percent there is an 11% increase in CAD (UKPDS study).

- ✓ Hence in these patient with diabetes a HbA1c of <7% should be the target to prevent macrovascular disease.
- ✓ Metformin - shown to decrease coronary symptoms in subjects if not contraindicated.

Control of blood pressure: target to keep the BP< 130/80 mmhg.drug therapy includes ACEI or ARB.

Lipoid management: Also plays an important role

Antiplatelets therapy: Aspirin therapy as a primary prevention strategy should be considered in those with type 1 or 2 diabetes with increase cardiovascular risk-men >40 years of age and female >60 years.

Muitiple risk factor modification: The STENO-2study showed that intensive therapy targeting multiple risk factors in addition to hyperglycemia can reduce cardiovascular mortality.

Cerebrovascular diseases:

It include:

1) cerebral artery diseases
2) Cardiac diseases which may adversely affect blood supply to the brain by changes in the blood pressure or as a source of emboli.

3) Blood disorders which leads to clotting impairment , which ultimately causes thrombosis in the cerebral vessels.

Stroke: is defined as sudden loss of function of brain due to alteration in blood supply to brain. stroke is not a diagnosis but a clinical syndrome with has variety of causes which may include:

- ✓ Cerebral infarction
- ✓ Intracerebral hemorrhage
- ✓ Subarachnoid hemorrhage
- ✓ Cerebral venous thrombosis

Main risk factors for stroke:[45]

Major risk factors:

1) Hypertension
2) Cardiac disease-IHD,atrial fibrillation
3) Transient ischemic attacks
4) Cigarette smoking
5) Alcohol
6) Hyperlipidemia –elevated LDL cholesterol
7) Oral contraceptives
8) Obesity
9) Diabetes mellitus

Associated risk factors:

1) Diabetes mellitus
2) Previous stroke
3) Raised hematocrit
4) High plasma fibrinogen
5) Antiplasmalipid antibodies (APLA)
6) Asmptomatic carotid arterial lesions

Ischemic stroke:

Transient ischemic attack (TIAs)-an episode of acute neurological deficit.

MRI must not show evidence of acute ischemia irrespective of the time period of recovery, occurring as a result of reduced flow to a vessel from fall in perfusion pressure. Or blockage of passage of flow by embolism arising from plaque in aortic arch, from heart.

Cardiac embolism from thrombus in left atrium or ventricle

Less common causes of stroke:

1) Hematological abnormalities: That promote thrombosis

   Eg: polycythemia and thrombocytopenia.

Anticardiolipin antibodies may cause acquired abnormalities of thrombolysis and are associated with stroke in younger patients. Thrombophilia may cause cerebral venous thrombosis.

2) subclavian steal :it is an uncommon cause of hemodynamic symptoms.if subclavian artery is occluded or stenosed before the origin of vertebral artery,arm exercise may cause retrograde flow down the vertebral artery at the expense of the vertebrobasilar circulation,resulting in brain stem TIA.
3) Magraine:is a rare cause of cerebral infarction. Headache is common in ischemic stroke and may be caused by collateral vasodilatation or carotid dissection.
4) Vasculitis :it is a rare cause of both hemorrhagic and ischemic stroke .these usually include SLE, polyarteritis nodosa(PAN), giant cell arteritis.
5) Silent cerebral infarction-many middle aged and elderly patients with hypertension without a history of stroke or TIA have small infarcts lacunes or patchy ischemic periventricular imaging abnormalities (leukoaraiosis) on CT or MRI.

Investigation and diagnosis of a cerebrovascular accident:

I. History:

1) Age- in a young patient consider :

- ✓ Cardiac disease-infective endocarditis,atrial fibrillation,mitral valve stenosis
- ✓ Vascular disease-severe hypertension, hypercoagulable state,vasculitis
- ✓ A-V malformation/aneurysm
- ✓ Intracranial space occupying lesion
- ✓ Encephalitis eg:HSV type 1
- ✓ Post-ictal
- ✓ Migraine
- ✓ Hysteria
- ✓ Hyperventilation

2) History of previous minor episodes:may suggest disease of carotico-vertebral system of embolic disease from arteries or from heart.history of migraine or epilepsy should take into consideration..

3) History of head injury:depressed fracture and subdural haematoma

4) History of drugs: eg-contraceptive pills,anticoagulants.
5) Family history-history of stroke and early age of onset may suggest familial trait to atherosclerosis
6) Past history: of diabetes, hypertension or cardiac disease

II. Physicial examination:

A. Neurologic :

1. State of consciousness-may vary from full alertness to lethargy,stupor,semiconscious or coma
2. Speech: should be evaluated to differentiate between slurred dysarthric speech and dysphasic speech.
3. Neck rigidity-subarachnoid hemorrhage and meningitis
4. Focal neurologic deficit-Tests for hemiparesis,hemianopia

B. General –

1. Blood pressure-for arterial hypertension B.P should be checked in both arms because of possibility of aortic arch syndrome.
2. Heart-for cardiac arrhythmia such as atrial fibrillation or recent MI
3. Bruits: due to stenosis .over carotid and subclavian arteries ,bruit produced by stenosis in vertebral arteries.

III. Investigations:

CT scan- To establish the pathological diagnosis (infarction or hemorrhage) and to exclude other conditions that mimic stroke (eg.subdural hematoma, intracranial tumour)

All patient must undergo scanning within 24 hours.

Magnetic resonance techniques: MRI is more sensitive to small areas of ischemia than CT and can detect traces of old hemorrhage

Carotid uitrasonography: To identify carotid artery stenosis,occlusion and dissection.

Management:[46]

Acute ischemic stroke:

General treatment - it has cardiac care , decrease the BP, prophylactic measures against DVT, aspiration pneumonia.

Specific treatment**:**

a) Thrombolysis is being with recombinant –tissue plasma activator (rT-PA) dose is 0.9mg/kg is given within 4 hours of ischemic stroke with 10% as bolus and remainder of the drug by infusion over 1 hour.

Indications of thrombolysis:

Absolute indications includes

- ✓ When patient reaches hospital within 3 hours of symptoms onset
- ✓ CT scan should not show any hemorrhage

Contraindications includes

- ✓ In last 3 months, there should not be any head trauma
- ✓ Systolic BP above 185 or diastolic >110 mg/dl
- ✓ When patient is recovering from weakness
- ✓ Symptoms of SAH
- ✓ Platelets count < 1,00,000

Peripheral vascular disease

The prevalence of peripheral artery disease (PAD) rises significantly with age, occurring after 40 years.[47] Thus PAD is causing a problem in the older individuals.

- So whenever examining the elder individuals, it should be kept in mind to ask questions related to history of PAD which includes -history of walking impairment after walking for some distance and, and the presence of nonhealing wounds.

- Risk factors for these peripheral artery disease includes - smoking, hypertension, hyperlipidemia, diabetes, and metabolic syndrome.

Other factors include age, gender, ethnicity, family history and genetic influences, and possibly homocysteinemia.

The following groups are at risk for developing PAD:

Age ≥70 years

Age 50 to 69 years with a history of smoking or diabetes

Age 40 to 49 with diabetes and at least one other risk factor for atherosclerosis

Leg symptoms suggestive of claudication with exertion or ischemic pain at rest[48]

Abnormal lower extremity pulse examination

Known atherosclerosis at other sites (eg, coronary, carotid, renal artery disease)

Prevalence of PAD rises with the age and occurs after 40 years. Individuals over 70 are at a significantly increased risk for PAD due to age alone, while the risk for younger individuals is due to other factors, most commonly cigarette smoking. Early-onset atherosclerosis, or premature atherosclerosis, is defined as PAD presenting prior to 50 years of age. Patients with early-onset atherosclerosis more often present with critical limb ischemia and have poor overall outcomes.

- Gender and ethnic-related differences in prevalence of PAD have been documented.

Peripheral vascular disease occurs more commonly in men when compared with female population. Another scenario is peripheral vascular disease is more common in females over 70 years of age when compared withmen of same age group.

- The natural history of peripheral artery disease in patients who present initially as asymptomatic or with mild to moderate intermittent claudication is relatively benign. Of those with intermittent claudication, 70 to 80 percent people have stable claudication, 10 to 20 % develop worsened claudication and only about 2 percent of population develops critical limb ischemia. [48]

The outcome for limb loss and survival is worsens in individual with early-onset atherosclerosis, patients with diabetes or end-stage renal disease, and for those who continue to smoke.

Management:

The management of patients with claudication due to atherosclerotic disease is aimed at lowering the risk of cardiovascular disease progression and complications, and improving claudication symptoms.

Medical management involves risk factor modification, exercise, and possibly pharmacologic therapy to improve walking distance

Claudication has more risk of MI , cerebrovascular, and renovascular illness. Thus peripheral artery disease is assumed to be equivalent to coronary cardiac disease.

To reduce the cardiovascular disease progression and complications, a secondary prevention strategy these includes antiplatelet therapy ,smoking cessation, control of blood sugar and blood pressure, lipid-lowering therapy, and dietary modifications to achieve the goals set in national guidelines.

Usually the use of dual antiplatelet therapy is not recommended in patients with claudication in the absence of other indications (eg, drug-eluting stent, prosthetic distal lower extremity bypass

For most patients with lifestyle-limiting claudication who do not have an improvement in symptoms with risk modification and exercise therapy, a therapeutic trial of naftidrofuryl or cilostazol (100 mg twice daily).

Naftidrofuryl has fewer side effects, [49]

We schedule follow-up after three months to assess the effectiveness of the initial medical therapy regimen for reducing symptoms. [50]

Patients who show improvement and who are satisfied with their progress can be scheduled for annual vascular examination.

For patients who have been compliant with risk reduction strategies, yet six months to a year of exercise therapy and adjunctive pharmacotherapy have failed to provide satisfactory improvement, referral for possible revascularization is appropriate.

Options for revascularization include percutaneous intervention, surgical bypass, or a combination of these, and the choice depends upon the level of obstruction (aortoiliac, femoropopliteal) and severity of disease, and the patient's risk for the intervention.

Mechanisms for both Micro and Macro vascular complications of Diabetes

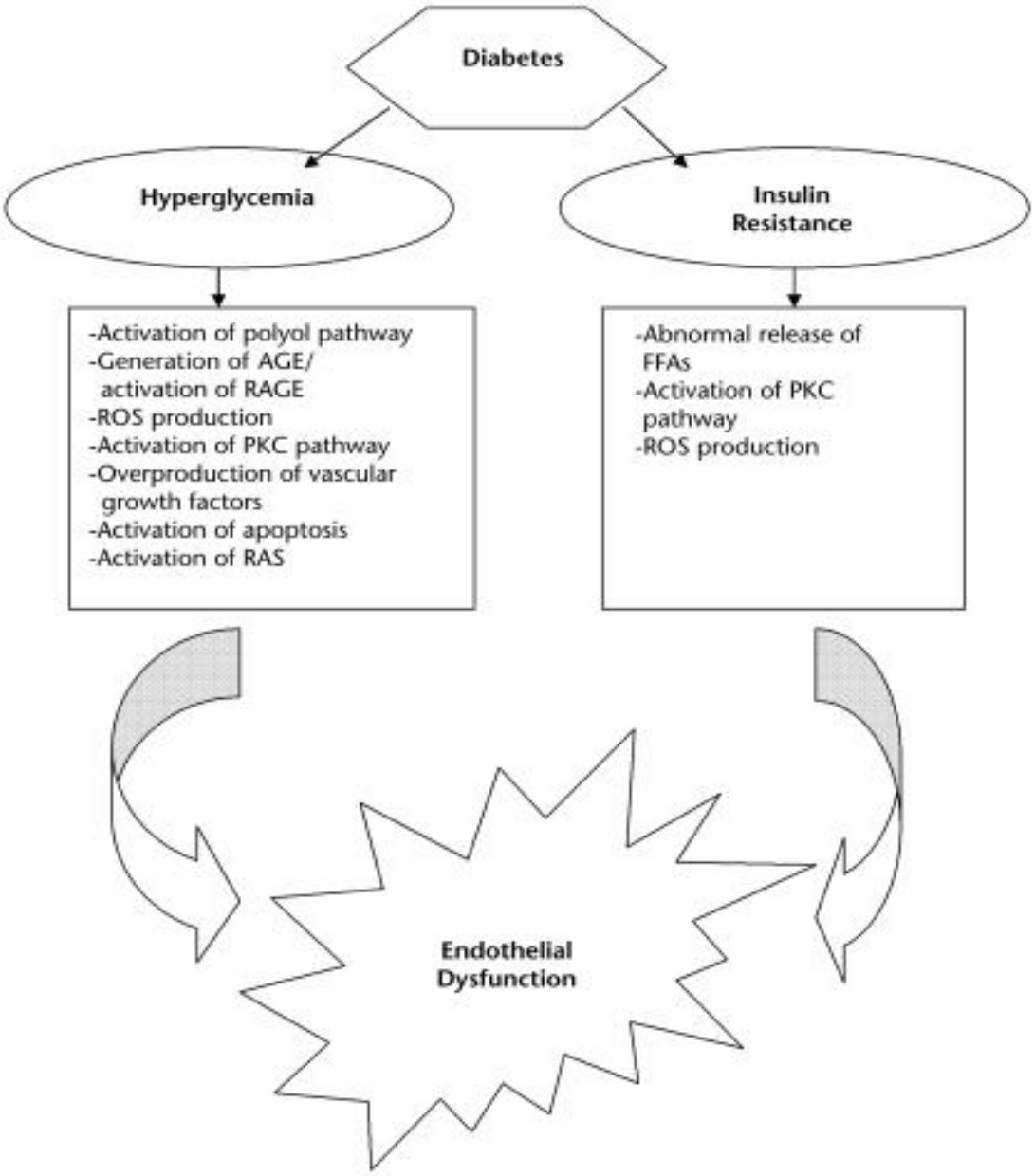

FIGURE 6

Mechanisms of diabetes –associated with dysfunction of endothelial cells

AGE - Advanced glycation end products

RAG - Receptors for AGE,

ROS - Reactive oxygen species

PKC - Protein kinase c

RAS – Renin angiotensin system

MANAGEMENT OF DIABETES MELLITUS:

Treatment of non insulin dependent DM:

Principles:

- ✓ Accurate diagnosis is important. So that diagnostic criteria can be applied.
- ✓ Management must not be considered decreasing the plasma glucose alone and also must look into any associated CVD risk factors.
- ✓ Management of NIDDM requires teamwork.
- ✓ Self monitoring improves quality and safety of treatment.

GENERAL OBJECTIVES OF DIABETIC MANAGEMENT:

- ✓ To improve the symptoms
- ✓ To treat the associated health issues and lower the mortality in the population
- ✓ To improve the productivity of a person and also the life quality of a person with diabetes

TREATMENT MEASURES:

Glucose control — good glucose control, significantly reduces the microvascular changes in type-2 DM individuals [57].

Every 1 % decrease in HBA1C the outcome of disease would be better

Along with lowering the blood glucose levels, we should also look into other factors such as cessation of smoking, use of clopidogrel and good control of blood pressure and also lowering the lipid levels and physical activity. All these thing plays a role in reducing the cardiovascular complications in patients with type-2 DM.

DIABETIC NURSING EDUCATION:

In patient with newly detected diabetics, the role of physical activity and life style modifications and good glycemic control should be told clearly in order to prevent future complications of diabetes.

In a small study ,it has been showed that, diabetic individuals who took part in diabetic nursing education has significantly reduces the Hba1c than people who have not participated in nursing education. [58]

Weight reduction — For people with diabetes those are overweight i.e BMI ≥ 25 to 29.9 and obese i.e BMI ≥30 should be told to decrease the intake of calories and to involve in physicial activity at least 1hr in a day.

Diet — Weight loss through diet modifications would benefit diabetes individual , including glycemic control and also hypertension.

Exercise — individual with diabetes are motivated to do physicial activity at least 30 to 60 minutes of moderate excreise, in most of the days in a week.

Regular physicial exercise has a role in diabetic individual,which is a independent factor for weight loss. Which improves glycemic control because of increased response to insulin; thus it may delays progression of decrease glucose tolerance to the established diabetes [59,60].

Pharmacologic therapy — drugs for the weight loss could be better in individual with diabetes, but it has got many side effects and more over it is not used as initial therapy in diabetics [61].

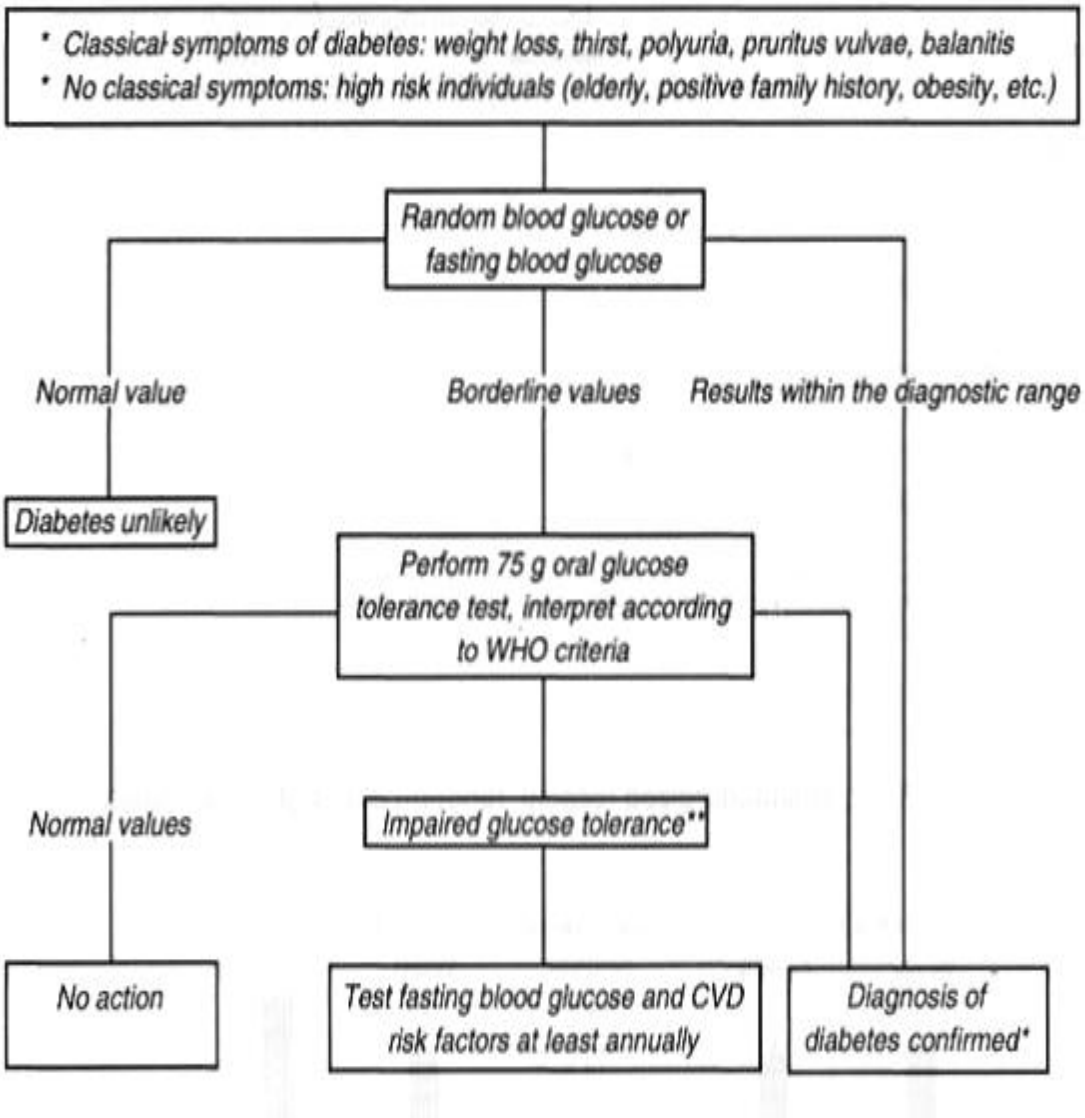

FIGURE 7

Factors favoring non insulin dependent diagnosis of DM:

- ✓ Classical diabetes features are absent
- ✓ Older age group people i.e more than 30 years
- ✓ Having obesity

Initial assessment :

A full history is required and also the symptoms and the focus must be emphasized on

- ✓ cardiovascular diseases Risk factors
- ✓ Cardiovascular complications symptoms include angina, heart failure and claudication
- ✓ Ocular symptoms
- ✓ Neuropathic complications symptoms includes numbness, pain, muscle weakness
- ✓ Drug history
- ✓ Gestational history

A complete examination includes

- ✓ Height and weight measurement
- ✓ Blood pressure measurement
- ✓ Examination of Cardiovascular system and peripheral pulses
- ✓ Fundus examination

Laboratory assessment should include:

- ✓ blood glucose measurement
- ✓ Urine for ketones bodies; glucose and also proteins
- ✓ All individual with proteinuria, s.creatinine is to be done
- ✓ ECG
- ✓ Blood cholesterol level
- ✓ HBA1c measurement

Management of DM:

The major component are :

1.Dietary modifications

2.OHA'S

3.Insulin treatment

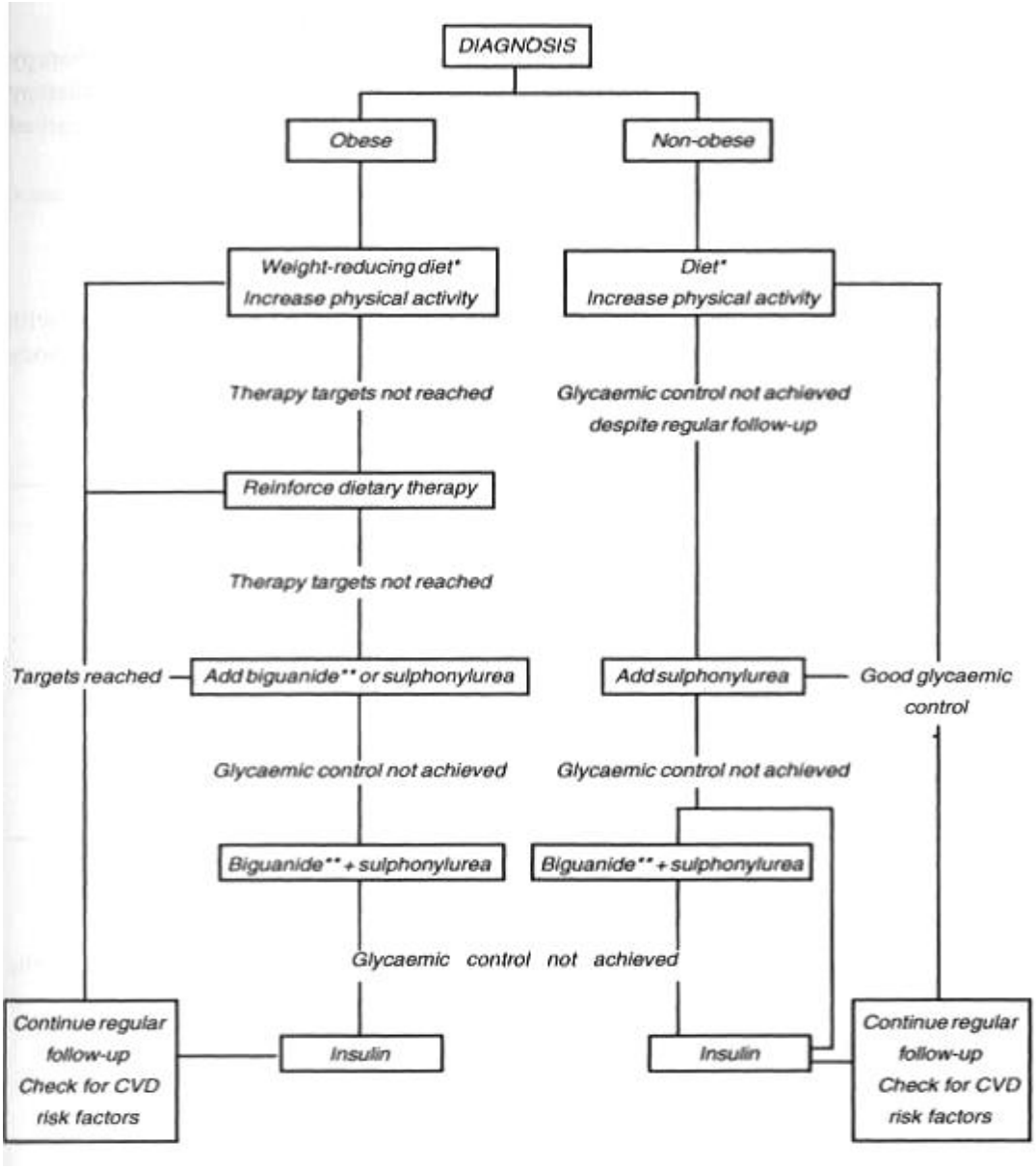

FIGURE 8

Source-WHO/EURO

*Drug therapy should be considered at this stage in presence of high sugar levels or conditions associated with infection.

** if no contraindication,can be used

Dietary management:

- Diet is essential in treatment of diabetes .

Dietary management must look at:

- ✓ Emphasis on control of weight
- ✓ Adequate nutritional requirement
- ✓ Allow better control of glycemic level

Meal planning:

- ✓ Diet counseling must be told in every visit
- ✓ Meals must be evenly distributed through out the day

Activity:

- ✓ Physical exercise ensures reduction in weight ,it mproves insulin sensitivity ,so that lowers the plasma sugars levels.

Drug management:

- ✓ Antidiabetic drugs are used only, when the diet and exercise are failed to achieve the better glycemic control.

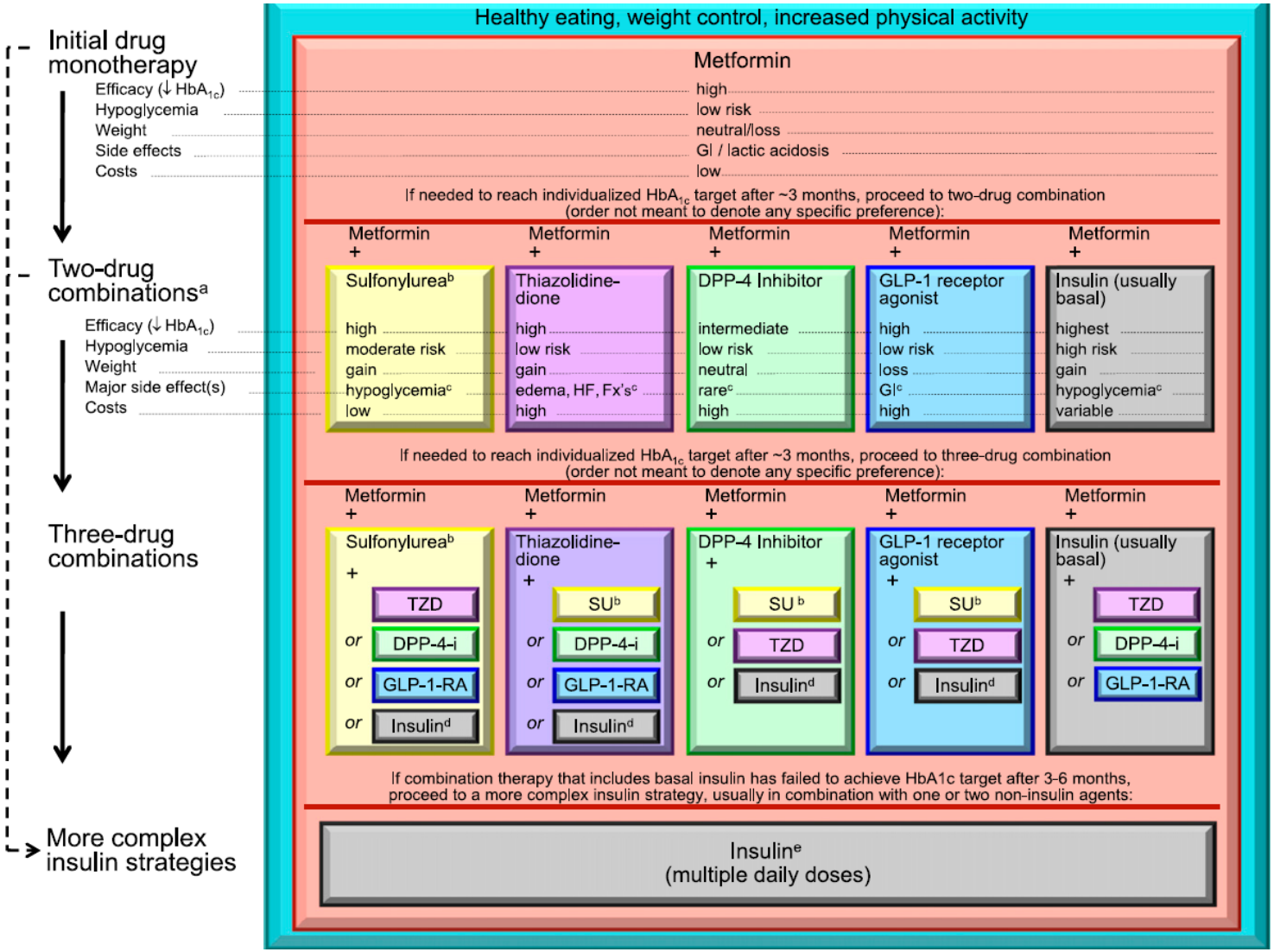
Healthy eating, weight control, increased physical activity
Initial drug monotherapy
Efficacy (↓ HbA1c)
Hypoglycemia
Weight
Side effects
Costs
Metformin
high
low risk
neutral/loss
GI / lactic acidosis
low
If needed to reach individualized HbA1c target after ~3 months, proceed to two-drug combination (order not meant to denote any specific preference):
Two-drug combinations[a]
Efficacy (↓ HbA1c)
Hypoglycemia
Weight
Major side effect(s)
Costs
Metformin +
Sulfonylurea[b]
high
moderate risk
gain
hypoglycemia[c]
low
Thiazolidine-dione
high
low risk
gain
edema, HF, Fx's[c]
high
DPP-4 Inhibitor
intermediate
low risk
neutral
rare[c]
high
GLP-1 receptor agonist
high
low risk
loss
GI[c]
high
Insulin (usually basal)
highest
high risk
gain
hypoglycemia[c]
variable
If needed to reach individualized HbA1c target after ~3 months, proceed to three-drug combination (order not meant to denote any specific preference):
Three-drug combinations
Metformin +
Sulfonylurea[b] +
TZD
or DPP-4-i
or GLP-1-RA
or Insulin[d]
Thiazolidine-dione +
SU[b]
or DPP-4-i
or GLP-1-RA
or Insulin[d]
DPP-4 Inhibitor +
SU[b]
or TZD
or Insulin[d]
GLP-1 receptor agonist +
SU[b]
or TZD
or Insulin[d]
Insulin (usually basal) +
TZD
or DPP-4-i
or GLP-1-RA
If combination therapy that includes basal insulin has failed to achieve HbA1c target after 3-6 months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents:
More complex insulin strategies
Insulin[e] (multiple daily doses)

FIGURE 9

Types of OHA:

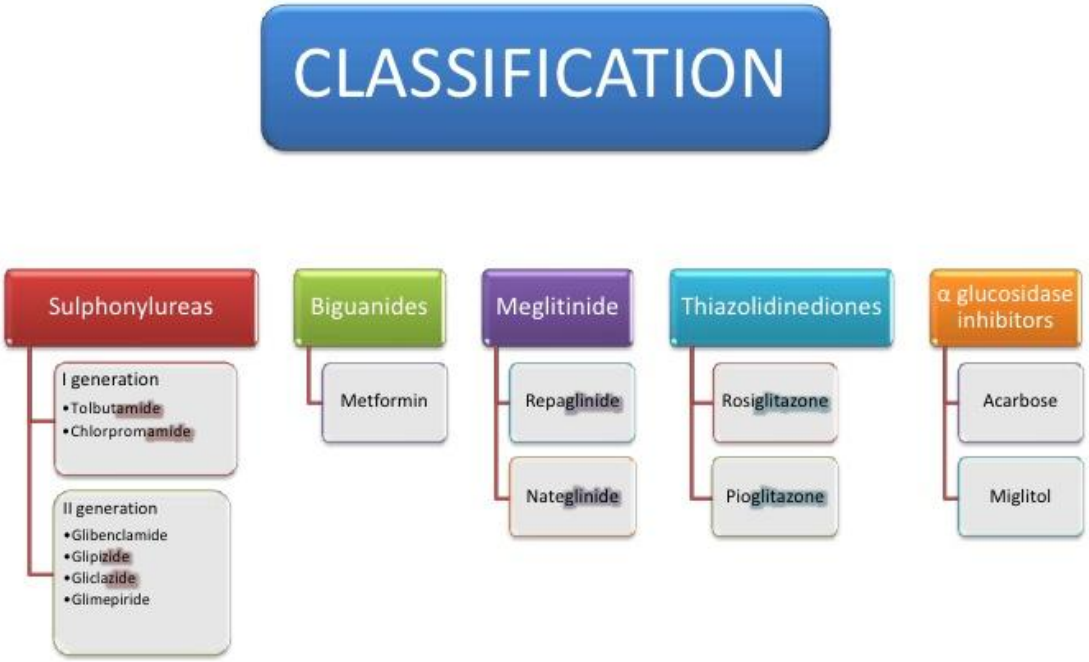

FIGURE 10

1) Sulphonylureas (sus) act on beta cells and relases the insulin and it promotes its action via extra pancreatic mechanism.

   Ex: glibenclamide,glipizide,gliclazide,glimepride

2) Biguanides acts by lowering the gluconeogenesis and increases peripheral glucose utililise by the cells.

   Ex:Metformin

As metformin causes lactic acidosis it is should not be used in

- ✓ Altered renal function
- ✓ Age group >70 years
- ✓ Patient with heart failure and hepatic impairment

Both SU and BGs must not be given during pregnancy and breast –feeding patients

3) Alpha glucosidase inhibitors: its acts by inhibiting carbohydrate absorption in the gut

   Ex:acarbose,

4) Thiazolidinediones: its improves peripheral insulin sensitivity

   Ex:pioglitazone, voglibose,miglitol

5) Dipeptidyl peptidase inhibitors(DPP): acts by glucose induced insulin response

   Ex:vildagliptin,sitagliptin,saxagliptin,linagliptin

6) Dopamine agonist: acts by hypothalamic dopamine release

   Ex:bromocriptine

Antidiabetic drugs with their mechanism of actions and limitations:

Class	Approved Drugs	Mechanisms of Action	Limitations
Sulfonylurea	four (1st generation) and two (2nd generation)	stimulates pancreas to release more insulin	hypoglycemia; may increase cardiovascular risk; contra-indicated in liver and renal dysfunction; hyperinsulinemia
Biguanide	metformin	reduces glucose production by liver; improves insulin sensitivity	lactic acidosis; GI side effects
Alpha-glucosidase inhibitor	acarbose	reduces glucose absorption by gut	GI side effects; requires frequent postprandial dosing
Thiazolidinedione	troglitazone (withdrawn) rosiglitazone pioglitazone	stimulates nuclear PPAR-gamma receptor; reduces insulin resistance	edema; contra-indicated in heart failure; long onset of action; weight gain; frequent liver function testing

In patients with non insulin dependent DM , insulin is used in few conditions :these are

- ✓ When adequate diet and OHAs are failed to lower hyperglycemia
- ✓ In gestational diabetes mellitus, even after dietary modifications
- ✓ Sometimes when these OHAs are being contra indicated
- ✓ In case of infections and when surgery is planned

Insulin management :

Individuals with diabetes must

- ✓ Be taught techniques of self measuring of glucose levels
- ✓ Keep a record of self monitoring results

MANAGEMENT OF INSULIN DEPENDENT DIABETES MELLITUS:(IDDM)

Specific objectives:

Goal in insulin dependent DM in the children is to make sure that they have adequate growth and the development . so the measure can be explained to the family members of a child.

Assessment:

- ➢ Thyroid function and thyroid function tests.
- ➢ Measure the height and weight of a child
- ➢ Monitor the growth regularly

Insulin therapy goals:

- ✓ Reaching the adequate metabolic control and mimicks the secretion of insulin physiologically
- ✓ Minimize the risk of hypoglycemia

Insulins are routinely administered by subcutaneous(s.c) route, and In diabetic ketoacidosis.(DKA) it can administered by either IM or IV routes.

In all individuals with insulin dependent DM, self monitoring shall be emphasised

Follow-up:

During review blood glucose monitored and measurement of Hba1c,urine glucose and ketones are checked. Annual eye examination and microalbuminuria are recommended.

INSULIN THERAPY:

Sources of insulin:

sources of insulin include: beef, pork, human

Classification of insulin:

These include meal time (bolus) and basal insulin.

- ✓ Meal time insulins are rapidly acting analogs or short acting regular human insulin .these have been used to stimulate high levels of insulin seen in individuals without diabetes after ingestion of food.
- ✓ Intermediate and long acting human insulins are Basal insulins and analog

Classification is based on duration of action

Basal insulis:

1) Neutral protamine hagedorn (NPH)
2) Isophane insulin
3) Ultralente (extended insulin zinc suspension)
4) Insulin analogs: Detemir, glargine

Bolus or meal time insulins:

1) Regular insulin
2) Analog forms:Aspart,lispro

Premixed Insulin:

The most commonly used premixed insulin is 30/70

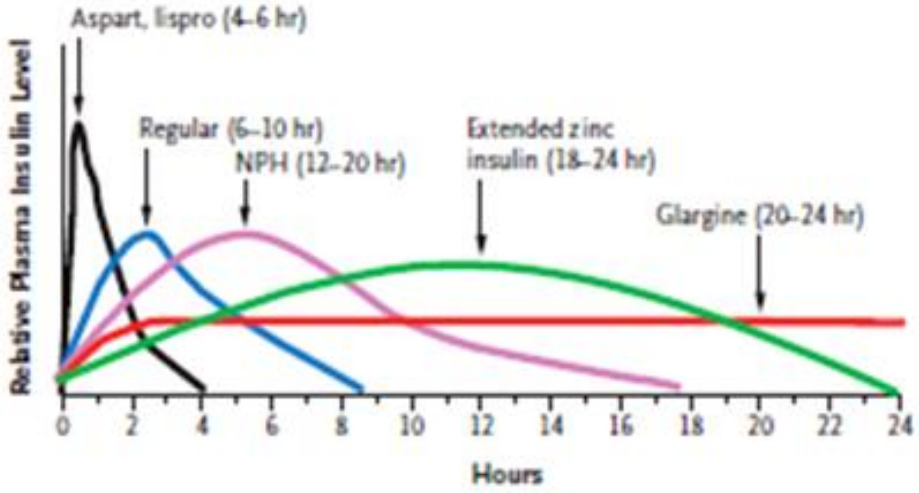

Figure 2. Approximate Pharmacokinetic Profiles of Human Insulin and Insulin Analogues.

The relative duration of action of the various forms of insulin is shown. The duration will vary widely both between and within persons.

HUMAN INSULIN ANALOGS

Source: NEJM

Table 1. Duration of Action of Standard Insulins and Insulin Analogues.*

Insulin	Onset of Action	Peak Action	Effective Duration
Standard			
Regular	30–60 min	2–3 hr	8–10 hr
NPH	2–4 hr	4–10 hr	12–18 hr
Zinc insulin (Lente)	2–4 hr	4–12 hr	12–20 hr
Extended zinc insulin (Ultralente)	6–10 hr	10–16 hr	18–24 hr
Analogues			
Lispro	5–15 min	30–90 min	4–6 hr
Aspart	5–15 min	30–90 min	4–6 hr
Glargine	2–4 hr	None	20–24 hr

* Serum insulin profiles are based on a subcutaneous injection of 0.1 to 0.2 unit per kilogram of body weight; large variation within and between persons may be noted. Data are from DeWitt and Hirsch.[6]

SOURCE:NEJM

INDICATIONS FOR INSULIN THERAPY:

- Type 1 diabetes
- Type 2 diabetes who have failed to achieve glycemic goals with the maximal dose of OAD's
- Gestational diabetes
- In type- 2 diabetes during physiological stress-surgery,infection,acute illness
- Diabetic ketoacidosis/ hyperosmolar hyperglycemic nonketotic coma
- Secondary diabetes (pancreatitis,steroids)
- Chronic renal failure
- Use of parenteral nutrition or high calorie supplements

Site for insulin administration :

1. **Anterior abdominal wall:** Rate of absorption of insulin is more rapid and more consistent in the abdomen than in the arms, thighs. reasons are easy self administration, larger surface area,.
2. Insulin is injected at least 4 finger breadths away from the umbilicus on all sides
3. Upper outer thigh:
    - ✓ Issue of privacy especially among women
    - ✓ Exercise may increase the insulin absorption

- ✓ And has very little subcutaneous tissue laterally, so injections in thigh are not preferred.

4. Upper outer arm:
    - ✓ Self administration of insulin in the arm is difficult.

Factors that affect the rate of insulin absorption:

Site of injection:

After injection into the arm and abdomen peak concentration of insulin is reached at 75min and 60 minutes respectively. The shorter absorption time from the abdominal site means that there is less destruction of insulin by subcutaneous tissue.

Temperature:

The warmer the area ,the faster is the absorption,the colder the area,the slower the absorption.

Exercise:

Exercise increase the rate of absorption of insulin by increasing the blood supply

Complication of insulin therapy:

- ✓ Hypoglycemia
- ✓ Weight gain
- ✓ lipohypertrophy

Alternative methods of insulin delivery:

- ✓ Temporary pen device
- ✓ Permanent pen device

Advantages of insulin pen devices over conventional insulin syringes :

- ➢ more convenient method and more accurate insulin delivery
- ➢ less pain because of smaller gauge needle
- ➢ improved quality of life
- ➢ improved social acceptability especially at schools

INSULIN PUMPS:

Continuous subcutaneous insulin infusion(CSII):

The system consists of a pump ,a reservoir syringe,and infusion set with a Teflon catheter that is inserted into subcutaneous tissue.The reservoir accommodates a volume of 3ml/300 u and has to be disposed after each use.The infusion set needs to be changed once in every 2 to 3 days to maximize the benefit of pump therapy.

Benefits of CSII:

- Closer to normal blood glucose levels throughout the day –with in the target range
- More approximate matching of insulin to food intake
- Improved changes for a long ,healthy life
- Increased coping with daily living
- Improved targeting of dawn phenomenon

Risks of CSII:

- Diabetic ketoacidosis
- Hypoglycemia
- Catheter site infection and contact dermatitis
- Weight gain

RESULTS

The study was conducted in 30 patients of type 2 diabetes mellitus who had been admitted in PSG hospitals attached to MGR HEALTH UNNIVERSITY, COIMBATORE,TAMIL NADU during the period from November 2014 to may 2015.All cases met inclusion and exclusion criteria.The observations made in this study are discussed here.

TABLE 1: AGE

Age group	Frequency	Percentage (%)
40-50 yrs	6	20.0
50- 60 yrs	10	33.3
60 – 70 yrs	12	40.0
>70 yrs	2	6.7
Total	**30**	**100.0**

In a study population of 30, 40% of people are between the age group of 60-70 years.

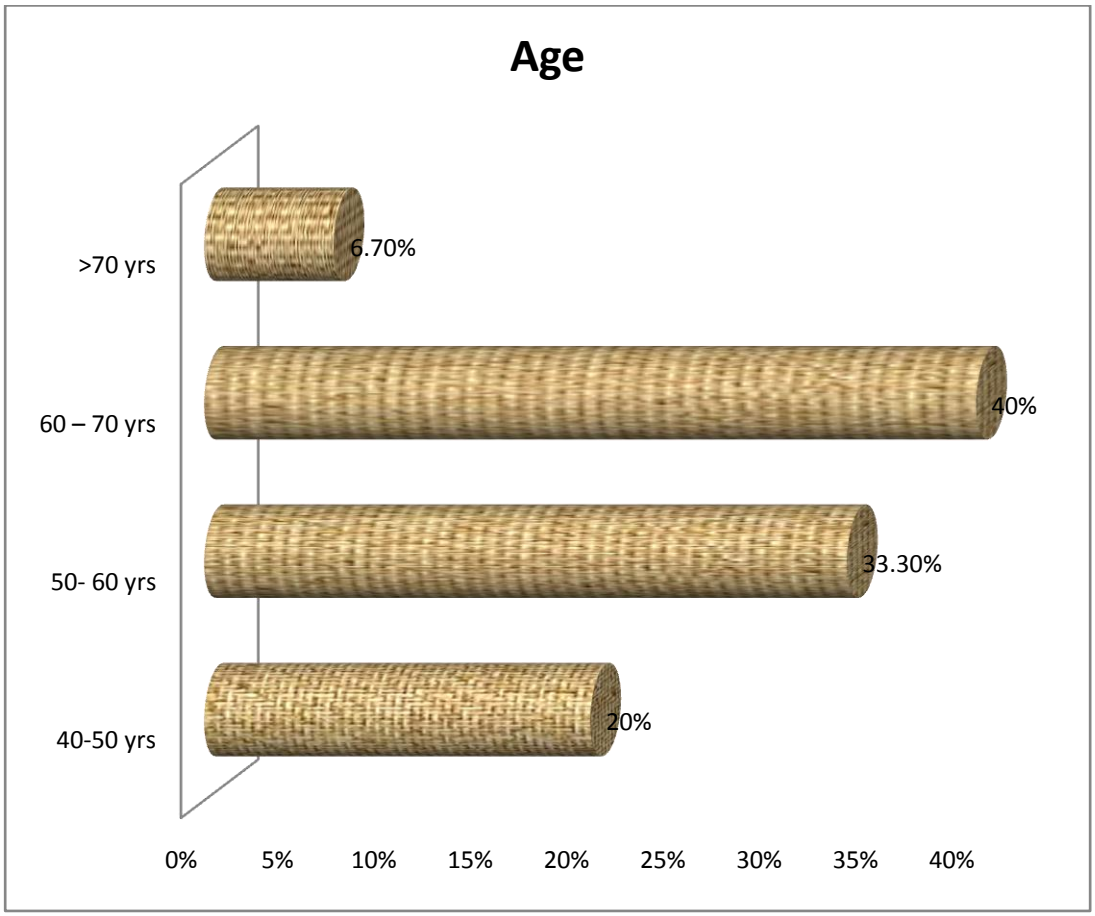
Age
>70 yrs
6.70%
60 – 70 yrs
40%
50- 60 yrs
33.30%
40-50 yrs
20%
0%
5%
10%
15%
20%
25%
30%
35%
40%

FIGURE 11

TABLE 2: GENDER

Sex	Frequency	Percentage (%)
Male	13	43.3
Female	17	56.7
Total	**30**	**100.0**

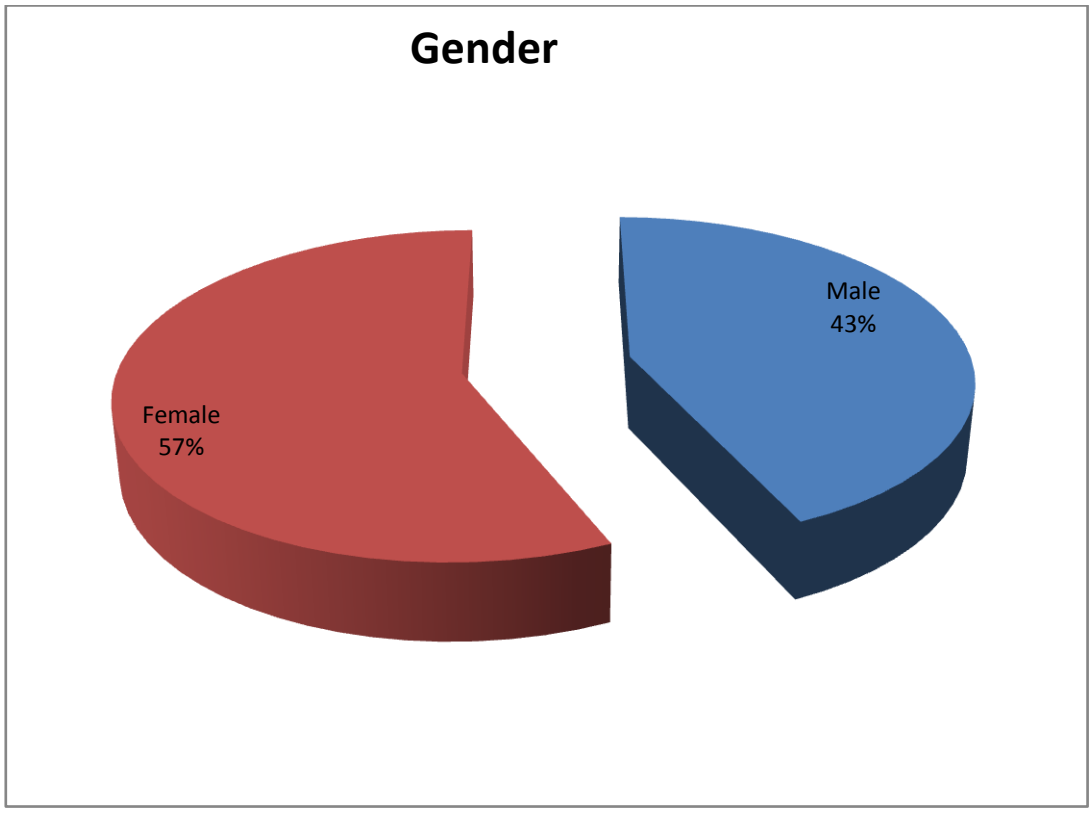

FIGURE 12

TABLE 3: HBA1C-At Baseline

HbA1c	Frequency	Percentage (%)
8-9	5	16.7
9-10	8	26.7
10-11	6	20.0
>11	11	36.7
Total	**30**	**100.0**

In the study population of 30 , 36.7% of people are having HbA1c of >11 % and 16.7% of people are having HbA1c between 8-9.

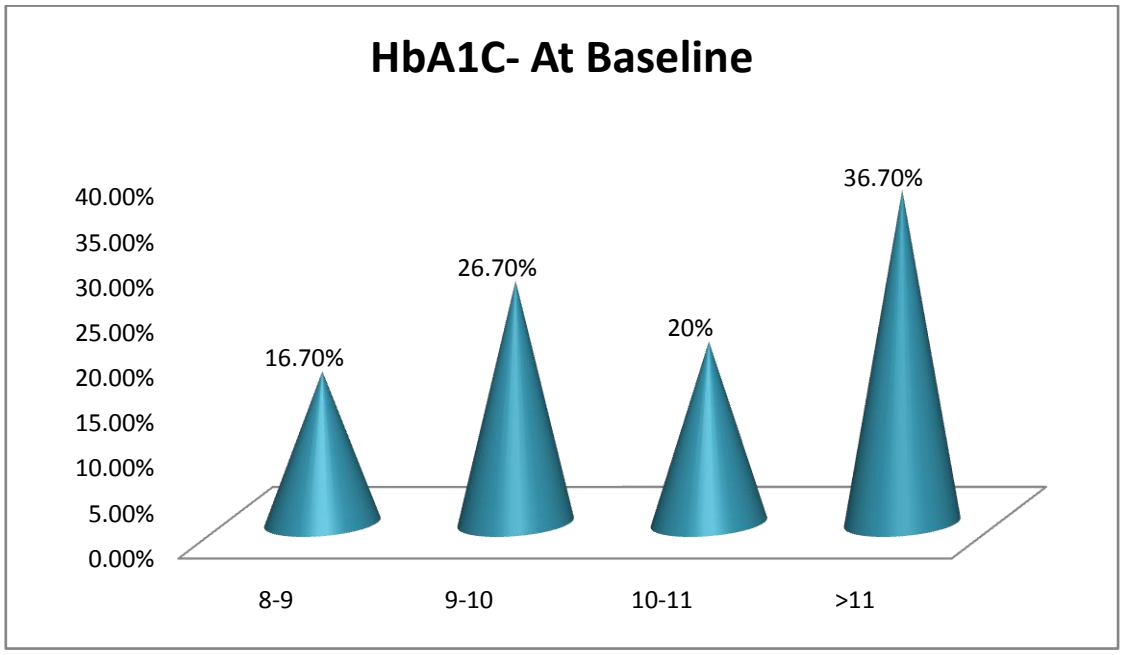

FIGURE 13

TABLE 4: HbA1C- After 6 months

HbA1c	Frequency	Percentage (%)
8-9	21	84.0
9-10	2	8.0
>11	2	8.0
Total	**25**	**100.0**

In the study population of 30,. after 6months ,84 % of people are having HbA1c between 8-9 and 8% of people are having 9-10 and >11 % respectively

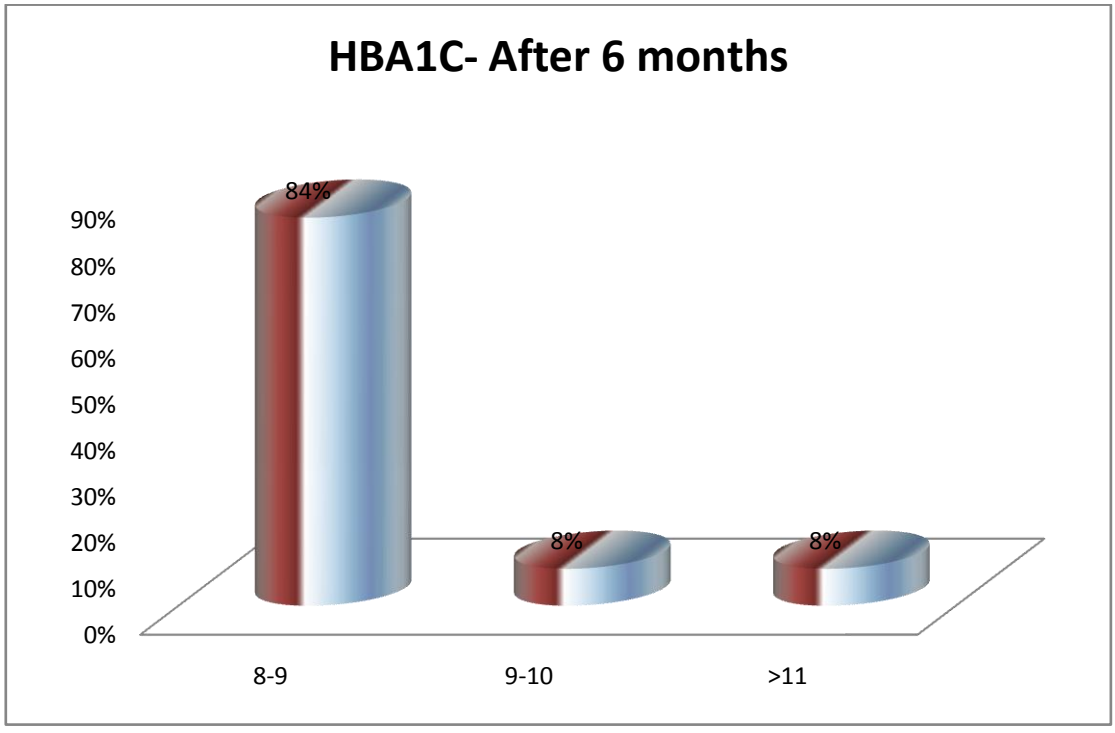

FIGURE 14

TABLE 5: HsCRP- At Baseline

HsCRP	Frequency	Percentage (%)
<5	19	63.3
5-15	3	10.0
15-25	6	20.0
>25	2	6.7
Total	**30**	**100.0**

In the study population of 30,at baseline 63% of people are having hsCRP of <5% and 6.7 % of people are having >25.

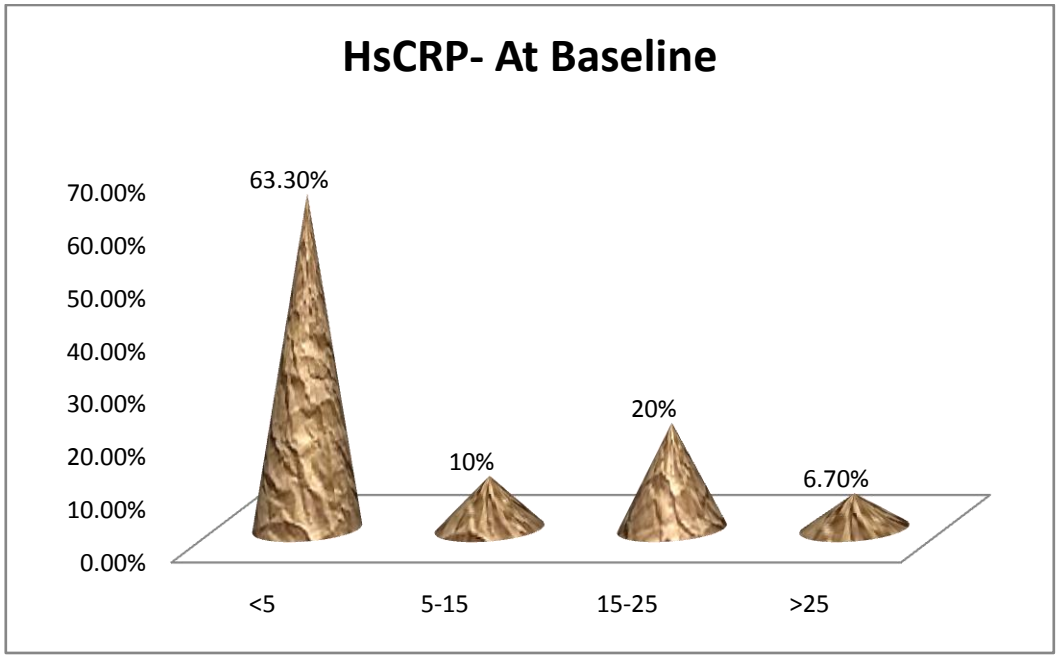

FIGURE 15

TABLE 6: HsCRP - After 6 months

HsCRP	Frequency	Percentage (%)
<5	12	48.0
5-15	11	44.0
15-25	2	8.0
Total	**25**	**100.0**

In the study population after 6 months, 48% of people are having hsCRP of <5 and 8% of people are between 15-25

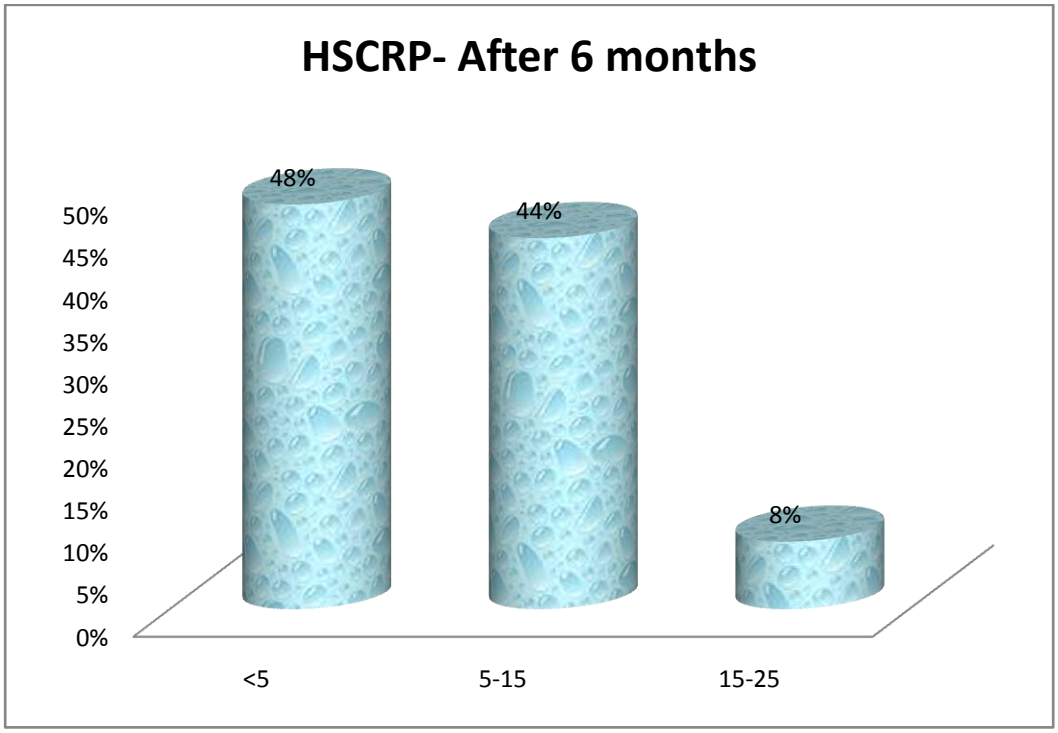

FIGURE 16

TABLE 7: Descriptive Statistics

	Mean	Std. Deviation	N
HBA1C- At baseline	10.4037	1.51596	30
HSCRP- At baseline	7.9047	9.75382	30
HBA1C- After 6 months	8.4296	1.84054	25
HSCRP- After 6 months	4.8780	5.41332	25

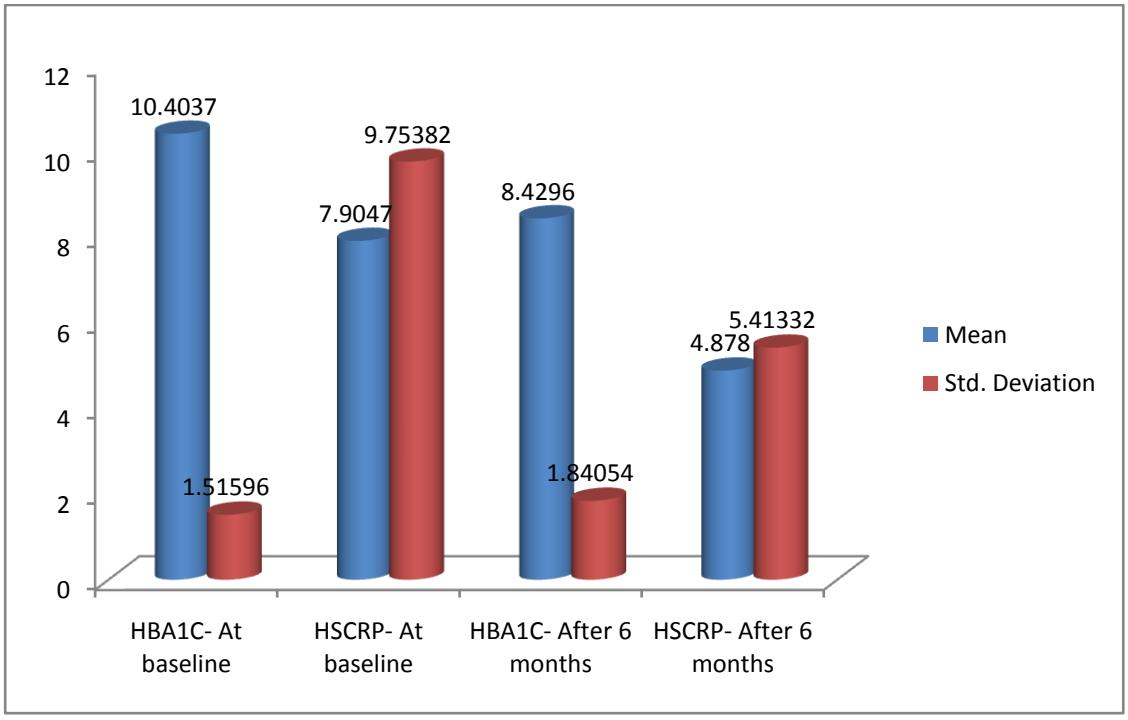

FIGURE 17

TABLE 8: Correlations

		HBA1C- At baseline	HSCRP- At baseline	HBA1C- After 6 months	HSCRP- After 6 months
HBA1C- At baseline	Pearson Correlation	1	.209	.105	.129
	Sig. (2-tailed)		.267	.619	.540
	N	30	30	25	25
HSCRP- At baseline	Pearson Correlation	.209	1	.183	.654**
	Sig. (2-tailed)	.267		.380	.000
	N	30	30	25	25
HBA1C- After 6 months	Pearson Correlation	.105	.183	1	.037
	Sig. (2-tailed)	.619	.380		.860
	N	25	25	25	25
HSCRP- After 6 months	Pearson Correlation	.129	.654**	.037	1
	Sig. (2-tailed)	.540	.000	.860	
	N	25	25	25	25

**. Correlation is significant at the 0.01 level (2-tailed).

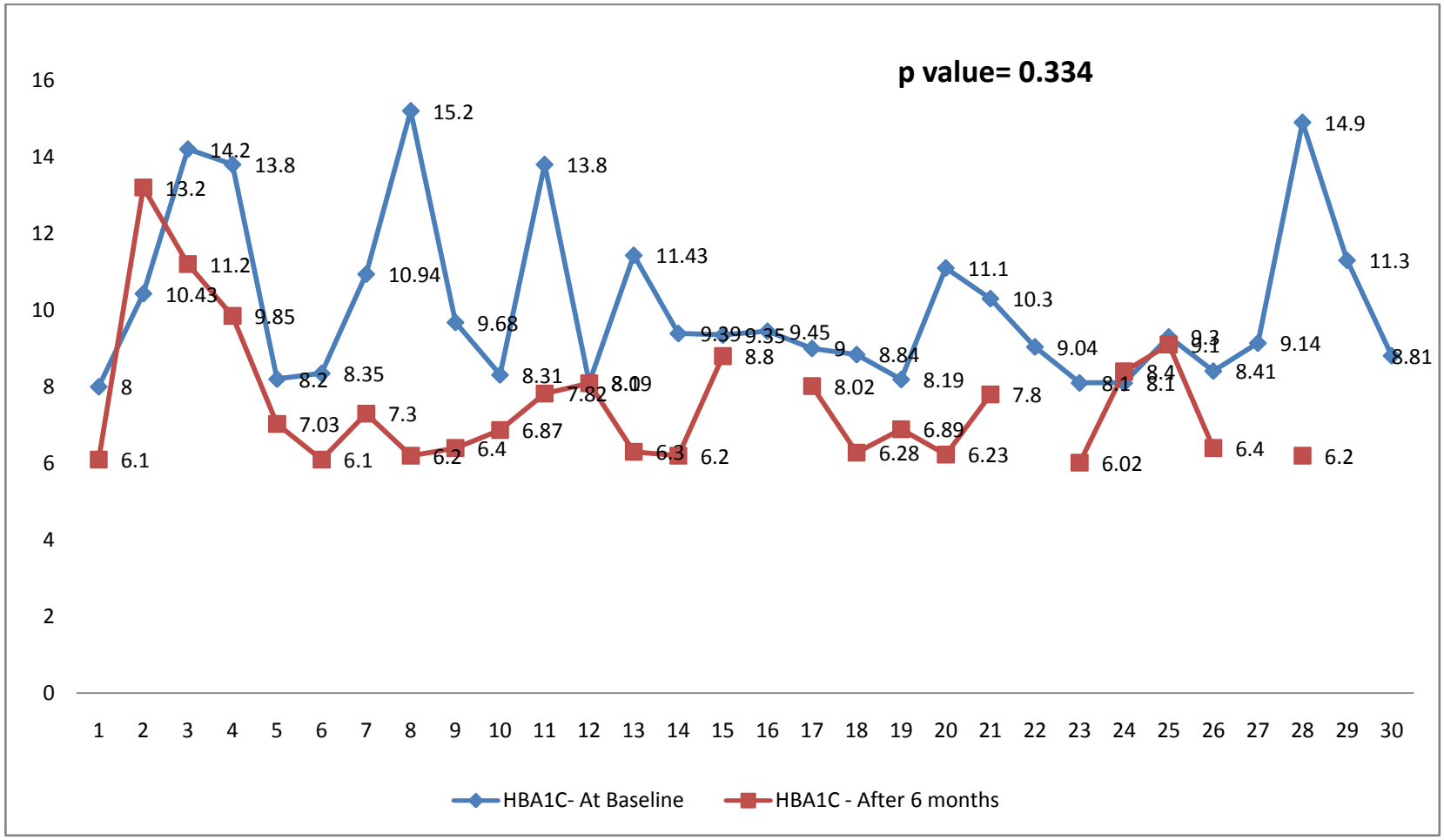
p value= 0.334
16
14
12
10
8
6
4
2
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
HBA1C- At Baseline
HBA1C - After 6 months

FIGURE 18

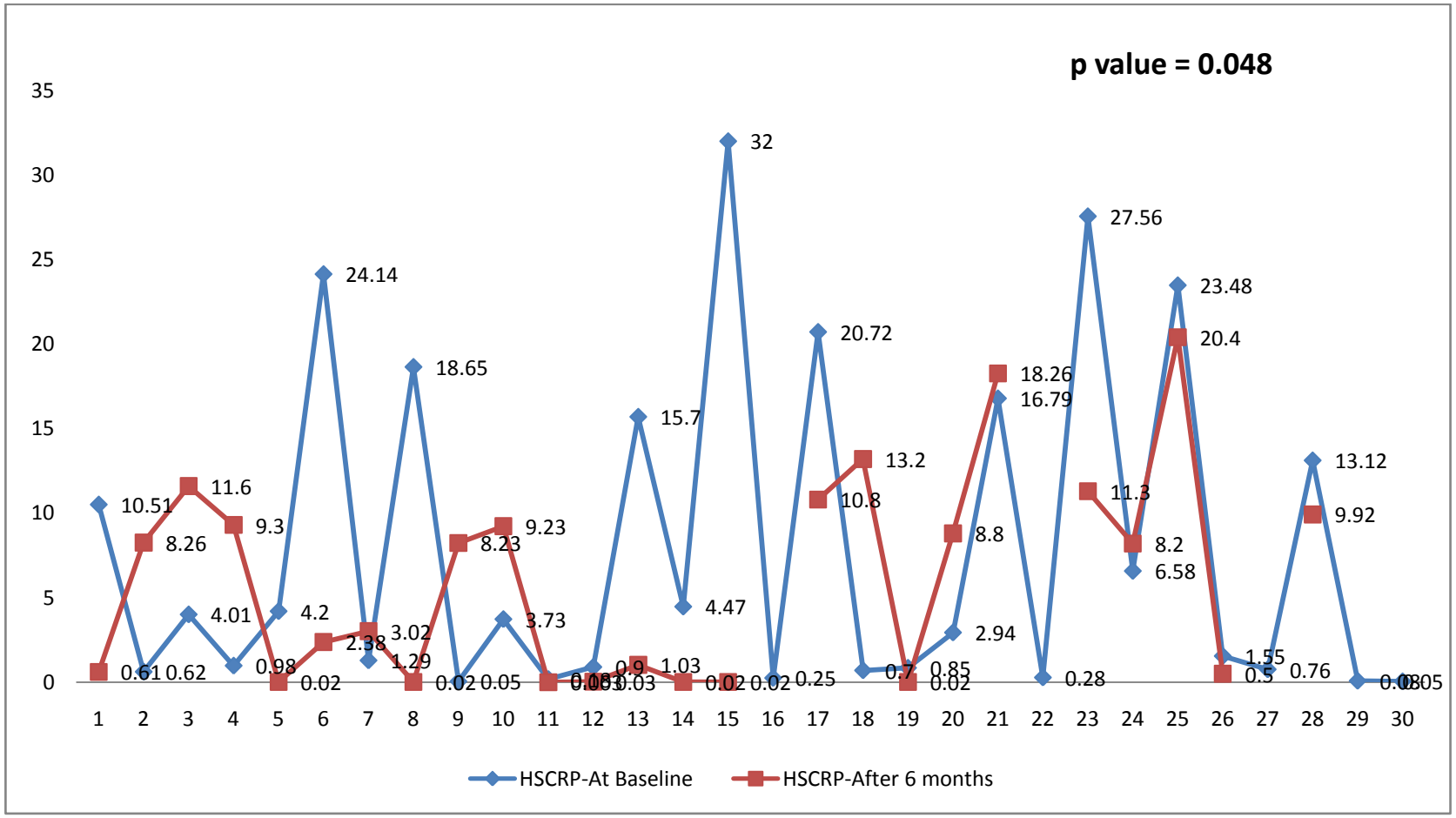

FIGURE 19

CONCLUSION

Hba1c at baseline, minimum value is 8 and maximum is 15.2. Hba1c after 6 months, minimum value is 6 and maximum is 8.3.

So in this study when hba1c is compared with baseline hba1c ,patient has got good glycemic control,but stastically not significant [$p>0.05$]

HSCRP at baseline, minimum value is 10 and maximum is 32. Hba1c after 6 months, minimum value is 2 and maximum is 20.4.

So in this study when HSCRP is compared with baseline HSCRP, shows stastically significant [$p<0.05$]

BIBLOIGRAPHY

1. United Kingdom Prospective Diabetes Study (UKDPS). 13: Relative efficacy of randomly allocated diet, sulphonylurea, insulin or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for three years. BMJ 1995;310:83.

2. Pepys MB, Hirschfield GM (Jun 2003). "C-reactive protein: a critical update". The Journal of Clinical Investigation **111** (12): 1805–12.doi:10.1172/ CI18921 1 PMC 161431. PMID 12813013.

3. NCBI Entrez Protein #CAA39671.

4. Pepys MB, Hirschfield GM (Jun 2003). "C-reactive protein: a critical update". The Journal of Clinical Investigation **111** (12): 1805–12.do i:10.n 1172/ JCI18921 PMC 161431. PMID 12813013.

5. "Normal results". C-reactive protein. MedlinePlus. Retrieved 23 April 2015.

6. Sindhu S, Singh HK, Salman MT, Fatima J, Verma VK (Oct 2011). "Effects of atorvastatin and rosuvastatin on high-sensitivity C-reactive protein and lipid profile in obese type 2 diabetes mellitus

patients". Journal of Pharmacology & Pharmacotherapeutics **2** (4): 261–5. doi:10.4103/0976-500X.85954. PMC 3198521.PMID 22025854.

7. **Jump up^** Jialal I, Stein D, Balis D, Grundy SM, Adams-Huet B, Devaraj S (Apr 2001). "Effect of hydroxymethyl glutaryl coenzyme a reductase inhibitor therapy on high sensitive C-reactive protein levels". Circulation **103** (15): 1933 5. doi:10.1161/01. CIR.103.15.1933. PMID 11306519.

8. "Hemoglobin A1c Fact Sheet". Michigan Diabetes Research & Training Center. Retrieved 2007-12-26.

9. Walid MS, Newman BF, Yelverton JC, Nutter JP, Ajjan M, Robinson JS (2009). "Prevalence of previously unknown elevation of glycated hemoglobin (HbA_{1c}) in spine surgery patients and impact on length of stay and total cost". J Hosp Med **5** (1): NA.doi:10.1002/jhm.541. PMID 19753643.

10. "Undetectable Glycosolated Hemoglobin in Autoimmune Hemolytic Anemia" (PDF).repository.oai.yamaguchi-u.ac.jp. Retrieved 2009-08-31.

11. Weiss R, Caprio S, Trombetta M, et al. Beta-cell function across the spectrum of glucose tolerance in obese youth. Diabetes 2005; 54:1735.

12. Elder DA, Hornung LN, Herbers PM, et al. Rapid deterioration of insulin secretion in obese adolescents preceding the onset of type 2 diabetes. J Pediatr 2015; 166:672.

13. Mayer-Davis EJ, Beyer J, Bell RA, et al. Diabetes in African American youth: prevalence, incidence, and clinical characteristics: the SEARCH for Diabetes in Youth Study. Diabetes Care 2009; 32 Suppl 2:S112.

14. Gungor N, Hannon T, Libman I, et al. Type 2 diabetes mellitus in youth: the complete picture to date. Pediatr Clin North Am 2005; 52:1579.

15. Sapru A, Gitelman SE, Bhatia S, et al. Prevalence and characteristics of type 2 diabetes mellitus in 9-18 year-old children with diabetic ketoacidosis. J Pediatr Endocrinol Metab 2005; 18:865.

16. Rewers A, Klingensmith G, Davis C, et al. Presence of diabetic ketoacidosis at diagnosis of diabetes mellitus in youth: the Search for Diabetes in Youth Study. Pediatrics 2008; 121:e1258.

17. Zeitler P, Haqq A, Rosenbloom A, et al. Hyperglycemic hyperosmolar syndrome in children: pathophysiological considerations and suggested guidelines for treatment. J Pediatr 2011; 158:9.

18. Rosenbloom AL. Hyperglycemic hyperosmolar state: an emerging pediatric problem. J Pediatr 2010; 156:180.

19. Morales AE, Rosenbloom AL. Death caused by hyperglycemic hyperosmolar state at the onset of type 2 diabetes. J Pediatr 2004; 144:270.

20. Hollander AS, Olney RC, Blackett PR, Marshall BA. Fatal malignant hyperthermia-like syndrome with rhabdomyolysis complicating the presentation of diabetes mellitus in adolescent males. Pediatrics 2003; 111:1447.

21. Fourtner SH, Weinzimer SA, Levitt Katz LE. Hyperglycemic hyperosmolar non-ketotic syndrome in children with type 2 diabetes*. Pediatr Diabetes 2005; 6:129.

22. American Diabetes Association. Standards of medical care in diabetes--2014. Diabetes Care 2014; 37 Suppl 1:S14.

23. DeFronzo RA. Lilly lecture 1987. The triumvirate: beta-cell, muscle, liver. A collusion responsible for NIDDM. Diabetes 1988; 37:667.

24. Frank RN. Etiologic mechanisms in diabetic retinopathy. Ryan SJ, ed. *Retina*. 1994. Vol 2: 1243-76.

25. Crawford TN, Alfaro DV 3rd, Kerrison JB, Jablon EP. Diabetic retinopathy and angiogenesis. *Curr Diabetes Rev*. 2009 Feb. 5(1):8-13. [Medline].

26. Boulton AJ, Malik RA. Diabetic neuropathy. *Med Clin North Am*. 1998 Jul. 82(4):909-29. [Medline].

27. Goetz CG, Pappert EJ. *Textbook of Clinical Neurology*. Philadelphia: WB Saunders Co; 1999.

28. Laing SP, Swerdlow AJ, Slater SD, Burden AC, Morris A, Waugh NR, Gatling W, Bingley PJ, Patterson CC: Mortality from heart disease in a cohort of 23,000 patients with insulin-treated diabetes. Diabetologia46 : 760-765,2003

29. Paterson AD, Rutledge BN, Cleary PA, Lachin JM, Crow RS: The effect of intensive diabetes treatment on resting heart rate in type 1 diabetes: the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study. Diabetes Care 30:2107 - 2112, 2007

30. Kannel WB, McGee DL: Diabetes and cardiovascular disease: the Framingham study. JAMA 241:2035 -2038, 1979

31. Lehto S, Ronnemaa T, Pyorala K, Laakso M: Predictors of stroke in middle-aged patients with non-insulin-dependent diabetes. Stroke27 : 63-68,1996

32. Avogaro A, Giorda C, Maggini M, Mannucci E, Raschetti R, Lombardo F, Spila-Alegiani S, Turco S, Velussi M, Ferrannini E: Incidence of coronary heart disease in type 2 diabetic men and women: impact of microvascular complications, treatment, and geographic location. Diabetes Care30 : 1241-1247,2007

33. U.K. Prospective Diabetes Study Group: Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. BMJ 317:713 -720, 1998

34. U.K. Prospective Diabetes Study Group: Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ317 : 703-713,1998

35. Heart Outcomes Prevention Evaluation Study Investigators: Effects of ramipril on cardiovascular and microvascular outcomes in people with

diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Lancet355 : 253-259,2000.

36. Beckman JA, Creager MA, Libby P: Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. JAMA287 : 2570-2581,2002

37. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998; 352:837.

38. Pal K, Eastwood SV, Michie S, et al. Computer-based diabetes self-management interventions for adults with type 2 diabetes mellitus. Cochrane Database Syst Rev 2013; 3:CD008776

39. Umpierre D, Ribeiro PA, Kramer CK, et al. Physical activity advice only or structured exercise training and association with HbA1c levels in type 2 diabetes: a systematic review and meta-analysis. JAMA 2011; 305:1790.

40. Jeon CY, Lokken RP, Hu FB, van Dam RM. Physical activity of moderate intensity and risk of type 2 diabetes: a systematic review. Diabetes Care 2007; 30:744.

41. Initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2006; 29:1963.

42. Ilanne-Parikka P, Eriksson JG, Lindström J, et al. ... in an elderly Swedish population. Acta Diabetol 2006; 43: 120-6. Liu J ... *Am J Med 2006*; *119*: *812*-9. Mottillo ...

43. ATP = Adult Treatment Panel. Expert Panel on Detection, Evaluation, and Treatment of High Blood. Cholesterol in Adults. *JAMA*. *2001*;*285*:*2486*-2497.

44. McGill HC Jr, McMahan CA, Zieske AW, et al. Association of Coronary Heart Disease Risk Factors with microscopic qualities of coronary atherosclerosis in youth. Circulation 2000; 102:374.

45. Brooks M. Migraine Linked to Double Risk for Silent Stroke. Medscape Medical News. Available athttp://www.medscape.com/ viewarticle/ 825451. Accessed: May 27, 2014.

46. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *N Engl J Med*. 1995 Dec 14. 333(24):1581-7. [Medline].

47. Meijer WT, Grobbee DE, Hunink MG, et al. Determinants of peripheral arterial disease in the elderly: the Rotterdam study. Arch Intern Med 2000; 160:2934.

48. Hiatt WR. Medical treatment of peripheral arterial disease and claudication. N Engl J Med 2001; 344:1608.

49. De Backer TL, Vander Stichele R, Lehert P, Van Bortel L. Naftidrofuryl for intermittent claudication. Cochrane Database Syst Rev 2008; :CD001368.

50. Mohler ER 3rd. Peripheral arterial disease: identification and implications. Arch Intern Med 2003; 163:2306.

PROFORMA

Name

Age/Sex

Address

Occupation

Chief complaints

H/o smoking, alcohol, diabetes, hypertension,

Family history of diabetes

CLINICAL EXAMINATION

General examination

Routine investigations:

Diabetic profile, Fasting lipid profile

Investigations:

Hba1c and C-reactive protein.

MASTER CHART

S.NO	NAME	AGE	SEX	SHT	AT BASELINE		AFTER 6 MONTHS	
					HBA1C	HSCRP	HBA1C	HSCRP
1	ARRUKKANIAMMAL	72	F	Y	9.1	10.51	8.5	9.45
2	SELVANAYAGAM.P	51	M	Y	10.43	0.62	8.11	0.41
3	PONNUSAMY.M	62	M	Y	12.8	4.01	9.02	2.08
4	KRISHNAMANICKAM	65	M	Y	12.11	0.98	9.85	0.88
5	CHANDRA.K	44	F	Y	10.7	4.2	7.03	2.02
6	RAJATHI N	58	F	Y	8.35	24.14	11.2	0.37
7	PANDIYAN.M	55	M	Y	10.94	1.29	7.3	0.46
8	CHINNAMMAL	68	F	Y	11.67	18.65	8.08	6.8
9	MOHMAD GANI	56	M	Y	9.68	0.05	6.4	0.02
10	KANNAMAL	56	F	Y	11.12	3.73	13	0.7
11	VASUDEVAN.S	62	M	Y	10.77	0.18	7.82	2.01
12	RATHINAMBAL	70	F	Y	9.39	0.9	8.09	2.5
13	VENKATACHALAM	72	M	Y	11.43	15.7	9.7	0.23
14	MURUGATHAL.S	65	F	Y	9.39	4.47	6.2	9.97
15	QUEENI	61	F	Y	11.8	32	8.8	13.5
16	PARVATHI	70	F	Y	9.45	0.25		
17	RAJA.R	40	M	Y	11.51	20.72	8.02	6.08
18	ANNAPOORNI	52	F	Y	8.84	0.7	7.02	0.4
19	RAMAMOORTHY	49	M	Y	8.19	0.85	6.89	0.5
20	INDRANI	60	F	Y	11.1	2.94	13.01	8.8
21	BATHRAPPAN.C	58	M	Y	10.3	16.79	7.8	8.05
22	SUBBULAKSHMI	69	F	Y	9.04	0.28		
23	DAISY RANI	45	F	Y	10.44	27.56	8.8	12.4
24	MICHAEL.S	50	M	Y	11.7	6.58	8.4	3.5
25	SAKTHIVEL.R	59	M	Y	9.3	23.48	9.1	20.4
26	VIJAYA.B	48	F	Y	8.41	1.55	6.4	0.5
27	SUSAIMARY	62	F	Y	9.14	0.76		
28	SHAMNUGAM.P	61	M	Y	14.9	13.12	6.2	9.92
29	BAGYALAKSHMI	55	F	Y	11.3	0.08		
30	SUBBULAKSHMI.M	66	F	Y	8.81	0.05		