THE IMPLICATION OF INCLUDING HBA1C ALONG WITH FASTING BLOOD GLUCOSE IN THE SCREENING CRITERION FOR THE DIAGNOSIS OF PREDIABETES

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In partial fulfilment of the requirements for the degree of

MD

in

General Medicine

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Dr. Niveditha.B.Kerodi

LIST OF ABBREVIATIONS USED

CBC	Complete Blood Count
CHD	Coronary Heart Disease
CVD	Cardiovascular Disease
DCCT	Diabetes Control and Complications Trial
DPP	Diabetes Prevention Program
FPG	Fasting Plasma Glucose
FBS	Fasting Blood Glucose
HbA1c	Glycosylated Haemoglobin
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
OGTT	Oral glucose tolerance test

ABSTRACT:

BACKGROUND AND OBJECTIVES:

Prediabetes screening followed by implementing lifestyle modification, weight reduction, physical activity and metformin drug therapy can significantly bring down the burden of diabetes in the population.[1,2,3] The existing criterion by American Diabetes Association for diagnosis of Prediabetes is fasting blood glucose between 100-125 mg/dl and/or IGT detected by oral GTT between 140-199mg/dl or detected by HbA1c 5.7-6.4%.[1]It seems any method used alone will miss many cases but if used in combination their detection rate increases. This study is an attempt to increase the detection rate of prediabetes by including both HBA1c and FBS in the screening criterion for prediabetes. Modification of screening criterion by ADA is necessary by making FPG and HBA1c both as mandatory investigations in the screening criterion for prediabetes.

METHODS:

This study was carried out in B.L.D.E.U's Shri B.M. Patil Medical College Hospital and Research Centre, Bijapur, Karnataka; during the period from October 2011 to June 2012. A total of 235 patients and their attenders accompanying the patient who satisfied the inclusion criteria were included in the study. The blood of the selected subjects were analysed for HBA1C and FBS levels.

RESULTS:

Incidence rate of pre diabetics by (HBA1c+FBS)	-	42.12%
Incidence rate of pre diabetics by FBS	-	28.9%
Incidence rate of pre diabetics by HBA1c	-	19.57%

CONCLUSION:

There is significant increase in the detection rate of prediabetes by considering both HbA1c and Fasting Blood Glucose in the diagnostic criterion for pre diabetes.The current ADA criteria needs to be modified and combination of FBS and HBA1c has to be included in the diagnostic criteria of prediabetes

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INTRODUCTION

India is currently the diabetic capital of the world and occupies 2nd position with respect to the number of people with prediabetes.[4] Prediabetes is defined by the American Diabetes Association as blood glucose levels that are higher than normal but not yet high enough to be diagnosed as diabetes.[1] According to American Diabetes Association; prediabetics have increased risk of microvascular complications like retinopathy, chronic kidney disease, neuropathy and cardiovascular disease.[2]

There are studies to show that, Prediabetes screening followed by implementing lifestyle modification such as weight reduction of 5% to 7% of total body weight ,moderate to intense physical activity of 30 to 60 minutes 5 days a week and metformin drug therapy can significantly bring down the burden of diabetes in the population.[1,3,5]

The existing criterion by American Diabetes Association for diagnosis of Prediabetes is fasting blood glucose between 100-125 mg/dl and/or impaired glucose tolerance i.e. oral GTT plasma glucose measurement after 2 hours of 75 mg of glucose load between 140-199 mg/dl or HbA1c 5.7-6.4%.[1] The cutoff values of all three tests are based on the appearance of retinopathy at these values. It seems any method used alone will miss many cases but if used in combination their detection rate increases.[6]

The following paragraphs explain why FBS misses many cases detected by HbA1C and vice versa. Fasting blood glucose depends on the previous 12 hour fasting status, which the patient may have failed to comply and may have been fasting for a longer duration. Unlike FBS, Hba1c does not require fasting and is not affected by

recent changes in diet or activity.[7] HbA1c is a widely used marker of chronic glycaemia, reflecting average blood glucose levels over a 2 to 3 month period of time as it is a reflection of average glucose concentration seen in the RBCs during their life span. HbA1c is a very useful investigation in the diagnosis of prediabetes; it has several advantages when compared to blood glucose measurements for example, the same HbA1c values can be reproduced on retesting the same individual within 2 weeks of the initial HbA1c testing unlike FBS which has a heavy variation in values. The other advantages of measuring HbA1c are less day-to-day perturbations during periods of stress and illness, elevated values of HbA1c has a very strong relationship with cardiovascular diseases, much stronger than FPG values.

The strategy of using the HbA1c level for identifying individuals with diabetes or at (high) risk for diabetes has however, been challenged based on the observation that several medical conditions are associated with alterations in HbA1c levels. Limitations of the HbA1c determination include specific haemoglobinopathies that interfere with HbA1c assays (e.g., foetal haemoglobin falsely increases and sickle cell haemoglobin/haemoglobin C lowers HbA1c levels). Diseases changing the turnover of red blood cells, such as haemolysis, shortened erythrocyte life, cirrhosis, acute or chronic blood loss, or transfusions, may also lead to abnormally low HbA1c levels. Patients with these conditions could, therefore, risk the possibility of a false-negative diagnosis. In contrast, the use of HbA1c levels could also lead to over diagnosis of diabetes (i.e., false-positive diagnosis) among the elderly, subjects with iron deficiency, or individuals genetically predisposed to greater levels of haemoglobin glycation.

Black individuals have higher HbA1c levels than white individuals, and there are several metabolic differences between males and females so males are found to have higher HBA1C values. Even though HBA1C is an invaluable investigation it cannot be the only investigation used for the diagnosis of prediabetes.

This study is an attempt at increasing the detection rate of Prediabetes by considering both HbA1c and FBS together as the diagnostic criterion for screening of Prediabetes.[8, 9]

AIMS AND OBJECTIVES OF THE STUDY

To find out whether there is increase in the detection rate of pre diabetes by considering both HbA1c and Fasting Blood Glucose in the diagnostic criterion for pre diabetes.

REVIEW OF LITERATURE

DEFINITION AND HISTORY OF PREDIABETES:

DEFINITION:

Diabetes refers to a group of common metabolic disorders that share the phenotype of hyperglycaemia. Several distinct types of diabetes are caused by a complex interaction of genetics and environmental factors. Prediabetes is defined as a hyperglycaemic state which is intermediate between normoglycaemia and diabetes where the patients have impaired fasting glucose (IFG) and or/ impaired glucose tolerance (IGT). Both categories (IGT and IFG) were referred to as prediabetes and are considered substantial risk factors for progression to diabetes.

HISTORICAL EVOLUTION OF THE DIAGNOSTIC CRITERIA FOR PREDIABETES (FROM 1979 TO 2013)

FROM DIABETES TO GLUCOSE INTOLERANCE: 1979 TO 1997

Before 1979 it was known that only **diabetes** was associated with microvascular and macrovascular complications but later studies showed the existence of an intermediate stage of hyperglycaemia- a level lower than that qualifying as diabetes which was a risk category for future development of vascular complications and diabetes, thus entity called **glucose intolerance** was recognised in 1979 by National diabetic data group. [10]

In **1979** the National diabetic data group (NDDG) [10] for the first time defined diabetes in adults according to the following criteria-

1. An unequivocal elevation of plasma glucose level, with the classical signs and symptoms of polyuria, polydipsia, weight loss and ketonuria.

2. Fasting Plasma Glucose-more than or equal to 140mg/dl on more than one occasion or

3. A two hour glucose level equal to or greater than 200mg/dl after 75gm of OGTT. In addition the NDDG defined glucose intolerance as an intermediate stage characterized by hyperglycaemia but at a level lower than that qualifying for the diagnosis of diabetes .All 3 of the following criteria had to be met before diagnosing IGT:

   - A FPG level lower than 140 mg/dL.
   - A glucose value between 140 and 199mg/dl at 120 minutes after OGTT
   - At least 1 glucose level more than 200 mg/dL at 30, 60, and 90 minutes after the OGTT.

The WHO stated in **1980** that glucose intolerance could be defined by a glucose value between 140 and 199mg/dL at 120 minutes after a 75-g OGTT and FPG level less than 140 mg/dL .[11]

PREDIABETES: 1997 TO 2013

1997 EXPERT COMMITTEE RECOMMENDATIONS:

In **1997** the Expert Committee and WHO defined 2 intermediate states of abnormal glucose regulation that exist between normal glucose homeostasis and diabetes. Thus, Impaired Glucose Tolerance was confirmed by a 2-hour plasma glucose level between 140 and 199 mg/dl after a 75-g OGTT and the second category Impaired Fasting Glucose by an Fasting Plasma Glucose level between 110 and 125 mg/dl. Impaired Fasting Glucose and Impaired glucose Tolerance could be observed

as intermediate stages in the hyperglycaemic disease reported in the Expert Committee Classification.[1 2]

IFG and IGT represent different pathophysiologic processes, even though these groups may overlap.[13] IFG and IGT cannot be interchanged, because patients with IFG did not always have IGT and the patients with IGT did not always have IFG, but both tests were useful in identifying the dysglycaemic conditions[12,13,14,15] .Patients with Impaired Fasting Glucose and IGT were considered as having a new condition referred to, for the first time, as prediabetes.[12]

According to the recommendations of the American Diabetes Association (ADA), FPG was the preferred test for diagnosing diabetes and prediabetes because of its ease of use, acceptability to patients, and lower cost. However, Expert committee stated that OGTT could be required when diabetes was still suspected despite a normal FPG level.[12]

1999 WHO REPORT ON DIAGNOSIS AND CLASSIFICATION OF DIABETES:

In the report published in 1999 the WHO adopted most of the above conclusions given by expert committee but stated that individuals with IFG should also undergo an OGTT to exclude IGT or diabetes[14.] IGT and IFG are not clinical entities in their own right, but rather risk categories for future diabetes and/or cardiovascular disease.

WHO also stated that IGT is often associated with the Metabolic Syndrome (Insulin Resistance Syndrome). IGT may not be directly involved in the pathogenesis of cardiovascular disease, but rather may serve as an indicator or marker of enhanced

risk by virtue of its correlation with the other elements of the metabolic syndrome. In 1999 the relationship between glucose intolerance cardiovascular disease was established by Coutinho M and colleagues in their study.[16] There is a progressive relationship between glucose levels below the diabetic threshold and cardiovascular complications because of the following reasons – glucose is related to atherosclerosis by causing oxidative stress, non-enzymatic glycation of LDL, non-enzymatic glycation of clotting factors and by forming advanced glycation end product formation in vessel wall and matrix.

2003 AMERICAN DIABETS ASSOCIATION GUIDELINES

The original Fasting Plasma Glucose range of 110 to 125mg/dL which was mentioned in 1997 expert committee recommendation, was further lowered in 2003 to 100 to 125 mg/dL so that the population's risk of developing diabetes with IFG would be similar to that with IGT.[17] Another effect of lowering the criterion for defining IFG was that individuals with IFG would more likely adopt earlier lifestyle interventions to reduce the potential risk of developing diabetes in the future.[17]

This lowering of IFG was not supported by WHO as it increased the prevalence by 5 fold dramatically in age group of 20-50yrs, 40% of all people above 65 yrs. happened to have IFG which had and an impact on the insurance companies who refused insurance benefits to the elderly with IFG.

2007 ADA EXPERT COMMITTEE REPORT ON DIAGNOSIS OF DIABETES BY HBA1C ASSAY AND IDENTIFICATION OF GROUP OF INDIVIDUALS AT INCREASED RISK OF DEVELOPING DIABETES.

The Expert committee for the first time recommended the use of the HBA1C to diagnose diabetes in its 2009 report.[18] Prior Expert Committees did not recommended use of the HbA1c for diagnosis of diabetes, in part due to lack of standardization of the assay. However, HbA1c assays are now highly standardized so that their results can be uniformly applied both temporally and across populations. It identified diabetic range of HBA1c as $\geq$6.5% but it did not formally identify an equivalent intermediate category for A1C to diagnose prediabetes. The group did note that those with A1C levels above the laboratory "normal" range-6% but below the diagnostic cut point for diabetes-6.5% (6.0 to 6.5%) are at very high risk of developing diabetes. Incidence of diabetes in people with A1C levels in this range-6%to6.5% is more than 10 times that of people with lower levels.[5]

2010 ADA CRITERION FOR DIAGNOSIS OF PRE DIABETES:

Prediabetes (IFG and/or IGT) should be viewed as a stage in the natural history of disordered glucose metabolism rather than as a distinctive clinical entity and it should be considered as a risk factor for (1) the development of diabetes (increased risk for diabetes) and (2) an increase in cardiovascular and possibly microvascular complications. The transition from prediabetes to diabetes may take many years but may also be rapid.[19, 20]

Criteria for prediabetes (categories of increased risk for diabetes) IFG: 100 to 125 mg/dl and /or IGT-Two-hour plasma glucose level after 75-g OGTT: 140 to 199 mg/dl, HbA1c: 5.7% to 6.4%.For all 3 tests, the ADA states that risk of developing diabetes and cardiovascular complications is present even below the lower limit of the cut off range of HBA1c, FBS and IGT and it becomes disproportionately greater at higher ends of the range. These conclusions were adopted by ADA from The International Expert Committee Report on the role of the A1C assay in the diagnosis of diabetes.[21]

2013:

Currently 2010 ADA guidelines are being followed.

EPIDEMIOLOGY OF PREDIABETES :

Prediabetes prevalence data of the world:

Numerous epidemiologic studies from many countries have documented the prevalence of IGT. These prevalence data are summarized in the International Diabetes Federation's (IDF's) Diabetes Atlas.[22] It is estimated that some 344 million people worldwide, or 7.9% in the age group of 20 to 79 years, have IGT in 2010. A vast majority of prediabetics were also found in low- and middle-income countries. By 2030, the number of people with IGT is projected to increase to 472 million, or 8.4% of the adult population. World estimates of IGT by the IDF (international diabetic federation) Region Prevalence: Africa- 8.1%, Europe- 8.9%,Middle East and North Africa -8.2%,North America and Caribbean- 10.4%, South and Central America 7.5%,Asia -6.2%, Western Pacific- 7.7%. The South-East Asian Region currently has the highest number of people with IGT with some 93 million and the highest prevalence rate with 13.2%.

Indian prevalence data:

The Indian prevalence is listed in the ICMR-INDIAB study. The results of the ICMR-INDIAB (Indian Council of Medical Research—India Diabetes) study released in 2011 for adults aged 20 and above showed that an average of 11% had pre-diabetes in India. The prevalence of pre-diabetes in urban areas was found to be higher (13.2%) than in rural areas (8.5%). The prevalence of prediabetes was 8.3%in Tamilnadu, 12.8% in Maharashrtra, 8.1% Jharkhand and 14.6% Chandigarah.[23] Maharashtra had 6 million individuals with diabetes and 9.2 million with prediabetes, Tamilnadu will have 4.8 million with diabetes and 3.9 million with prediabetes, Jharkhand will have 0.96 million with diabetes and 1.5 million with prediabetes, and

Chandigarh will have 0.12 million with diabetes and 0.13 million with prediabetes. Projections for the Southeast Asian population by 2025 is 13.5% ie.146 million people will have impaired glucose tolerance.[4]

Rural prevalence vs. urban prevalence:

Recently published data from a large population-based sample of more than 45,000 people 20 years and older in China found rates of IGT and IFG of 15.5% double the rate reported in the Diabetes Atlas. Rates of prediabetes were slightly higher in rural than in urban areas, the opposite of what has been reported in the past. The implication of these figures for the future burden of diabetes is of particular concern.

Prevalence of IFG vs. IGT:

The Diabetes epidemiology: Collaborative analysis of Diagnostic Criteria in Europe study-(DECODE) data show that in European people with a fasting plasma glucose level of 110–125 mg/dL, 64.8% have isolated IFG, 28.6% have IGT, and 6.6% actually have diabetes based on the 2-hour post–glucose-load plasma glucose level.[24] Similarly, Diabetes Epidemiology: Collaborative Analysis Of Diagnostic Criteria in Asia (DECODA) data show that among Asian people with a fasting plasma glucose level of 110–125 mg/dL alone, 45.9% have isolated IFG, 35.2% have IGT, and 18.9% have diabetes.[25]

Age and sex predisposition of prediabetes:

IGT is typically more common in women than in men, and the prevalence varies across age groups. In the Diabetes Epidemiology: Collaborative analysis of Diagnostic criteria in Europe (DECODE) study, the prevalence of isolated IGT is

2.9% in 30 to 39 year-old men , which increased to 15.1% in 70 to 79 year old men. The prevalence of prediabetes is 4.5% in 30 to 39 year old women and 16.9% in 70- to 79-year-old women.[24]A similar pattern was observed in Asian populations, with the prevalence of IGT increasing with age up to 70 to 89 years. However, some populations were different. For example, in India, where the overall prevalence of IGT is higher, there is not much change with age.[25]

Change in the prevalence data of prediabetes on repeating the blood glucose assay on the same individual within a span of 6 weeks:

The reproducibility of IGT values with retesting within 6 weeks is only moderate. If fasting plasma glucose test is repeated within 6 weeks, only 50% to 60% of the patients classified as having IFG on the first test will be having IFG on repeat test. The rest will be reclassified as normal and less than 10% as having diabetes with repeat testing.[26] Similarly, in the proportion of people diagnosed with IGT on the first oral glucose tolerance test (OGTT), on retesting with OGTT only in 33% to 48% of them were found to be having IGT, with 39% to 46% being reclassified as normal and 6% to 13% as having diabetes on repeat testing.[26]

ETIOLOGY OF DIABETES:

Diabetes mellitus (DM) comprises a group of metabolic disorders that share the common phenotype of hyperglycaemia. DM is currently classified on the basis of the pathogenic process that leads to hyperglycaemia. Type 1 DM is characterized by insulin deficiency and a tendency to develop ketosis, whereas type 2 DM is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and excessive hepatic glucose production.[27]

Other specific types include DM caused by genetic defects [maturity-onset diabetes of the young (MODY)], diseases of the exocrine pancreas (chronic pancreatitis, cystic fibrosis, hemochromatosis), endocrinopathies (acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism), drugs (nicotinic acid, glucocorticoids, thiazides, protease inhibitors), and pregnancy (gestational DM).[27]

ETIOLOGIC CLASSIFICATION OF DIABETES MELLITUS[27]

I. TYPE 1 DIABETES (²-cell destruction, usually leading to absolute insulin deficiency)

A. Immune mediated

B. Idiopathic

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

III. OTHER SPECIFIC TYPES

A. Genetic defects of ²-cell function

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

B. Genetic defects in insulin action

1. Type A insulin resistance
2. Leprechaunism
3. Rabson-Mendenhall syndrome
4. Lipoatrophic diabetes
5. Others

C. Diseases of the exocrine pancreas

1. Pancreatitis

2. Trauma/pancreatectomy

3. Neoplastic

4. Cystic fibrosis

5. Hemochromatosis

6. Fibrocalculous pancreatopathy

7. Others

D. Endocrinopathies

1. Acromegaly

2. Cushing's syndrome

3. Glucagonoma

4. Pheochromocytoma

5. Hyperthyroidism

6. Somatostatinoma

7. Aldosteronoma

8. Others

E. Drug or chemical induced

1. Vacor

2. Pentamidine

3. Nicotinic acid

4. Glucocorticoids

5. Thyroid hormone

6. Diazoxide

7. β 2-adrenergic agonists

8. Thiazides

9. Dilantin

10. Gamma-Interferon

11. Others

F. Infections

1. Congenital rubella

2. Cytomegalovirus

3. Others

G. Uncommon forms of immune-mediated diabetes

1. “Stiff-man” syndrome

2. Anti-insulin receptor antibodies.

H. Other genetic syndromes sometimes associated with diabetes

1. Down syndrome

2. Klinefelter syndrome

3. Turner syndrome

4. Wolfram syndrome

5. Friedreich ataxia

6. Huntington chorea

7. Laurence-Moon-Biedl syndrome

8. Myotonic dystrophy

9. Porphyria

10. Prader-Willi syndrome

IV. GESTATIONAL DIABETES MELLITUS

VASCULAR COMPLICATIONS IN PREDIABETES

- **Microvascular**
- Eye disease
  - Retinopathy (non-proliferative/proliferative)
  - Macular edema
- Neuropathy
  - Sensory and motor (mono- and polyneuropathy)
  - Autonomic
- Nephropathy
- **Macrovascular**
- Coronary heart disease
- Peripheral arterial disease
- Cerebrovascular disease

Macrovascular complication: Numerous reports have documented that macrovascular complication like Cardiovascular Disease risk is increased in prediabetes (impaired glucose tolerance [IGT] and impaired fasting glucose [IFG]) by 10% to 40% compared with populations with normal glucose regulation.[28, 29] CVD risk in individuals with prediabetes may be increased further by the coexistence of other metabolic syndrome components like obesity, dyslipidaemia, and hypertension. [30] Some studies have shown that the metabolic syndrome components are more pronounced in IGT than in IFG.[31, 32]

Microvascular complications:

Risk to develop microvascular complications like retinopathy, nephropathy, and neuropathy is present prediabetes. The pathogenesis of the microvascular complications of diabetes is related to duration and severity of hyperglycaemia and the presence of other metabolic factors. Hyperglycaemia following OGTT i.e. IGT, is characterized by greater skeletal muscle (peripheral) insulin resistance and compensatory hyperinsulinemia which predisposes to microvascular complications. In contrast IFG is associated with hepatic insulin resistance and excessive endogenous glucose production unlike IGT where the patients have insulin resistance.[33] Individuals with combined IGT and IFG seem to have a more severe metabolic defect, higher risk of progression to diabetes and a more adverse CVD and microvascular complication risk profile.[32]

PATHOGENESIS OF DEVELOPMENT OF CVD IN INSULIN RESISTANCE/HYPERINSULINEMIA:

Insulin resistance is characteristic of prediabetes (especially IGT) and insulin resistance is a CVD risk factor. The following paragraph explains how insulin resistance acts as a risk factor in the development of CVD.

ATEROSCLEROSIS: The insulin causes signalling of phosphatidyl inositol 3-kinase (PI 3-kinase) which regulates the production of nitric oxide (NO) from the endothelium via stimulation of endothelial nitric oxide synthase (eNOS) activity. Nitric oxide synthesised from endothelium has multiple roles in vascular physiology, including vasodilation, inhibits vascular smooth muscle proliferation, and inhibition of expression of cellular adhesion molecules (e.g., vascular cell adhesion molecule 1 [VCAM-1], e-selectin) that are involved in initiation of atherosclerotic plaque formation, Nitric oxide has anti- atherosclerotic action.[34] Nitric oxide also acts locally to inhibit platelet aggregation. The production of Nitric oxide is impaired in states of insulin resistance because the endothelial cells are resistant to insulin action and hence signalling via the PI 3-kinase pathway is impaired. Hence Nitric oxide is not produced from the endothelium thus leading to attenuation of Nitric Oxide's beneficial vascular effects leading to atherosclerosis.

Other pathogenesis of vascular complications is as follows: Mitogen-activated protein kinase (MAP-kinase) pathway mediates the growth-promoting effects of insulin and remains intact in insulin-resistant states unlike PI 3 –Kinase pathway. When there is insulin resistance there is compensatory hyperinsulinemia, and thus promotion of mitogenesis (cell proliferation), increased smooth muscle proliferation

and vasoconstriction and other factors that promote atherosclerosis ultimately leading to vascular complications.

IMPAIRED INSULIN-MEDIATED GLUCOSE TRANSPORT INTO MYOCYTES:

In addition to its effects on the endothelium, insulin resistance may also have direct effects on the myocardium. In normal conditions, energy for myocardial contraction is obtained from oxidation of free fatty acids (in the fasting state) or glucose (in the fed state). During myocardial ischemia, glucose seems to be the preferred substrate for energy production. But in the presence of insulin-resistance there is impaired insulin-mediated glucose transport into myocytes, which has been proposed as a mechanism contributing to the occurrence of cardiac events and poor outcomes in insulin-resistant individuals.[35] Alterations in insulin-mediated changes in myocardial blood flow may also predispose to ischemic events.[36]

Endothelial dysfunction:

Endothelial dysfunction is the initiating factor in the development of atherosclerosis. There is also evidence that dyslipidemia, including the increased levels of free fatty acids in patients with obesity coexisting with prediabetes, further reduces Nitric oxide availability by generation of reactive oxygen species (ROS), which act by absorbing Nitric oxide.

THROMBOSIS AND FIBRINOLYSIS:

In prediabetes there is increased levels of plasminogen activator inhibitor-1 (PAI-1),which results in impaired fibrinolysis, thus tipping the balance in favour of thrombosis. PAI-1 levels are closely associated with obesity and insulin resistance. Increased PAI level also predicts the development of type 2 diabetes.[38, 39]

There is substantial evidence for prothrombosis in prediabetes and the metabolic syndrome.[40]

HYPERGLYCEMIA CONTRIBUTING TO VASCULAR DAMAGE:

The processes by which hyperglycaemia per se contributes to vascular damage are multiple and complex. Studies in vitro have shown that high glucose exposure results in activation of the pro-inflammatory transcription factor-NF-kB, production of advanced glycation end products, generation of Reactive oxygen species, enhanced monocyte adhesion to endothelial cells, and inhibition of NO production.[40]All these factors contribute to atherosclerosis. Increased ROS generation further leads to oxidation of LDL, rendering it significantly more atherogenic.

Hyperglycaemia also seems to induce a prothrombotic state by inducing platelet activation and increasing the synthesis of PAI-1, the mechanism by which PAI-1 causes thrombosis was explained previously. Overproduction of superoxide by the mitochondrial electron transport chain, has been proposed as the key process involved in vascular damage.[41]

NEPHROPATHY:

Diabetic nephropathy is the leading cause of ESRD and a leading cause of DM-related morbidity and mortality. Both microalbuminuria and macroalbuminuria in individuals with DM are associated with increased risk of cardiovascular disease. Individuals with diabetic nephropathy commonly have diabetic retinopathy. Like other microvascular complications, the pathogenesis of diabetic nephropathy is related to chronic hyperglycaemia. The mechanisms by which chronic hyperglycaemia leads to ESRD, though incompletely defined, involve the effects of soluble factors (growth factors, angiotensin II, endothelin, AGEs), hemodynamic alterations in the renal

microcirculation (glomerular hyperfiltration or hyperperfusion, increased glomerular capillary pressure), and structural changes in the glomerulus (increased extracellular matrix, basement membrane thickening, mesangial expansion, fibrosis). Some of these effects may be mediated through angiotensin II receptors. [27]

Smoking accelerates the decline in renal function. Because only 20–40% of patients with diabetes develop diabetic nephropathy, additional susceptibility factors remain unidentified. One known risk factor is a family history of diabetic nephropathy. Glomerular hyperperfusion and renal hypertrophy occur in the first years after the onset of DM and are associated with an increase of the GFR. During the first 5 years of DM, thickening of the glomerular basement membrane, glomerular hypertrophy, and mesangial volume expansion occur as the GFR returns to normal. After 5–10 years of type 1 DM, 40% of individuals begin to excrete small amounts of albumin in the urine. Microalbuminuria is defined as 30–299 mg/d in a 24-h collection or 30–299 g/mg creatinine in a spot collection (preferred method). Once macroalbuminuria is present, there is a steady decline in GFR, and 50% of individuals reach ESRD in 7–10 years. [27]

Once macroalbuminuria develops, blood pressure rises slightly and the pathologic changes are likely irreversible. Impaired glucose regulation is associated with albuminuria and renal dysfunction. The National Health and Nutrition Examination Survey (NHANES) data from 1999 to 2006 revealed that the prevalence of chronic kidney disease (urinary albumin/creatinine ratio of >30 mg/g or eGFR <60 mL/min per 1.73 m^2) was 17% in those with IFG compared with 12% in those with NGT.[42]

There seems to be a threshold effect for this phenomenon, with a doubling in prevalent albuminuria (to 20%) at a HbA1c level of 6.1%.[43] Microalbuminuric subjects with IGT or IFG have significantly higher eGFR compared with those with Normal Glucose Tolerance, suggesting that the hyperfiltration associated with early diabetic nephropathy exists even in the prediabetic state.[44] Albuminuria is also a predictor of CVD events and mortality, even in the absence of progression to clinical nephropathy.[45,46]

RETINOPATHY

DM is the leading cause of blindness between the ages of 20 and 74 in the. The gravity of this problem is highlighted by the finding that individuals with DM are 25 times more likely to become legally blind than individuals without DM. Blindness is primarily the result of progressive diabetic retinopathy and clinically significant macular oedema. Diabetic retinopathy is classified into two stages: non-proliferative and proliferative. Non-proliferative diabetic retinopathy usually appears late in the first decade or early in the second decade of the disease and is marked by retinal vascular micro aneurysms, blot haemorrhages, and cotton-wool spots. Mild non-proliferative retinopathy progresses to more extensive disease, characterized by changes in venous vessel calibre, intraretinal microvascular abnormalities, and more numerous micro aneurysms and haemorrhages.[27]

The pathophysiologic mechanisms invoked in non-proliferative retinopathy include loss of retinal pericytes, increased retinal vascular permeability, alterations in retinal blood flow, and abnormal retinal microvasculature, all of which lead to retinal ischemia. The appearance of neovascularization in response to retinal hypoxemia is the hallmark of proliferative diabetic retinopathy. These newly formed vessels appear

near the optic nerve and/or macula and rupture easily, leading to vitreous haemorrhage, fibrosis, and ultimately retinal detachment. Not all individuals with non-proliferative retinopathy develop proliferative retinopathy, but the more severe the non-proliferative disease, the greater the chance of evolution to proliferative retinopathy within 5 years. This creates an important opportunity for early detection and treatment of diabetic retinopathy.[27]

Clinically significant macular oedema can occur when only non-proliferative retinopathy is present. Fluorescein angiography is useful to detect macular edema, which is associated with a 25% chance of moderate visual loss over the next 3 years. Duration of DM and degree of glycaemic control are the best predictors of the development of retinopathy; hypertension is also a risk factor. Non-proliferative retinopathy is found in many individuals who have had DM for >20 years (25% incidence with 5 years, and 80% incidence with 15 years of type 1 DM). Although there is genetic susceptibility for retinopathy, it confers less influence than either the duration of DM or the degree of glycaemic control.[27]

The prevalence of typical early diabetic retinopathy in populations with prediabetes has been reported to be as high as 8%, with higher rates observed with more severe hyperglycaemia (combined IFG and IGT).[47] However, the clinical significance of retinopathy in prediabetes is uncertain, because it is described in most studies as very mild, often a single microaneurysm or haemorrhage that may regress during follow-up.[48]

NEUROPATHY

The most common form of diabetic neuropathy is distal symmetric polyneuropathy. It most frequently presents with distal sensory loss, but up to 50% of patients do not have symptoms of neuropathy. Hyperesthesia, paresthesia, and dysesthesia also may occur. Any combination of these symptoms may develop as neuropathy progresses. Symptoms may include a sensation of numbness, tingling, sharpness, or burning that begins in the feet and spreads proximally. Neuropathic pain develops in some of these individuals, occasionally preceded by improvement in their glycaemic control. Pain typically involves the lower extremities, is usually present at rest, and worsens at night. Both an acute (lasting <12 months) and a chronic form of painful diabetic neuropathy have been described. As diabetic neuropathy progresses, the pain subsides and eventually disappears, but a sensory deficit in the lower extremities persists.[27]

Physical examination reveals sensory loss, loss of ankle reflexes, and abnormal position sense. Diabetic polyradiculopathy is a syndrome characterized by severe disabling pain in the distribution of one or more nerve roots. It may be accompanied by motor weakness. Intercostal or truncal radiculopathy causes pain over the thorax or abdomen. Involvement of the lumbar plexus or femoral nerve may cause severe pain in the thigh or hip and may be associated with muscle weakness in the hip flexors or extensors (diabetic amyotrophy). Fortunately, diabetic polyradiculopathies are usually self-limited and resolve over 6–12 months. Mononeuropathy (dysfunction of isolated cranial or peripheral nerves) is less common than polyneuropathy in DM and presents with pain and motor weakness in the distribution of a single nerve.

A vascular etiology has been suggested, but the pathogenesis is unknown. Involvement of the third cranial nerve is most common and is heralded by diplopia. Physical examination reveals ptosis and ophthalmoplegia with normal pupillary constriction to light. Sometimes other cranial nerves IV, VI, or VII (Bell's palsy) are affected. Peripheral mononeuropathies or simultaneous involvement of more than one nerve (mononeuropathy multiplex) may also occur.[27]

AUTONOMIC NEUROPATHY

Individuals with long-standing type 1 or 2 DM may develop signs of autonomic dysfunction involving the cholinergic, noradrenergic, and peptidergic (peptides such as pancreatic polypeptide, substance P, etc.) systems. DM-related autonomic neuropathy can involve multiple systems, including the cardiovascular, gastrointestinal, genitourinary, sudomotor, and metabolic systems. Autonomic neuropathies affecting the cardiovascular system cause a resting tachycardia and orthostatic hypotension. Reports of sudden death have also been attributed to autonomic neuropathy.

Gastroparesis and bladder-emptying abnormalities are often caused by the autonomic neuropathy seen in DM (discussed below). Hyperhidrosis of the upper extremities and anhidrosis of the lower extremities result from sympathetic nervous system dysfunction. Anhidrosis of the feet can promote dry skin with cracking, which increases the risk of foot ulcers. Autonomic neuropathy may reduce counterregulatory hormone release (especially catecholamines), leading to an inability to sense hypoglycemia appropriately (hypoglycemia unawareness), thereby subjecting the patient to the risk of severe hypoglycemia and complicating efforts to improve glycemic control.[27]

Peripheral and autonomic neuropathies have been found in association with prediabetes, with the prevalence appearing to be higher in prediabetes (13% and 11.3% in IGT and IFG, respectively), compared with age-matched Normal Glucose Tolerance subjects (7.4%).[49] The precise prevalence is difficult to estimate because the neuropathy caused by diabetes is not distinct in its symptoms or examination findings from neuropathies from other causes. Neuropathy occurring in prediabetes generally affects small unmyelinated or lightly myelinated axons that transmit pain and autonomic signals.[50]

PATHOPHYSIOLOGY OF PREDIABETES:

GLUCOSE HOMEOSTASIS:

The glucose system is highly homeostatic. Alterations in plasma glucose concentrations rarely exceed 54 mg/dL in normal people. At any given time, the plasma glucose concentration represents a balance between entry of glucose into and exit from the circulation via cellular metabolism or excretion; excessive release or defective removal (or combinations of the two) results in increasing glucose levels. Entry and exit of glucose are subject to multiple regulatory mechanisms, with insulin and glucagon principally controlling entry and insulin governing exit.

A preliminary consideration is the unique organization of the insulin/glucagon system. The action of hormones is modulated by at least 1, often 2, hierarchical hormonal feedback pathway (example: Corticotropin-releasing hormone and adrenocorticotropic hormone for cortisol, gonadotropin-releasing hormone and gonadotropins for sex steroids). In these cases, the hormone action is brought about by the circulating hormone concentrations acting on specific hormone receptors located on target tissues as well as on the master gland of the feedback loop (example: the pituitary). In the case of insulin and glucagon, there is no major pituitary or hypothalamic relay; target tissues control secretion directly. Thus, the circulating concentrations of substrates i.e. glucose, amino acids, free fatty acids and ketone bodies is regulated by insulin action on the target receptors.

Sensitivity gating is provided by insulin and glucagon receptors on target tissues. An additional level of regulation is paracrine in nature, i.e., insulin receptors on the β-cell and the α-cell.

PATHOPHYSIOLOGY OF INCREASED GLUCOSE RELEASE IN PREDIABETES:

Under normal circumstances of a short (10–14 hours) overnight fast, most glucose is produced by the liver, with the kidney making a marginal contribution.[51] Within the liver, glucose is both synthesized and taken up by gluconeogenesis and glycogenolysis respectively. With the use of labelled glucose, the amount of glucose released in the fasting state (endogenous glucose production, EGP) can be measured. In non-diabetic healthy men and women with normal glucose tolerance (NGT) and in individuals with either impaired fasting glucose (IFG, fasting glucose between 110–126 mg/dL and a 2-hour glucose level less than 200 mg/dL on OGTT) or impaired glucose tolerance, Endogenous Glucose Production is dependent on free fat-mass and plasma glucose concentration.

Endogenous Glucose Production depends upon the mass of metabolically active tissues: the larger the mass, the higher EGP. When fat mass increases example, during phases of weight gain, glucose consumption increases proportionately and minimally, resulting chronic reductions in blood glucose levels. Hence the liver releases more glucose by autoregulation[52]; other metabolic factors, for example, circulating FFAs, may also contribute to increased glucose release.

As individuals with IFG/IGT frequently have higher body mass index than those with NGT, their EGP tends to be higher, especially in individuals with IFG. If the adaptive changes in EGP were perfect, FPG would be identical in individuals with IFG/IGT and in those with NGT. As this is not the case, fasting glycaemia is significantly higher in individuals with IFG/IGT than in those with NGT. The reason for this response is insulin resistance. In fact, fasting plasma insulin concentrations are

significantly higher in individuals with IFG/IGT than in those with NGT indicating that the ability of the insulin to reduce EGP is impaired.[53] once overt diabetes ensues, EGP further increases, especially in poorly controlled patients.[54, 55]

During absorption of a glucose load or a mixed meal, EGP is substantially suppressed in individuals with NGT.[56] But this suppression does not occur in patients with diabetes.[57] The prediabetes is an intermediate condition where EGP is suppressed to normal levels but this suppression of EGP occurs only at higher prevailing plasma insulin concentrations in prediabetes. This occurs because the insulin release to block postprandial glucose output will be lacking. In addition the postprandial hyperglycaemia insufficiently inhibits glucagon and in fact, glucagon may increase paradoxically.[58, 59]

Insulin-mediated glucose uptake by the liver is impaired in patients with type 2 diabetes, as severity of hyperglycaemia increases glucose uptake by liver proportionally reduces.[60] A lesser extent of impairment is present in prediabetes, although this has not been directly determined in these patients. In the liver of the prediabetic patients, insulin resistance is manifested as a reduced ability of insulin to restrain glucose release, especially from gluconeogenesis, and reduced ability to stimulate glucose uptake.

In recent years, it has become evident that body fat distribution is an additional factor in the control of EGP (and in general, of liver function). Independent of total body fat mass, accumulation of adipose tissue within the visceral/abdominal region and the liver is associated with an accentuation of insulin resistance of

gluconeogenesis.[61] Inflammatory changes in adipose depots and consequent release of inflammatory cytokines are probable mechanisms for insulin resistance.[62]

PATHOPHYSIOLOGY OF DEFECTIVE GLUCOSE DISPOSAL IN PREDIABETES:

Peripheral insulin resistance is an important metabolic feature of prediabetes independent of factors, such as gender, age, and obesity, which themselves affect insulin action. Even in subjects with NGT, individuals with higher glucose increments during a standard dynamic test such as the OGTT are more insulin resistant than those whose glucose levels are lower.

As skeletal muscle represents approximately 40% of body weight, it becomes a major tissue responsible for mediating impaired insulin-mediated glucose uptake.[63] However; adipose tissue makes a significant contribution to whole body glucose disposal, as demonstrated by an 18FDG-PET study,[64] especially in an overweight phenotype as the prediabetic individual.

PATHOPHYSIOLOGY OF DEFECTIVE BETA-CELL FUNCTION IN PREDIABETES:

Plasma glucose concentrations increase minimally even in the presence of profound insulin resistance as long as the β-cell response is adequate; the hyperglycaemia that defines prediabetes ensues only when some critical aspect of β-cell function becomes defective. The normal β-cell adaptive response to insulin resistance is an up regulation of its set point and increasing insulin secretion. At each

plasma glucose concentration there is higher insulin secretion rates, in insulin-resistant individuals than in insulin-sensitive individuals.

The cause of hyperglycaemia is the reduced ability of the b-cell to respond to increasing glucose levels in a timely fashion during stimulation, which is clearly shown when plotting insulin secretion rates against concomitant glucose levels. For each increment in glucose concentration during an OGTT, insulin secretion is less in prediabetic states than in NGT states.[65]

The two main pathophysiologic defects responsible for the loss of glucose tolerance are insulin resistance and beta-cell glucose insensitivity. Both of these pathophysiologic mechanisms tend to occur together in prediabetes as well as overt diabetes.[66]

Insulin resistance, at the level of the liver and peripheral tissues, and defective glucose sensing at the β-cell are the central pathophysiologic determinants that together cause and predict hyperglycaemia. Although genetic influences affect beta-cell function, becoming overweight is the main acquired challenge to insulin action.[67]

Treatment of prediabetes

Screening should be done in all adults who are overweight (body mass index [BMI] 25 kg/m^2) and have other risk factors. In adults with normal weight and without any risk factors, screening must begin at age 45. Fasting plasma glucose (FPG), HbA1c, or OGTT can be used for the screening purpose. If the screening test is normal, then screening should be repeated every 3 years.

TREATMENT OF PREDIABETES INVOLVES THE FOLLOWING:

- Lifestyle modification
- Metformin
- Thiazolidinediones
- Enteric enzyme inhibitors
- Surgical approaches.

1) LIFESTYLE MODIFICATION:

Lifestyle modification with mild to moderate calorie reduction with or without exercise demonstrates the most consistent and reproducible reduction in diabetes progression. Many studies have shown that there is almost a 51% reduction in risk of development of diabetes in the later life if lifestyle modifications are implemented in the prediabetic patients. Indian Diabetes Prevention Program (IDPP) study[68] and the Finnish study[69] provides robust and reproducible evidence of the efficacy and generalizability of lifestyle modification in different age, ethnic, and socioeconomic populations.

2) METFORMIN THERAPY:

Metformin is a biguanide that reduces hepatic glucose production and causes mild weight loss, has been studied in Indian Diabetic Prevention Program(IDDP).[68] The IDPP, recommended using a dose of 850 mg twice a day, noted a 31% reduction in diabetes conversion compared with placebo in the core study. Detailed predefined analysis of the DPP database showed metformin effective in preventing diabetes,

particularly in younger individuals, those with a BMI greater than 35, and women with a history of Gestational diabetes mellitus .Using a lower dose of 250 mg of metformin showed a reduction in risk of development of diabetes by 26%.

3) THIAZOLID INIDIONES:

This class of drugs improves insulin sensitivity, despite causing weight gain. The studies which support this treatment modality are Troglitazone in the Prevention of Diabetes (TRIPOD) [70] study of women with a history of GDM and Act Now for the Prevention of Diabetes Trial (ACTNOW Trial).[71]

4) ENTERIC ENZYME INHIBITORS:

Enteric enzyme inhibitors like, Acarbose, an alpha-glucosidase inhibitor, not only reduced the incidence of diabetes by 25% but also suggested a positive impact on the development of CVD events, in the Study to Prevent Noninsulin-Dependent Diabetes Mellitus (STOP-NIDDM).[72] Orlistat blocks fat absorption, resulting in weight loss either through steatorrhea or through behaviour modification of eating behaviour. In the Prevention of Diabetes in Obese Subjects Study, [73] Orlistat reduced diabetes incidence by 37% but was severely limited by gastrointestinal side effects.

5) SURGICAL APPROACHES:

Bariatric surgical approaches intend to affect weight loss by limiting calorie intake via mechanical obstruction or by impairing nutrient absorption through intestinal bypass. Significant weight loss is seen in most subjects able to tolerate the procedures. Bypass procedures also result in significant incretin hormone changes with remarkable increases in glucagon-like peptide well before weight loss occurs.

Some reports of gastric bypass surgery reported reversion to normal glucose tolerance in 78% of individuals with diabetes and 98% of those with IGT.[74]

6) TREATMENT RECOMMENDATIONS FOR PREDIABETES BY ADA:

Lifestyle modification and/or metformin for IFG and/or IGT and at least one of the following: age <60 y, BMI >35 kg/m^2, family history of diabetes in first-degree relatives, elevated triglycerides, reduced HDL-C, hypertension, HbA1c >6.0%.

TREATMENT RECOMMENDATIONS FOR PREDIABETES BY INDIAN HEALTH SERVICES GUIDELINES FOR CARE OF ADULTS WITH PREDIABETES AND/OR THE METABOLIC SYNDROME IN CLINICAL SETTING:

Lifestyle changes, Consideration of metformin on an individualized basis, depression screening and cardiovascular risk reduction also recommended.

If we fail to detect prediabetes in the early stage and implement lifestyle modifications and pharmacotherapy according to the guidelines, we as physicians will be contributing to the global burden of diabetes. By diagnosing and implementing treatment we can reduce almost 50% risk of future development of diabetes.

HBA1C

Hemoglobin A (Hb A) constitutes 90% hemoglobin of adults and children above 6 months age. When Hb A is passed through a chromatographic column it separates into Hb AO, the major component and minor components – Hb A1A, HbA1B and HbA1C collectively called Hb A1.37 HbA1c is the most abundant of the minor hemoglobin components. This is structurally identical to Hb A, except for a hexose group linked to the N-terminal amino acid (valine) of the beta chain. Hence, this is called "Glycosylated hemoglobin" or HbA1c.[75]

RELATION HBA1C TO DIABETIC HYPERGLYCAEMIA.[75,76,77]

From structural and biosynthetic information available this is clear that HbA1c is formed slowly and almost irreversibly by the condensation of glucose and Hb in RBC. With simultaneous accumulation of HbA1c, it is evident that the amount of this component should be a reflection of average glucose concentration seen by the RBCs during their life span. Direct evidence for this relationship derives from atleast three lines of evidence which include

1. A reduction of HbA1c levels after diabetic patients are brought under optimal blood glucose control.
2. A plethora of studies which demonstrate a relationship between HbA1c levels and a variety of indices of diabetic glycaemia and
3. Excellent correlations between clinical evaluation of the patients level of control and HbA1c level.

METHODS FOR MEASURING GLYCOSYLATED HEMOGLOBIN [76,78,79,80]

1. Chromatographic method (Kynoch and Lehmann)

2. Colorimetric Method (Fluckiger and Winterhalter).

3. Electrophoretic method

4. Radio Immuno Assay.

Among these, chromatographic method has been widely used to estimate HbA1c. It is a simple and rapid method (microchromatography). It has better resolution and more precision. It requires small amount of sample and no special equipment. Its cost and use of cyanide as buffer are the main disadvantages.

Ion exchange chromatographic method has been used in this study. The principle and the procedures of the method are dealt below.

Principle

Whole blood is mixed with a lysing reagent to prepare a hemolysate. This is then mixed with a weakly binding cation exchange resin. The non-glycosylated haemoglobin binds to resin leaving Glycosylated Hemoglobin (HbA1c) free in the supernatant. The HbA1c % is determined by measuring the absorbance of the HbA1c fraction and of the total Hb.

Reagents and apparatus

1. Ion exchange Resin (Bio-Rex 70)

2. Hemolysing Reagent

    0.3 g white saponin

    0.5 g potassium cyanide

    Dissolved in a Buffer pH 6.7 to make 1 litre

3. Control (lyophilized).

4. Apparatus – Plastic Tubes and Resin Separators.

Specimen

Whole blood is collected in EDTA bulb. Heparin may also be used. HbA1c in blood is found to be stable for one week at 2-8^{O}C.

Equipment Required

1. Spectrophotometer/photocolorimeter

2. Cuvettes

3. Test tubes

4. Vortex Mixer

5. Pipettes and Micropipette.

Reagent Preparation

Reagents 1 and 2 are ready to use. HbA1c control (3) is dissolved in 1 ml. of deionized water by inverting / swirling. Reconstituted control is stable for 30 minutes only at Room temp or 15 days at -20^{0}C.

Procedure

Assay Temperature: 23 ± 2^{0}C

Wave length: 415 nm (Hg 405 nm)

Step 1: Hemolysate preparation

1. 0.5ml of lysing reagent (2) is pipetted into a test tube.

2. To it 0.1ml of well mixed whole blood sample is to be added.

3. Mixed and allowed to stand at room temperature for 5 minutes.

Step 2: Hb A1C Separation and Assay.

1. 3.0 ml of Ion Exchange Resin (1) is pipetted into the plastic tube which was mixed well before use.

2. 1.0ml of the hemolysate is added (from step 1)

3. The resin separator is positioned in the plastic tube so that the rubber sleeve is approximately 2 cms above the liquid level.

4. Plastic tube is placed on cortex mixer and is mixed for 5 minutes.

The resin separator is pushed down in the plastic tube until the resin is firmly packed.

6. The supernatant is poured directly into a cuvette and absorbance is measured against deionized water within 60 minutes.

Step: 3 Total Hemoglobin (THB) Assay

1. 5.0ml of deionized water is pipetted into test tube.

2. 0.02ml of hemolysate (from step 1) is pipetted into it.

3. Mixed and absorbance is read against deionized water within 60 minutes.

Calculations

$$\text{HbA1c \%} = \frac{\text{Absorbance of HbA1c}}{\text{Absorbance of THb}} \times 10 \times \text{Temp. Factor (Ff)}$$

Tf for Assay at $23 \pm 20^{C} = 1.0$

Tf for Assay at $300^{C} = 0.7$

Finally, the pooled information is analysed using appropriate statistical methods.

The interpretation of HbA1c test in this study is as follows:

Normal = 4 - 6%

Good Control = 6.1 - 7%

Fair Control =7.1 - 8%

Poor Control => 8%

MATERIALS AND METHODS

SOURCE OF DATA:

The patients and the bystander accompanying the patient, attending to medicine OPD and admitted to B.L.D.E.U's Shri. BM Patil Medical College Hospital and Research Centre, Bijapur, who fulfill the inclusion criteria from October 2011 to April 2013, are studied.

SAMPLE SIZE:

The detection rates of prediabetes by fasting blood glucose is 26.2%, HbA1C is 14.2%, combined detection rate of HbA1c and Fating Blood Glucose is 32.2%.[6]

Considering 95% confidence interval the sample size calculated,

$$n = \frac{(Z_\alpha + Z_\beta)^2 P(1-P)}{d^2} \times 2$$

$$P = \frac{(26.2+14.2)}{2} = 20.2\%$$

Z_α= for α=1.96

Z_β= for β=1.282

d= difference between two methods

n=23. Hence, the minimum of 235 cases will be included in the study to compare individual detection rates of HBa1c and Fasting blood glucose with their combined prediabetes detection rates.

STATISTICAL ANALYSIS:

Detection rate of FBS is calculated.

Detection rate of HBA1C is calculated.

Combined detection rate of both FBS and HA1c is calculated.

7.2 METHOD OF COLLECTION OF DATA

A detailed history, physical and systemic examination will be performed on all bystanders accompanying the patient to the hospital who are of age ≥45 yrs. with known risk factors for developing diabetes.

The biochemical investigations like estimation of HbA1c and Fasting Blood Glucose, Lipid profile, serum creatinine will be conducted. Other investigations like, Hb% and peripheral smear study to rule out any abnormalities of hemoglobin and iron deficiency.

INCLUSION CRITERIA:

The patient as well as the by standers accompanying the patients to medicine outpatient department irrespective of their gender.

1. Age ≥45 yrs.
2. BMI≥25kg/m^2
3. First degree relative with diabetes.
4. History of gestational diabetes.
5. Hypertension.

6. Dyslipidemia.
7. History of cardiovascular disease.

EXCLUSION CRITERIA:

Factors that affect HbA1C:

1. Acute blood loss.
2. Renal failure.
3. Patients on aspirin.
4. Iron deficiency anemia.
5. Erythrocyte abnormalities.
6. Patients with overt type II DM.
7. Patients on ART drugs.
8. Chronic liver disease.
9. Pregnancy.

Factors that affect glucose concentration:

1. Major surgery.
2. Drugs like corticosteroids, sympathomimetic, Isoniazid, Niacin.
3. Prolonged fasting or starvation.
4. Sepsis.

5. Oral hypoglycemic agents.

6. Antibiotics.

7. Chloroquine and quinine.

8. Acetaminophen overdose.

9. Alcohol.

METHOD OF TEST

SAMPLE COLLECTION

Oral and written consent will be taken from the subjects prior to the collection of specimens. Approximately 5 ml of venous blood will be collected from each subject and transported to the laboratory**.**

HBA1C ESTIMATION:

IMMUNO CHROMATOGRAPHIC METHOD: 2 ml of venous blood sample is taken and RBC's are lysed, the labile part is eliminated, haemoglobins are retained by a cationic exchange resin. Haemoglobin A1C is specifically eluted after washing away haemoglobin 1a+b fraction and is quantified by direct photometric reading at 415 nm. The estimation of relative concentration of Hba1c is made by the measure of total haemoglobin concentration by direct photometric reading at 415 nm. The estimation of the relative concentration of haemoglobin A1C is made by the measure of total haemoglobin concentration by direct photometric reading at 415 nm**.**

ESTIMATION OF FASTING BLOOD GLUCOSE.

It is estimated by GOD-PAP method. This test is done by enzymatic colorimetric determination of glucose according to the following reaction.

$$\text{Glucose} + O_2 \longrightarrow \text{Gluconic acid} + H_2O_2$$

$$2H_2O_2 + \text{Phenol} + \text{4-Aminoantipyrine} \xrightarrow{\text{peroxidase}} \text{Red Quinonimine} + 4H_2O$$

INVESTIGATIONS

All the subjects are subjected to the following investigations

- Hb%, Peripheral Smear Study.
- Serum creatinine.
- Fasting blood glucose
- HbA1C.
- Serum creatinine.
- Lipid profile.

OBSERVATION AND RESULTS

OBSERVATIONS: Out of 235 patients:

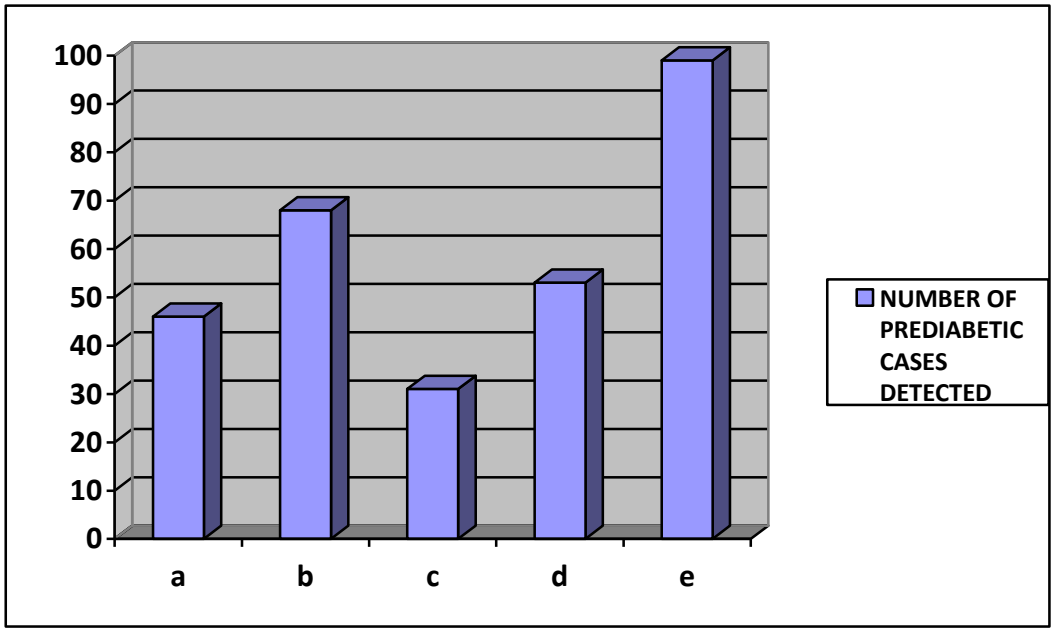
a) No. of patients of prediabetes detected by HBA1c- 46.

b) No. of patients of prediabetes detected by FBS- 68.

c) No. of patients detected by HBA1C but missed by FBS-31.

d) No. of patients detected by FBS but missed by HBA1C- 53.

e) Combined detection by FBS + HBA1C– 99.

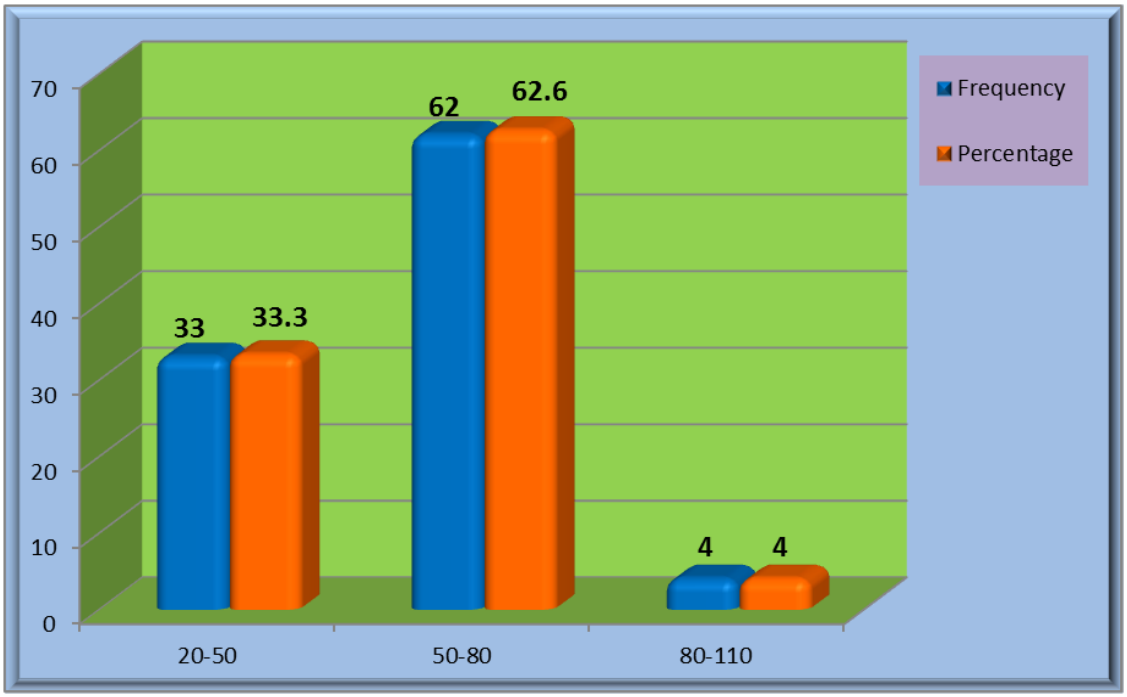


Bar chart representing the number of patients of prediabetes detected by FBS, HBA1c and number of patients missed by each method. X axis represents number of patients, yaxis represents various methods used for detection.

Table No 1: frequency and percentage distribution of patients according to age

	Prediabetic		
Age	**Frequency**	**Percentage**	**P-value**
20-50	33	33.3	< 0.0008
50-80	62	62.6	
80-110	4	4.0	
Total	99	100.0	

Graph No 1: frequency and percentage distribution of patients according to age

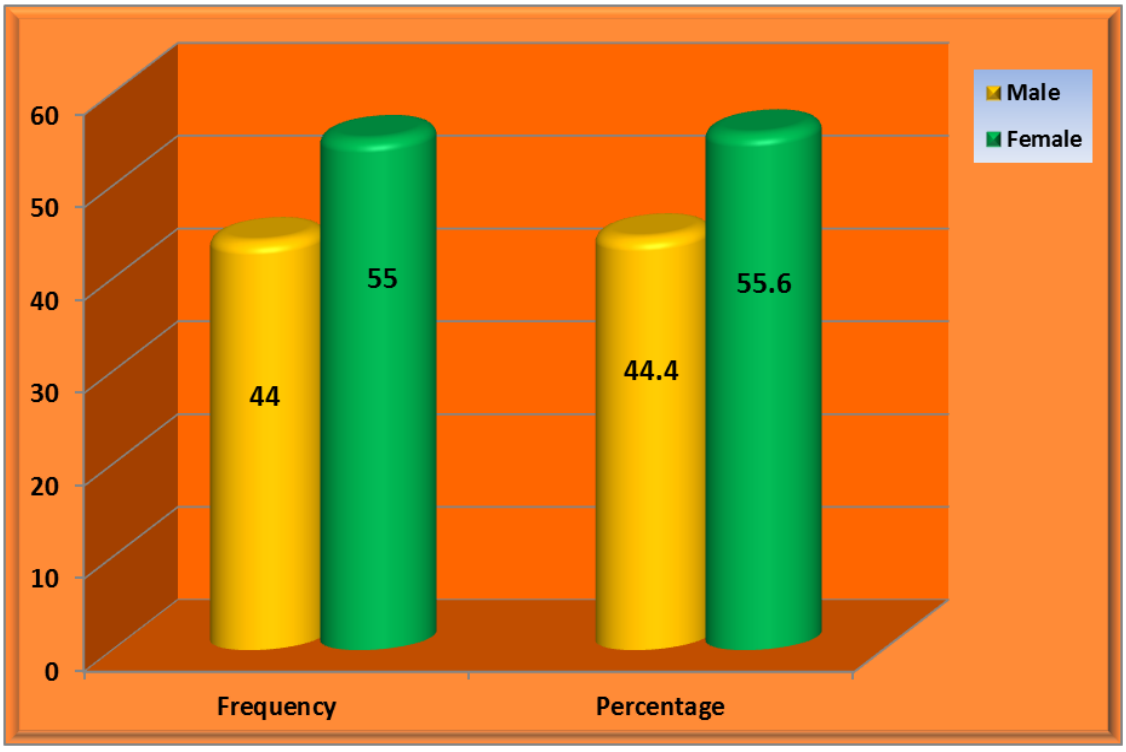


This is a bar chart showing the incidence according to age. X axis represents the number of patients y axis represents the age group .The incidence of prediabetes is highest among the age group of 50 -80.

Table No 2: Frequency and Percentage Distribution of patients according to sex

	Prediabetic	
Sex	**Frequency**	**Percentage**
Male	44	44.4
Female	55	55.6
Total	99	100.0

Chart No 2: Frequency and Percentage Distribution of patients according to sex

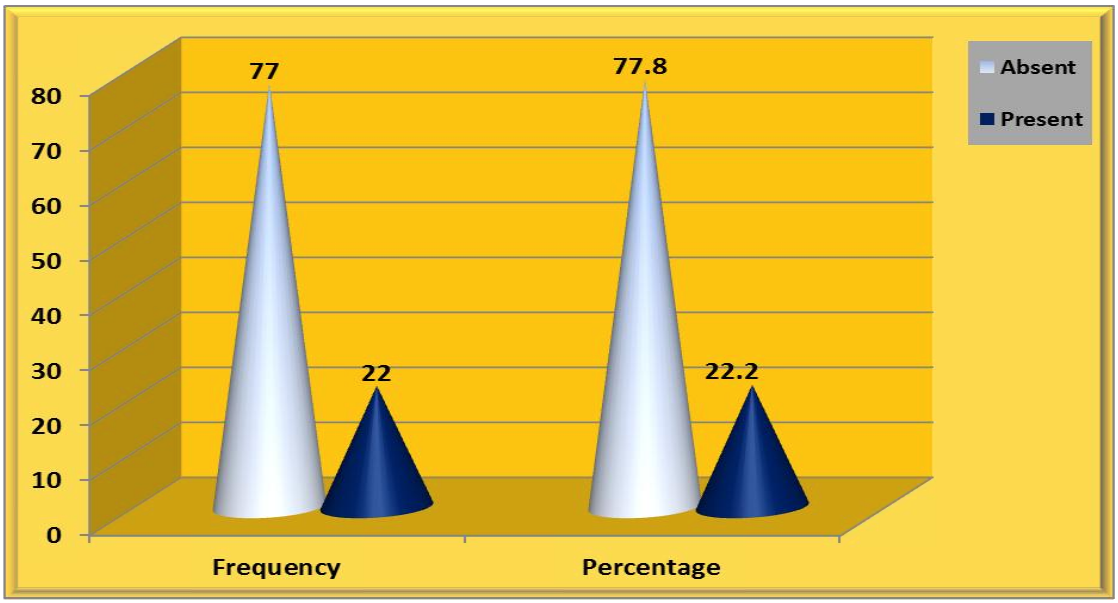


This is a bar chart representing the incidence of prediabetes according to age. X axis represents number of people Y axis represents gender. According to our study the incidence of prediabetes is more in females compared to males.

Table No 3: Distribution of patients according to Hypertension.

	Prediabetic		
Hypertension	**Frequency**	**Percentage**	**P-value**
Absent	77	77.8	< 0.001
Present	22	22.2	
Total	99	100.0	

Graph No 3: Frequency and Percentage Distribution of patients according to Hypertension.

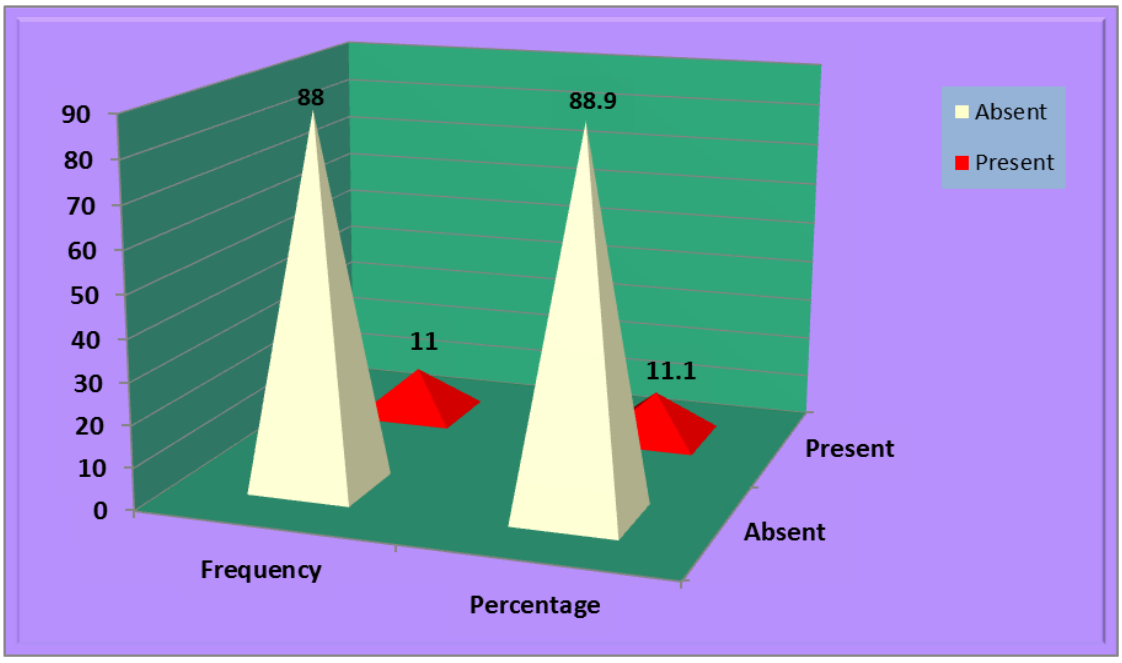


This is a bar chart representing the presence of Hypertension in patients with prediabetes. X axis represents number of people; Y axis represents prediabetic patients with Hypertension and without Hypertension. 22% of the patients with prediabetes had Hypertension as a risk factor**.**

Table No 3: Frequency and Percentage distribution of patients according to Ischemic Heart Disease.

	Prediabetic		
IHD	**Frequency**	**Percentage**	**P-value**
Absent	88	88.9	< 0.0001
Present	11	11.1	
Total	99	100.0	

Graph No 3: Frequency and Percentage distribution of patients according to Ischemic Heart Disease

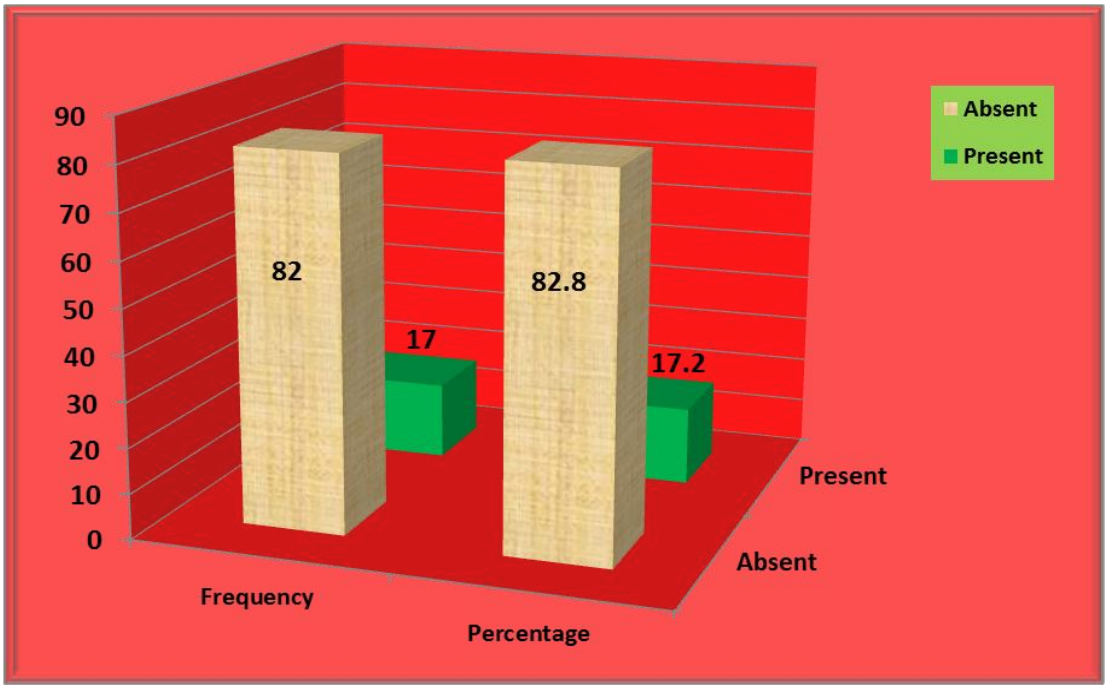


This is a bar chart representing the presence of Ischemic Heart Disease as a risk factor in prediabetics. X axis represents number of people Y axis represents presence or absence of Ischemic Heart Disease. 11% of the patients with prediabetes had Ischemic heart disease as the risk factor**.**

Table No 5: Frequency and Percentage Distribution of patients according to family history of IHD/HTN/T2DM

	Prediabetic		
Family History	**Frequency**	**Percentage**	**P-value**
Absent	82	82.8	< 0.0002
Present	17	17.2	
Total	99	100.0	

Graph NO 5: Percentage Distribution of patients according to family history of HTN/IHD/T2DM.

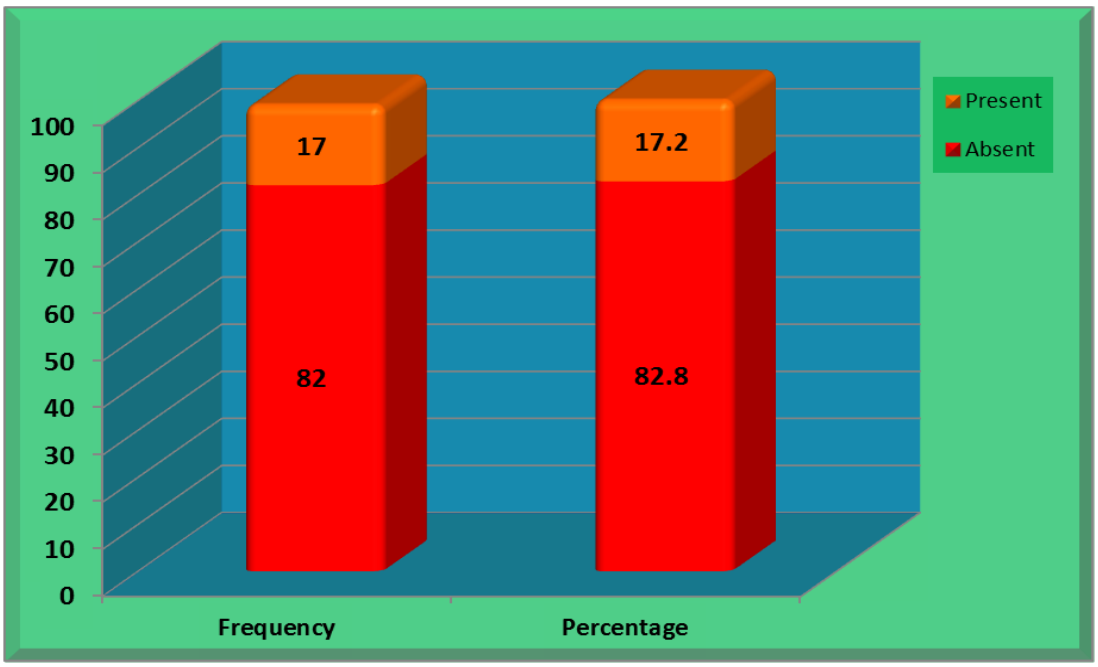


This is a bar chart representing the percentage of prediabetes patients having a positive family history of diabetes or HTN or IHD. X axis number of people Y axis presence of absence of family history. 17.2% of prediabetes patients had a positive family history.

Table No 6: Frequency and Percentage Distribution of patients according to hyperlipidaemia

	Prediabetic		
Hyperlipidaemia	**Frequency**	**Percentage**	**P-value**
Absent	82	82.8	< 0.0002
Present	17	17.2	
Total	99	100	

Graph NO 6: Percentage Distribution of patients according to Hyperlipidaemia

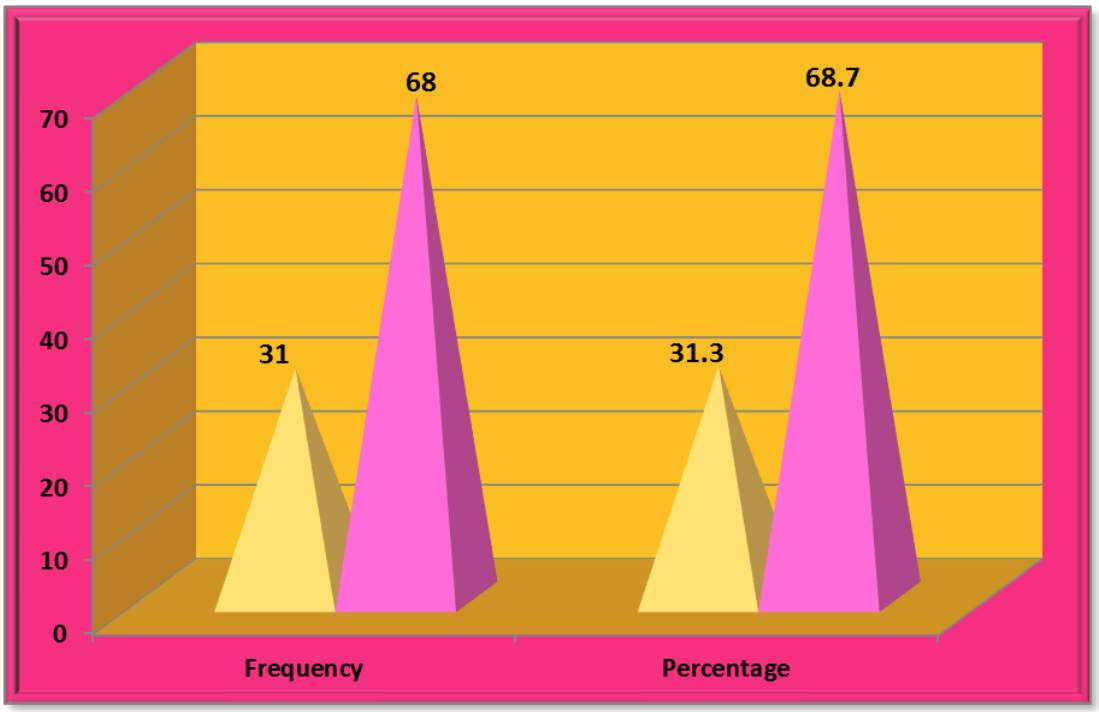


This is a bar chart representing the percentage of prediabetes patients having hyperlipidaemia .X axis number of people Y axis presence of absence of hyperlipidaemia. 17.2% of the patients with prediabetes had hyperlipidaemia as a risk factor.

Table No 7: Number of patients of prediabetes detected by FBS as compared to number of patients missed by FBS but detected by HbA1c.

	Prediabetic		
FBS	**Frequency**	**Percentage**	**P-value**
No.of cases missed by FBS	31	31.3	< 0.0001*
No. of cases detected by FBS	68	68.7	
HBA1C+FBS	99	100	

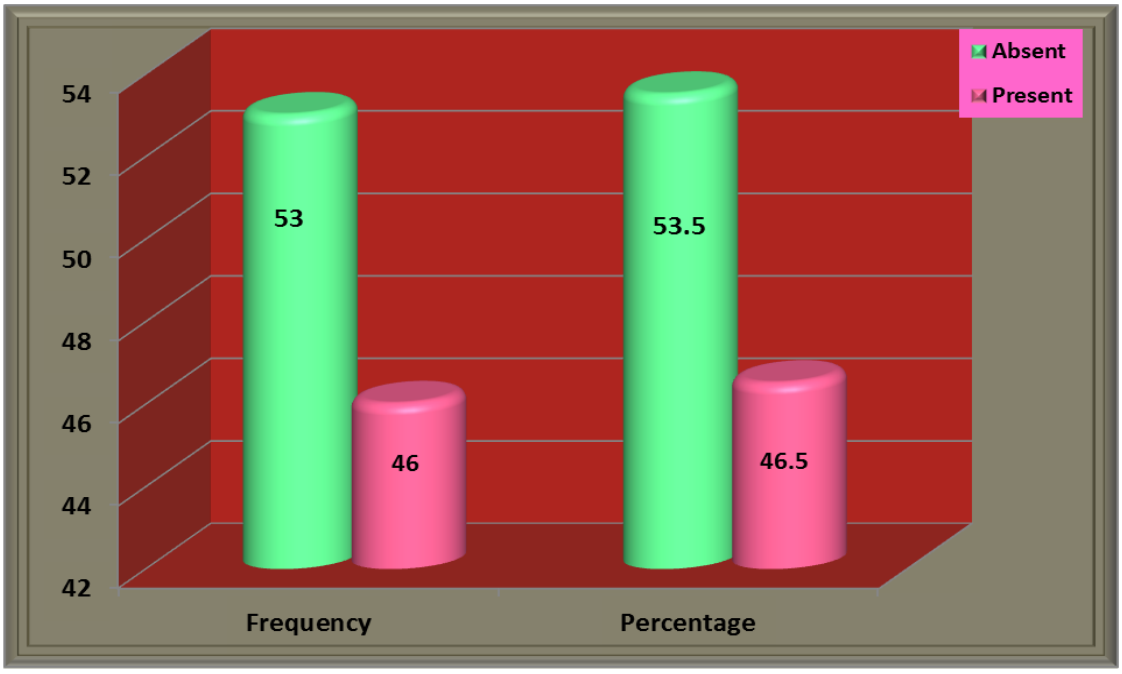
Graph NO 7:



This is bar chart representing number of patients of prediabetes detected by FBS and number of patients missed detection by FBS but detected by HbA1c. X axis number of patients Y axis-yellow pyramid represents number of patients missed by FBS pink pyramid represents number of patients detected by FBS .Number of patients detected by FBS-68,number of patients missed by FBS but detected by HbA1c-31.

Table No 8: Number of patients of prediabetes detected with HBA1c and number of patients missed by HbA1c but detected by FBS.

	Prediabetic		
HBA1C	**Frequency**	**Percentage**	**P-value**
No.of cases missed by HBA1C	53	53.5	< 0.0001*
No. of cases detected by HBA1C	46	46.5	
HBA1C+FBS	99	100.0	

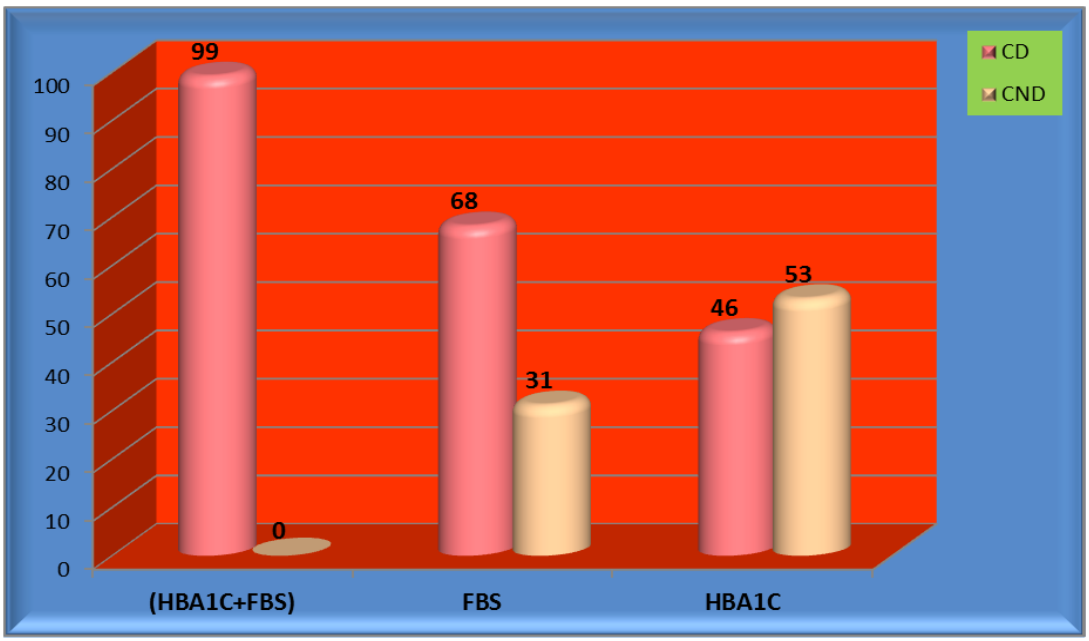


This is bar chart representing number of patients of prediabetes detected by HbA1c and number of patients missed detection by HbA1c but detected by FBS. X axis number of patients Y axis-green cylinder represents number of patients missed by HbA1c but detected by FBS, pink cylinder represents number of patients detected by HbA1c.Number of patients detected by HbA1c-46, number of patients missed by HbA1c but detected by FBS-53.

Table No 9: Comparison of HBA1c and FBS .

	No. of cases detected(CD)	No. of cases not detected(CND)	Incidence
FBS	68	31	29.05
HBA1C	46	53	19.65

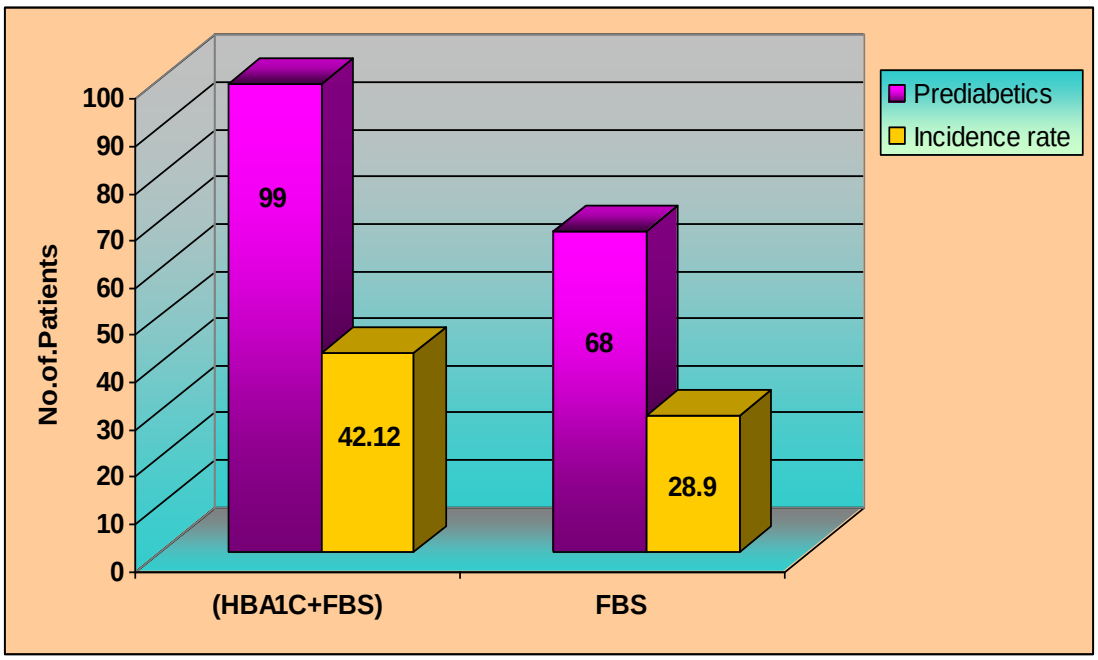
Graph No 10: Comparison of HBA1c and FBS (HBA1C+FBS) in detecting Pre diabetes



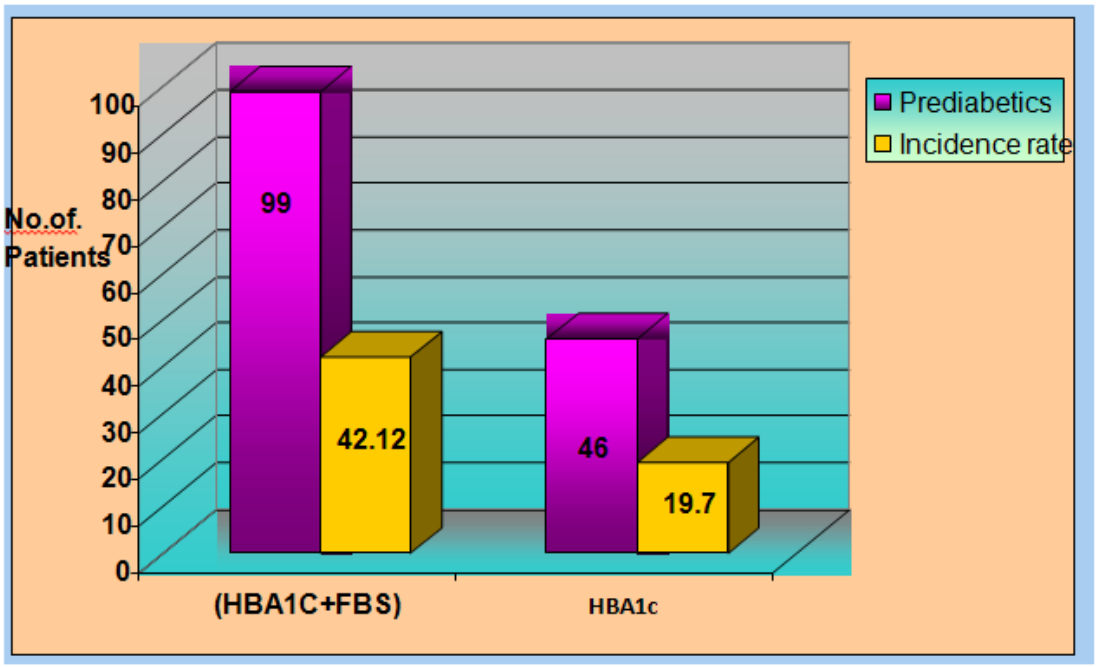
Total no. of cases detected by (HBA1c+FBS)	-	99
Incidence rate of pre diabetics by (HBA1c+FBS)	-	42.12%
Total no. of cases identified by FBS	-	68
Incidence rate of pre diabetics by FBS	-	28.9%
Total no. of case identified by HBA1c	-	46
Incidence rate of pre diabetics by HBA1c	-	19.57%

Table representing incidence of HbA1c, FBS, combined incidence of both HBA1c and FBS.

(N=235)	(HBA1c+FBS)	FBS	HBA1c
Prediabetics	99	68	46
Incidence rate of pre-diabetics	42.12	28.9	19.57



Combined incidence of (HBA1c +FBS)-42% as compared to FBS alone-28%



Bar chart representing combined incidence of (HBA1c +FBS)-42% as compared to HBA1c alone 19.2%

DISCUSSION

Type 2 Diabetes mellitus is a significant cause of death, disability and health care burden in India. Prediabetes which is a prodromal stage of Diabetes mellitus is highly associated with cardiovascular risk factors and has been found to confer risk of risk of development of cardiovascular and other microvascular complications. The present study included 235 subjects attending medicine OPD, patients admitted to BLDEU's Shri B M Patil Medical College and also the bystander accompanying the patient who fulfilled the inclusion and exclusion criteria.

There were a total of 140 males and 95 females included in our study. Out of total number of prediabetics 44.4 % of them were males and 55.6 % of them were females. According to the age distribution, incidence of Pre Diabetes was highest in the age group of 50-80. These results were comparable with other studies conducted by Cherie James[3], Kazuo Inoue,[81] Heianza Y [9] study. In this study, it was found that, including only FBS in diagnosis of Pre Diabetes resulted in a preponderance of males which was also found by Cherie James[6] and colleagues in their study. They implicated metabolic differences in males and females as the reason for the gender bias in the results. Hence, it is important to use both FBS and HbA1c in combination for the diagnosis of Pre Diabetes.

According to our study, 22% of the pre Diabetics had hypertension, 11% of them had IHD and 17.2 % had family history of hypertension or diabetes or IHD. 17% had hyperlipidaemia as a risk factor. 70 % of Pre Diabetics had one or the other risk factor. Similar results were reported by Kazuo Inoue [81] in their study.

Some studies state that, using only one test for diagnosis of Pre Diabetes risks misdiagnosing large number of patients especially African, Mediterranean or south east Asian heritage because of the metabolic differences in them. However, this study included a small group of 235 subjects which consisted population only of North Karnataka and did not include various races.

Our study confirms prior observations of various international studies that there is considerable discordance between HbA1c and FBS results i.e. HbA1c test does not detect the same individuals detected by FBS and vice versa. In our study we found that HBA1c did not detect 53 cases detected by FBS and FBS missed 31 cases detected by HBA1c. Hence, these two tests have to be used in combination to increase the detection rate. However, using both these tests identifies almost 1/3 $^{rd.}$ of the study group as pre diabetics , which is a large number, whether they really develop Diabetes in future can only be detected by subsequent follow up FBS and HbA1C tests. The limitation of this study is that it is only a cross sectional study which does not include follow up of the patient to know whether they really develop overt Diabetes in the future or not. There a very few such follow up studies on prediabetes.

According to our study, HbA1C identified fewer individuals as having pre diabetes than FBS based criteria which is consistent with other studies by Cherie James[3] and Mann DM.[82] But HbA1C is a more convenient test as compared to FBS as it does not require fasting and is not altered by recent changes in diet or activity. HbA1C may not accurately reflect levels of glycaemia in some situations like haemoglobinopathies, but when compared to FBS measurements; it has greater analytic stability and less temporal variability as shown by Samir Malkani and colleagues in their study – implication of using Hba1C for diagnosis of Diabetes Mellitus[6]. But the drawback of HbA1C is it identifies fewer individuals with Pre

Diabetes. Strength of HbA1C is that, it correlates well with all microvascular diabetic complications, much stronger than that of fasting blood glucose as shown by Tapp RJ and colleagues in their study.[83]

The reason that HbA1c is inferior to FPG or post-load glucose values at predicting type 2 diabetes is because the existence of haemoglobin or red cell abnormalities can increase the variability of HbA1c values. This variability may contribute to its inferior prediction of diabetes compared with fasting or post-load glucose values. In addition, FPG and HbA1c may reflect different aspects of glucose metabolism. While HbA1c can reflect a variety of factors in glucose metabolism, FPG levels mainly depend on insulin resistance and hepatic glucose production.

COMPARISON WITH OTHER STUDIES:

1. In comparison with The Isfahan Diabetes Prevention Study, Our study also showed that the detection of prediabetes by FBS was superior to that of HbA1c and the combined detection rate by FBS and HbA1c is higher than any method used alone. A study by Mohsen Janghorbani and Masoud Amini 'The Isfahan Diabetes Prevention Study' Comparison of Fasting Glucose with Post-Load Glucose Values and Glycated Hemoglobin for Prediction of Type 2 Diabetes also suggested FBS to be superior to HbA1c but it did not answer the question whether combined use of FPG and HbA1c predicts the incidence of diabetes more accurately than either test alone in individuals at risk of diabetes, and their study was a longitudinal study which involved follow up of the study group for 3 years to check for the development of overt diabetes. [84] Where as our study was a cross sectional study which did not involve follow up. Their study also included OGTT, due to the cumbersomeness of OGTT it

was not included in our study. Some other studies also suggest that the combined use of FPG and HbA1c predicts the incidence of diabetes more accurately than either test alone in individuals at risk of diabetes.

2. Comparison with the Kazuo Inoue et al study- The combination of fasting plasma glucose and glycosylated haemoglobin predicts type 2 diabetes in Japanese workers.[81]

   This was the first study that reported the potential value of combining FPG and HbA1c to predict incident diabetes in otherwise low risk individuals. This indicates that the combination of FBS 5.55 mmol/l and high HbA1c levels may help to identify effectively individuals in the general population for whom preventive measures for diabetes should be applied. Whereas our study only included patients who already have the risk factors for development of diabetes and demonstrated that combination of FBS and HBa1c detects more number of individuals.

3. The National health and nutrition Examination Survey in the United States did a study in which they concluded that the prevalence of prediabetes is 12.6% by Hba1c and 28.2% by fasting glucose criterion.[6]

4. In a study done by Cowie CC, Rust, et al they detected a substantially lower prevalence of individuals with “high risk of diabetes” using Hba1c criterion than detected with the fasting blood glucose criterion.[85]

5. Fajan SS, Oral EA et al in their study recommend that it is both acceptable and prudent to use a combination of different diagnostic criterion to establish or exclude diagnosis of prediabetes due to low sensitivity of Hba1c.[8]

6. A study by Heianza Y, Hara S et al drew the conclusion that screening by HbA1c alone missed 61% of the prediabetic individuals diagnosed by a combination of impaired fasting glucose and HbA1c.[9]

CONCLUSIONS

1. There is significant increase in the detection rate of prediabetes by considering both HbA1c and Fasting Blood Glucose in the diagnostic criterion for pre diabetes. The current ADA criterion needs to be modified and combination of FBS and HBA1c has to be included in the diagnostic criteria of prediabetes.

2. HBA1c detects less number of individuals as compared to FBS.

SUMMERY

1) There were a total of 140 males and 95 females included in our study. Out of total number of prediabetics 44.4 % of them were males and 55.6 % of them were females.
2) According to the age, the incidence of Pre Diabetes was highest in the age group of 50-80.
3) 70 % of Pre Diabetics had one or the other risk factor.
4) Total number of cases identified by FBS -68.
5) Incidence rate of pre diabetics by FBS -28.9%.
6) Total no. of case identified by HBA1c -46.
7) Incidence rate of pre diabetics by HBA1c-19.57%.
8) Total no. of cases detected by (HBA1c+FBS) out of 235 subjects- 99.
9) Incidence rate of pre diabetics by (HBA1c+FBS)-42.12%.

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ANNEXURE-I

ANNEXURE-II
CONSENT FORM

TITLE OF RESEARCH: "The implication of including hba1c along with fasting blood glucose in the screening criterion for the diagnosis of prediabetes."

GUIDE: DR. MS MULIMANI

P.G. STUDENT: DR. NIVEDITHA. B. KERODI.

PURPOSE OF RESEARCH:

I have been informed that the purpose of this research is to study the implication of including hba1c along with fasting blood glucose in the screening criterion for the diagnosis of prediabetes.

PROCEDURE:

I understand that a detailed medical history of mine will be taken & that I shall have to undergo a complete physical examination and be subjected to investigations.

RISKS AND DISCOMFORTS:

I understand that there is no risk involved and I may experience mild pain during the above-mentioned procedures.

BENEFITS:

I understand that my participation in this study will help in determining study the implication of including hba1c along with fasting blood glucose in the screening criterion for the diagnosis of prediabetes.

CONFIDENTIALITY:

I understand that the medical information produced by the study will become a part of hospital record and will be subjected to confidentiality and privacy regulations of hospital. If the data is used for publications, the identity of the patient will not be revealed.

REQUEST FOR MORE INFORMATION:

I understand that I may be asked for more information if required, for inclusion into study at any time.

REFUSAL OR WITHDRAWAL OF PARTICIPATION:

I understand that my participation is voluntary and I may refuse to participate or withdraw from the study at any time.

INJURY STATEMENT:

I understand that, in the unlikely event of injury to me anytime during the study, I shall get medical treatment for the same but no further compensations.

CONSENT STATEMENT

I, _____ unreservedly and in my full sense give my complete consent to take part in this study. The risk and benefits as mentioned above have been read by me/explained to me in my vernacular language.

Signature of Patient

ANNEXURE – III

BLDEU'S SHRI BM PATIL MEDICAL COLLEGE
HOSPITAL AND RESEARCH CENTRE, BIJAPUR

"THE IMPLICATION OF INCLUDING HbA1c, ALONG WITH FASTING BLOOD GLUCOSE, IN THE SCREENING CRITERION FOR THE DIAGNOSIS OF PRE DIABETES."

PROFORMA

Name:
Age:
Sex:
Occupation:
Religion:

IP. No:
Address
Date of Admission:
Date of Discharge:
Status at Discharge:
Unit:

Chief complaints:

Present history:

Past history:

History of (H/o) hypertension
H/o myocardial infarction / Angina
H/o diabetes mellitus
H/o drug intake:

1) Corticosteroids: yes/no
2) Sympathomimetics: yes/no
3) Isoniazid: yes /no
4) Niacin: yes/no
5) Salicylates: yes/no
6) Chloroquine or quinine: yes /no
7) Anti- Retroviral therapy:

Personal history:

Diet:
Appetite:
Sleep:
Bladder and bowel habits:

Family history:

GENERAL PHYSICAL EXAMINATION

Pallor:
Icterus:
Cyanosis:
Clubbing:
Lymphadenopathy:
Edema:

VITAL SIGNS:

Pulse rate:
Blood pressure:
Temperature:
Respiration rate:

SYSTEMIC EXAMINATION

PER ABDOMEN:

RESPIRATORY SYSTEM

CARDIOVASCULAR SYSTEM

CENTRAL NERVOUS SYSTEM

INVESTIGATIONS:

HAEMATOLOGY -

Hemoglobin	mg/dl
PS Study	

BIOCHEMISTRY-

Fasting blood sugar.	
Serum creatinine	
HbA1C	

HDL	
VLDL	
LDL	
Sr. Triglycerides	
Total Cholesterol	

ANNEXURE-IV

MASTER CHART

NO	AGE	SEX	HTN	IHD	FAMILY HISTORY	HYPERLIPIDAEMIA	FBS	HBA1C	FBS+HBA1C
21566	45	F	+	-	-	-	91	5.6	-
21575	85	F	+	-	-	+	117	8.4	-
11629	61	M	+	-	+	-	180	7	-
13876	67	M	+	+	-	+	190	6.6	-
7317	72	F	-	-	+	+	198	7.1	-
19176	75	M	-	+	-	+	258	8	-
18740	60	M	-	-	+	-	222	7.3	-
768	79	M	+	+	-	-	125-PD	5.8-PD	+
18237	65	M	+	-	-	-	225	7.5	-
18322	46	M	+	-	-	+	138	6.2	-
25111	75	M	-	+	-	-	131	11.4	-
25385	45	F	+	-	-	-	147	5.2	-
16355	70	M	-	-	-	+	125-PD	5	+
15249	65	F	+	-	-	-	161	7.3	-
15379	45	M	-	-	-	+	108-PD	4.9	+
7902	80	F	+	+	-	-	106-PD	5.4	+
7399	69	M	+	-	+	-	120-PD	5.3	+
21656	60	F	-	+	-	-	98	4.9	-
21666	72	M	+	+	-	-	102-PD	4.7	+
21443	70	F	-	-	+	-	80	5.9-PD	+
19176	75	M	-	+	-	+	258	8	-
20870	50	F	+	+	-	-	60	8.7	-
9644	44	M	+	+	-	+	208	7.8	-
11553	65	M	+	-	-	-	69	5.5	-
10949	65	F	+	+	-	-	218	7.3	-
13195	70	M	-	-	+	-	90	4.4	-
10818	45	F	+	-	-	-	199	6.8	-

10637	32	M	-	-	-	-	103-PD	5.4	+
11057	50	M	-	-	+	-	310	9.6	-
10594	61	M	-	-	+	-	300	8.2	-
20905	70	F	-	-	-	-	109-PD	5.6	+
20420	45	F	-	-	-	-	112-PD	4.7	+
20166	45	M	-	-	-	-	115-PD	4.9	+
11162	102	M	-	-	-	-	208	7.6	-
8704	60	M	-	-	-	-	103-PD	5.2	+
10532	65	F	+	-	-	-	202	5.7-PD	-
10536	74	M	-	-	-	-	193	6.4 -PD	-
4623	70	F	-	-	-	-	125	5	-
18003	70	M	-	-	-	+	280	7.3	-
13051	45	F	-	-	-	+	117-PD	5.2	+
13207	55	F	-	-	-	-	165	6.8	-
8309	62	M	-	-	+	+	123-PD	5.8-PD	+
9946	63	M	-	-	+	+	124-PD	5.9-PD	+
26020	60	M	-	-	-	-	360	8.5	-
26609	45	M	-	-	+	-	137	6.4-PD	+
8860	65	F	-	-	+	-	121-PD	6-PD	+
8428	72	F	-	-	+	-	110-PD	5.2	+
14330	45	M	-	-	-	-	118-PD	5	+
13972	45	M	-	-	-	+	100-PD	4.6	+
14461	65	F	+	-	-	+	109-PD	6.3-PD	+
13051	45	F	-	+	-	-	103-PD	5.2	+
141222	40	M	-	-	-	+	97	5	-
11954	65	M	+	-	-	-	110-PD	4.7	+
12932	60		+	-	-	-	98	4.8	-

		M							
12169	45	F	-	-	-	-	98	4.9	-
13525	58	M	-	-	-	-	87	5.2	-
19727	46	M	-	-	-	-	98	5.2	-
12932	80	M	-	-	-	-	96	4.8	-
13088	68	M	-	+	-	-	103-PD	5	+
17946	45	M	-	-	-	-	95	4.2	-
13525	58	M	-	-	-	-	88	5.2	-
12924	106	F	-	-	-	-	103-PD	4.7	+
9516	60	M	+	-	-	+	80	5.3	-
9200	55	M	-	-	-	-	98	5.1	-
8827	48	M	-	-	-	-	124-PD	5	+
9681	48	F	-	-	-	-	104	6.8	-
13427	88	M	-	-	-	+	85	4.1	-
8864	75	F	+	-	-	-	89	5.2	-
23368	70	M	+	+	-	-	287	7.4	-
7446	65	M	-	+	-	-	146	6.7	-
12984	74	F	+	+	-	-	126	6.1-PD	+
13076	60	M	+	+	-	-	128	6.3-PD	+
908	70	F	-	-	-	-	130	5.2	-
13063	60	M	-	-	-	+	182	6.7	-
13065	70	F	+	-	-	-	129	6.1-PD	+
19726	74	F	+	-	-	-	301	6.1	-
14575	75	M	+	-	-	-	134	5	-
14197	56	M	+	-	-	-	183	8	-
15798	75	F	-	-	-	-	182	7	-
8723	53	M	-	-	-	-	80	6.2-PD	+
18198	48	M	+	-	-	-	261	7.9	-
30331	55	F	-	+	-	-	139	5.5-PD	+
15269	45	F	+	-	-	-	127	6.6-PD	+
23195	55	F	-	-	-	-	145	6.6	-
18322	46	M	+	-	-	+	138	6.2-PD	+
15798	75	F	-	+	-	+	182	7	-
16102	80	F	-	-	-	-	240	7.2	-
25245	46	M	+	-	-	-	140	7.2	-
25762	73	F	-	-	-	-	135	9	-
15968	67	M	-	-	+	-	172	5	-
17808	62	M	-	-	-	-	80	4.7	-

17814	65	M	+	-	-	-	125-PD	4.8	+
17895	53	M	-	-	-	+	86	4.8	-
15830	65	F	-	-	+	-	95	5.6	-
13814	52	F	-	-	-	-	214	6	-
13743	66	M	-	-	-	-	91	5.9-PD	+
13637	65	M	-	-	-	-	85	6.5	-
13630	82	M	-	-	-	+	138	5.2	-
17819	75	M	-	+	-	-	254	7.4	-
13214	60	F	-	-	-	+	212	6.4	-
11057	50	M	-	-	-	+	326	9.6	-
13866	60	M	-	-	-	-	175	6.5	-
9644	44	M	-	-	-	-	208	7.8	-
17031	60	F	-	-	-	-	98	5.8-PD	+
91080	50	M	-	-	-	-	80	6.6-PD	+
8905	72	M	-	-	+	-	180	7.2	-
1020	51	M	-	+	-	-	251	7.4	-
18057	63	M	-	-	-	-	93	4.8	-
17895	53	M	-	-	-	-	86	4.4	-
17814	65	M	-	-	+	-	97	4.8	-
17809	68	M	-	-	-	+	120-PD	5.6-PD	+
12147	50	F	-	-	-	-	106	4.7	-
18060	72	M	-	-	-	+	262	10.7	-
18427	50	M	-	-	-	-	97	4.8	-
18326	65	M	-	-	-	-	177	7.8	-
18513	64	F	-	-	-	+	97	5.2	-
16102	80	F	-	-	-	-	240	7.2	-
16004	67	M	-	-	+	-	170	7.3	-
18157	65	M	-	-	-	-	81	5.3	-
18291	83	M	-	-	-	-	161	5.9-PD	+
18344	55	F	-	-	-	-	95	5.1	-
29014	50	F	-	-	+	-	83	6-PD	+
13195	70	M	-	-	-	+	90	4.7	-
4357	65	M	-	-	-	+	92	5.8-PD	+
37329	58	M	-	-	-	-	105-PD	5-PD	+
4335	40	F	-	-	-	+	113-PD	5.7-PD	+
18541	38	F	-	-	-	-	92	6.3-PD	+
9078	55	F	-	-	-	+	113-PD	5.9-PD	+
9725	65	F	+	-	-	-	110-PD	9	+
8970	52	M	-	-	-	-	93	5.2-PD	+
9784	58	F	-	-	-	-	118-	5.8-PD	+

							PD		
13941	65	M	-	-	-	-	100-PD	5-PD	+
28469	70	M	-	-	-	-	76	5.5	-
13057	54	M	-	-	-	+	100-PD	5.1	+
28854	58	M	-	-	-	-	112	6.8	-
28729	80	M	-	-	-	+	91	5	-
28586	65	M	-	-	-	-	93	5	-
10363	55	M	-	-	-	-	92	6.5	-
845	55	M	-	-	-	+	75	5.8-PD	+
25382	49	M	-	+	-	-	102-PD	5.8-PD	+
26297	37	M	-	-	-	-	115-PD	5.6	+
27091	86	M	+	-	-	+	88	5.2	-
18851	62	F	+	+	-	-	87	6.1-PD	+
18700	60	F	-	-	-	+	125-PD	6.5	+
16384	75	F	+	+	-	-	77	5	-
16330	70	M	-	-	-	-	90	5	-
16338	34	M	+	-	+	-	103-PD	6-PD	+
14824	45	F	-	-	-	-	97	5	-
15069	70	M	+	-	-	-	110-PD	5.2	+
27214	45	M	+	-	-	-	100-PD	5.7-PD	+
27047	45	M	-	-	-	+	80	5.2	-
17173	45	M	-	-	-	-	97	5	-
18262	60	F	-	+	-	-	101-PD	5	+
13056	52	F	+	-	-	-	319	11.5	-
9132	50	M	-	-	-	-	130	6.8	-
26130	65	M	-	-	-	-	120-PD	5.8-PD	+
26317	45	F	-	-	-	-	95	5.9-PD	+
26226	46	F	-	-	-	+	100-PD	5.2	+
26703	60	M	-	-	+	-	103-PD	5.1	+
24019	70	M	-	-	+	-	95	5.9-PD	+
24279	96	M	-	-	+	-	97	5	-
2390	24	F	-	-	-	-	88	5.7-PD	+
24147	45	F	-	-	-	+	94	5.4	-
25992	80	M	+	-	-	-	91	5.8-PD	+
24364	68	M	-	-	-	-	95	5.6	-

24368	55	M	-	-	-	-	98	5.8-PD	+
624437	62	F	-	-	-	-	100-PD	5.5	+
25698	50	M	-	-	-	-	100-PD	5.1	+
25846	47	F	-	-	-	-	81	6-PD	+
14058	45	M	-	-	-	-	85	5	-
16377	65	F	-	-	-	-	110-PD	5.2	+
16461	55	M	-	-	-	-	97	5	-
26867	48	M	-	-	-	-	98	8.6	-
18662	70	M	+	-	-	-	119-PD	5.8-PD	+
4618	80	F	-	-	+	-	85	6-PD	+
917	65	M	+	-	-	-	82	5.5	-
3299	75	F	-	-	-	-	89	5	-
4039	80	F	-	-	-	-	80	5	-
4150	82	F	-	-	-	-	92	5.5	-
4286	55	F	-	-	-	-	85	5.2	-
4281	65	M	-	-	-	-	105-PD	5.3	+
18863	47	M	-	-	-	-	86	6-PD	+
25175	61	F	+	-	-	-	70	5.2	-
14740	65	F	+	-	+	-	109-PD	5.4	+
24687	65	M	-	-	-	-	106-PD	5.8-PD	+
29144	70	M	-	-	-	-	100-PD	6.1-PD	+
29171	50	M	-	-	-	-	97	5.2	-
24553	70	M	-	-	-	-	89	6.4-PD	+
24491	47	M	-	-	-	-	97	6.1-PD	+
9112	55	F	-	-	-	-	85	5.5	-
9013	45	M	-	-	-	-	92	4.7	-
30357	75	M	-	-	-	-	116-PD	5.2	+
16078	73	M	-	-	-	-	97	4.9	-
15557	70	F	-	-	-	-	103-PD	5.3	+
22389	46	M	-	-	+	-	101-PD	5.3	+
22537	70	M	+	+	-	-	98	5.2	-
22568	45	F	-	-	-	-	113-PD	6.1-PD	+
22253	40	M	-	-	+	-	97	5	-
22294	60	M	+	-	-	-	86	5.6	-
22249	68	M	+	-	-	-	80	5.7-PD	+

22230	82	F	-	-	+	-	100-PD	5.7-PD	+
22589	83	M	-	-	+	-	125-PD	5.6	+
22760	53	M	-	-	-	-	91	6.2-PD	+
22973	58	F	+	-	-	-	95	4.6	-
6282	55	F	-	-	-	-	106-PD	6.5	+
6156	65	F	-	-	-	-	99	4.2	-
6367	45	M	-	-	-	-	114-PD	5.4	+
6785	45	F	+	-	-	-	100-PD	5	+
29955	70	-	-	-	-	-	118-PD	6.4-PD	+
29533	46	-	-	-	-	+	108-PD	6.3-PD	+
30357	75	-	-	-	-	-	116-PD	5.2	+
30331	55	-	-	-	-	-	106-PD	5.5	+
25151	60	+	-	-	-	-	100-PD	5	+
25477	70	+	-	-	-	-	115	7	-
17137	31	-	-	-	-	-	110-PD	4	+
25398	63	-	-	-	-	-	120-PD	5.8-PD	+
23492	60	-	-	-	+	-	112-PD	5.9-PD	+
23665	53	F	+	-	-	-	96	5	-
23619	60	F	-	-	+	-	96	5.5	-
4637	45	M	-	-	-	-	98	5.3	-
7482	60	F	-	-	-	-	97	5.1	-
9788	55	F	-	-	-	-	88	5.4	-
21799	65	F	+	+	-	+	158	5.5	-
21876	55	F	+	-	-	-	144	5.2	-
21877	50	M	-	-	-	-	80	5	-
21016	70	M	-	-	-	-	89	4.7	-
34567	89	M	-	-	+	-	79	4.7	-
25467	70	F	-	-	+	-	89	5.4	-
34256	89	F	-	-	-	+	90	5.5	-
33322	67	F	-	-	-	+	96	5.4	-
32454	78	M	-	-	-	+	90	6.8	-
22567	56	M	-	-	-	-	79	5.4	-
22678	66	F	-	+	-	-	90	4.7	-
28795	56	M	-	-	+	-	88	4.9	-
23478	50	F	_	-	+	-	79	5	-