A STUDY ON SERUM FERRITIN, CRP LEVELS AND ITS CORRELATION WITH HBA1C IN TYPE 2 DIABETES MELLITUS

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INTRODUCTION

The lifestyle disorder Type 2 Diabetes Mellitus (T2DM) is on the rise around the world.T2DM is a complicated disorder influenced by hereditary and environmental variables. Patients with T2DM have insulin resistance (IR) and abnormal beta-cells.

Insulin resistance in T2DM is typically caused by post-binding abnormalities in insulin activity. Research and clinical practice are becoming more interested in the connection between T2DM and iron metabolism.

According to scientific research, either higher body iron reserves or impacts from a number of inflammatory disorders will induce elevated serum ferritin levels to have an impact on Insulin resistance and T2DM. Since ferritin is an acute phase reactant as well, it is speculated that ferritin levels in the blood may not correctly reflect the body's iron stores but rather may represent other processes, such as systemic inflammation.

Two acute-phase proteins that are hypothesised to play a role in insulin resistance at the cellular level are serum ferritin and high-sensitivity C reactive protein (hs-CRP), which are both formed in the liver as a result of inflammation. In the present study, serum ferritin and hs-CRP levels are assessed in type 2 diabetes mellitus, and the link between serum ferritin and hs-CRP and HBA1C is examined.

OBJECTIVE OF THE STUDY:

A STUDY ON SERUM FERRITIN , CRP LEVELS AND THEIR CORRELATION WITH HBA1c IN TYPE 2 DIABETES MELLITUS

REVIEW OF LITERATURE

INTRODUCTION

The metabolic illnesses known as diabetes mellitus affect protein, lipid, and carbohydrate metabolism. It is characterised by persistent hyperglycemia, which can be caused by disorders with insulin secretion, insulin action, or a combination of both. (1)

The two main types of diabetes mellitus are type 1 (insulin-dependent) and type 2. (non-insulin-dependent).

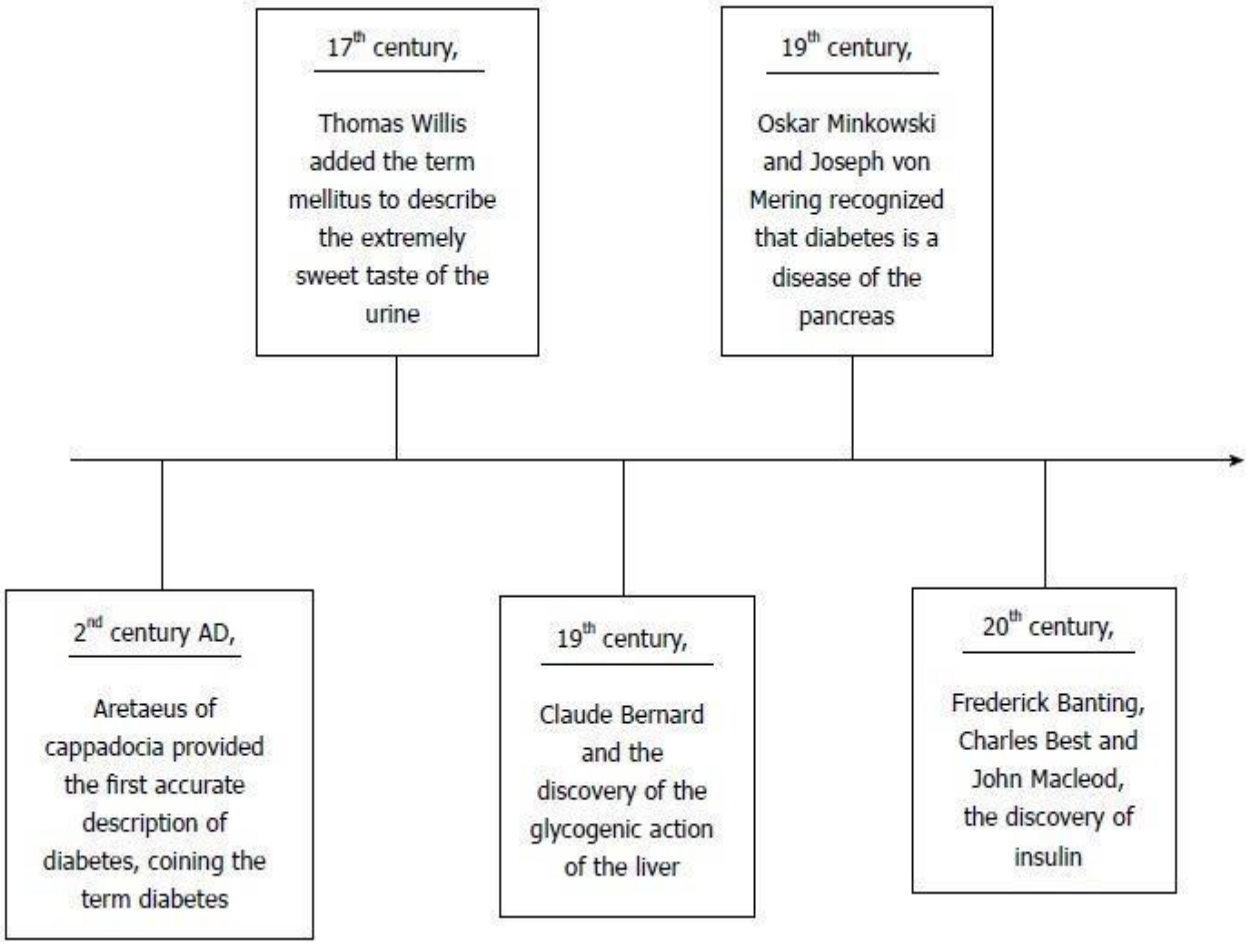
The immune system targeting the pancreatic islet beta cells causes type 1 diabetes. Type 2 diabetes is brought on by decreased insulin synthesis and resistance to the effects of insulin. (2)

Recent epidemiological data show that diabetes mellitus affects 9% of adults over the age of 18, and that 1.5 million people are estimated to have perished from it in 2012. According to the World Health Organization, diabetes will be the 7th most common cause of death by 2030. (3)

Graham Bell created the first insulin for humans in 1980. Humulin, the first synthetic insulin, was created in 1982. Syringes first arrived in 1961, but because they were made of glass, they carried the risk of infection that went along with them until disposable plastic ones were introduced. (4)

Metered insulin doses were available only 15 years after Derata introduced the first needle-free insulin administration method. In recent years, oral sprays, insulin pumps, and inhaled insulin have demonstrated the future of administration simplicity. (4)

FIGURE 1



IDENTIFYING THE GENES RESPONSIBLE FOR DIABETES MELLITUS

Twin studies imply that type 2 diabetes may have a hereditary component.. There is proof that a variety of mutations affect the chance of developing type 2 diabetes. Gene mutations that control the regulation of glucose levels can generally increase the risk of type 2 diabetes. The following genes are among them: (5)

- The synthesis of glucose

- The production and regulation of insulin

Type 2 diabetes is associated with certain genes, including:

• TCF7L2, which affects the production of glucose and the release of insulin

• ABCC8 is an insulin-regulating enzyme.

• CAPN10 is associated with type 2 diabetes risk among Mexican Americans.

• GLUT2, which enhances the transportation of glucose to the pancreas

• GCGR, a glucagon hormone that regulates blood sugar levels (5)

CLASSIFICATION

Diabetes can be categorized broadly into the following groups:

• Type 1 Diabetes (due to autoimmune b-cell destruction, usually leading to absolute insulin deficiency, including latent autoimmune diabetes of adulthood)

• Type 2 Diabetes (due to a progressive loss of adequate b-cell insulin secretion frequently on the background of insulin resistance)

• Particular kinds of diabetes brought on by external factors, such as exocrine pancreas illnesses (like cystic fibrosis and pancreatitis), monogenic diabetes syndromes (like neonatal diabetes and maturity-onset diabetes in the young), drug- or chemical-induced diabetes (such

as the use of glucocorticoids, in the treatment of HIV/AIDS, or after organ transplantation)

• Gestational diabetes mellitus, which is a form of pregnancy-related diabetes that is only discovered in the second or third trimester but was not previously evident; (6)

HBA1c

The HBA1c test is an indirect indicator of blood sugar levels. In addition to glycemia, other factors are taken into consideration, including hemodialysis, pregnancy, HIV therapy, age, race/ethnicity, genetic background, and anemia/hemoglobinopathies.

TABLE 1

Table 2.2—Criteria for the diagnosis of diabetes

FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; WHO, World Health Organization; 2-h PG, 2-h plasma glucose. *In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.

TABLE 2

Table 2.3—Criteria for screening for diabetes or prediabetes in asymptomatic adults

1. Testing should be considered in adults with overweight or obesity (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) who have one or more of the following risk factors:
   - First-degree relative with diabetes
   - High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - History of CVD
   - Hypertension (≥140/90 mmHg or on therapy for hypertension)
   - HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
   - Women with polycystic ovary syndrome
   - Physical inactivity
   - Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
2. Patients with prediabetes (A1C ≥5.7% [39 mmol/mol], IGT, or IFG) should be tested yearly.
3. Women who were diagnosed with GDM should have lifelong testing at least every 3 years.
4. For all other patients, testing should begin at age 35 years.
5. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.
6. People with HIV

CVD, cardiovascular disease; GDM, gestational diabetes mellitus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

TABLE 3

Table 2.4—Risk-based screening for type 2 diabetes or prediabetes in asymptomatic children and adolescents in a clinical setting (254)

Screening should be considered in youth* who have overweight (≥85th percentile) or obesity (≥95th percentile) **A** and who have one or more additional risk factors based on the strength of their association with diabetes:

- Maternal history of diabetes or GDM during the child's gestation **A**
- Family history of type 2 diabetes in first- or second-degree relative **A**
- Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander) **A**
- Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small-for-gestational-age birth weight) **B**

GDM, gestational diabetes mellitus. *After the onset of puberty or after 10 years of age, whichever occurs earlier. If tests are normal, repeat testing at a minimum of 3-year intervals (or more frequently if BMI is increasing or risk factor profile deteriorating) is recommended. Reports of type 2 diabetes before age 10 years exist, and this can be considered with numerous risk factors.

The term “prediabetes" refers to those with aberrant carbohydrate metabolism but whose blood sugar levels do not meet the requirements

TABLE 4

Table 2.5—Criteria defining prediabetes*

FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)
OR
2-h PG during 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)
OR
A1C 5.7–6.4% (39–47 mmol/mol)

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; 2-h PG, 2-h plasma glucose. *For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range.

FIGURE 2

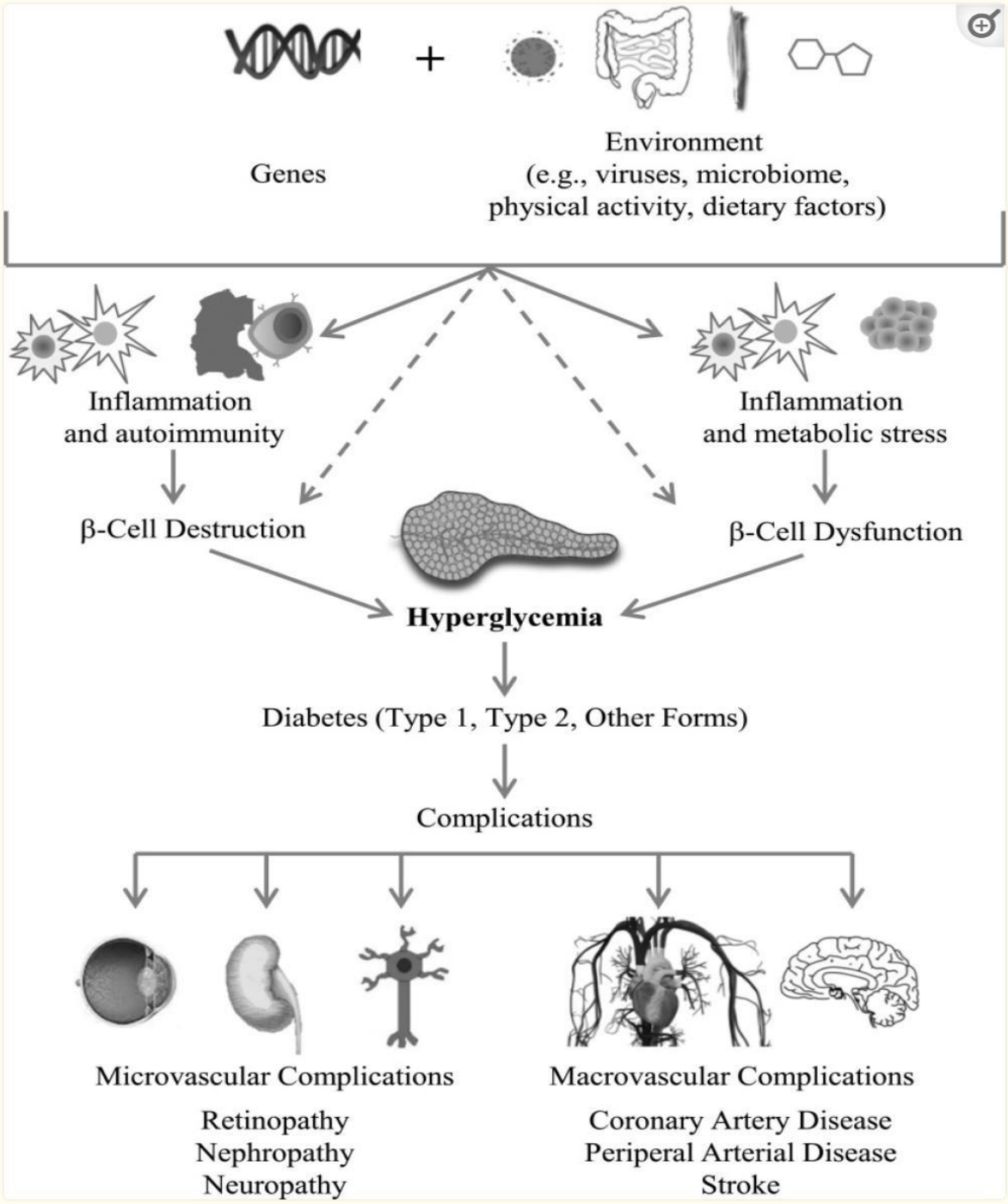


Figure 1

Genetic and environmental risk factors impact inflammation, autoimmunity, and metabolic stress. These states affect β-cell mass and/or function such that insulin levels are eventually unable to respond sufficiently to insulin demands, leading to hyperglycemia levels sufficient to diagnose diabetes. In some cases, genetic and environmental risk factors and gene–environment interactions can directly impact β-cell mass and/or function. Regardless of the pathophysiology of diabetes, chronic high blood glucose levels are associated with microvascular and macrovascular complications that increase morbidity and mortality for people with diabetes. This model positions β-cell destruction and/or dysfunction as the necessary common factor to all forms of diabetes.

Type 2 Diabetes Mellitus

In the context of elevated insulin resistance, type 2 diabetes often arises when -cells cannot release enough insulin to meet demand. Only a few percentage of persons with type 2 diabetes mellitus also show signs of islet autoimmunity. With a complex genetic and environmental etiology, obesity is a significant risk factor for type 2 diabetes mellitus. Insulin resistance is a result of ectopic fat deposition in the liver and muscle. Additionally, fat deposition in the pancreas has been linked to islet inflammation, a reduction in cell function, and ultimately cell death.(7)

Type 2 diabetes mellitus strikes at various BMI/body fat composition ratios in different people, including Asians and Asian Americans, with lower BMI. There might be a personal “fat threshold” for each vulnerable person, above which ectopic fat accumulation worsens insulin resistance and causes - β-cell decompensation.(8)

Weight loss enhances skeletal muscle and liver insulin sensitivity and may also lessen pancreatic fat growth. With caloric restriction and weight loss, defects in insulin secretion are at least partially reversible in type 2 diabetes and prediabetes. (9)

Obesity and diabetes are linked to decreased sleep quality and increased sleep quantity. Obstructive sleep apnea lowers sleep quality and is related to metabolic syndrome, type 2 diabetes, and other health conditions. Sleep deprivation may increase type 2 diabetes risk. Furthermore, although there are correlations with other environmental elements, direct causal links have not yet been shown.

A vital component of the pathogenesis of type 2 diabetes mellitus is defective insulin secretion. Insulin secretion varies widely in response to insulin sensitivity to maintain adequate glucose levels. The disposition index measures the curvilinear relationship between insulin secretion and insulin sensitivity.(10)

Type 2 diabetes have a low disposition index and are unable to increase insulin production enough to fight insulin resistance. Therefore, despite the fact that the absolute insulin levels in insulin-resistant obese type 2 diabetes patients may be higher than those in insulin-sensitive lean control subjects, the levels are still too low given the severity of their insulin resistance. (10)

Particularly in response to stimulation by glucose, first-phase insulin production is significantly decreased or eliminated. In type 2 diabetes, proinsulin to insulin (C-peptide) ratios are elevated, and hyperglycemia-induced potentiation of insulin responses to nonglucose stimuli is dramatically reduced. The condition of hyperglycemia typically gets worse and is harder to treat. The main factor contributing to type 2 diabetes' progressive nature is often the ongoing loss in -cell function.(11)

Absolute criteria are used to identify prediabetes and diabetes, whereas dysglycemia is a continuum that evolves from normal to overt diabetes. A window for treatment that could halt or delay the disease's progression and impact is created by early detection.

A person who is prediabetic has blood sugar levels that are higher than average but not yet in the diabetic range, as well as impaired glucose tolerance or impaired fasting glucose. Currently, the majority of

practitioners do not adequately regulate blood glucose levels in these patients. Therapy intensification for individuals with frank diabetes is routinely delayed even after treatment begins, raising the risk for years of hyperglycemia.

Numerous studies have shown that treatment, whether in the form of drugs or a change in lifestyle, can delay the onset of diabetes from prediabetes. Early treatment has also been associated with therapeutic benefits, including as reductions in retinopathy, cardiovascular disease, and overall mortality. According to this information, the progression of prediabetes could be influenced by early identification and keeping blood glucose levels close to normal.

There are several different drugs available today to treat hyperglycemia, each with a different mechanism of action and target at a different pathophysiology aspect of type 2 diabetes. Many medications (metformin, SGLT2 inhibitors, DPP-4 inhibitors, GLP-1 receptor agonists, and PPAR agonists) are started earlier in the course of the disease or are taken in combination.(12)

Due to their modest effects on insulin secretion, the medicines are typically taken after -cell mass or function has decreased past a critical point. A significant portion of type 2 diabetics eventually require insulin therapy, which is due to long-standing type 2 diabetes and significantly reduced -cell function, but also likely includes people with slowly progressing autoimmune diabetes with adult onset (LADA) or other ambiguous forms of diabetes.(12)

There are few data from randomised controlled trials including type 2 diabetics under the age of 18 or over the age of 65. Years are necessary for complications to benefit from strict glucose management. Rather than focusing solely on chronological age, glucose control goals should take into account factors like life expectancy, frailty, biological age, and social context. In order to prevent catabolic conditions and acute consequences of diabetes, overt hyperglycemia must be treated.

Diabetes frequently results in kidney damage. Additionally, it is an independent comorbidity that type 2 diabetics frequently experience due to vascular complications. Due to contraindications (such as metformin) or the requirement for adequate kidney function (such as SGLT2 inhibitors) for efficacy, the range of therapeutic options becomes more constrained, leaving many patients with only insulin therapy.(13)

Given that kidney impairment also increases the risk of hypoglycemia, glucose management goals may need to be adjusted for the group with kidney impairment. Because of reduced red blood cell survival, erythropoietin use, haemoglobin changes (such as carbamylation), and mechanical red blood cell destruction during dialysis, the use of HbA1c is difficult in persons with kidney disease.

A multifactorial strategy is needed to treat cardiovascular complications, which includes managing cholesterol levels and blood pressure. Arrhythmias and death are associated with hypoglycemia in patients who have had previous cardiovascular events. Strict glucose control should be sought out when it is possible to use medicines that do not cause hypoglycemia.

In this demographic, drugs like GLP-1 receptor agonists and DPP-4 inhibitors are safe. Some medications, like metformin and pioglitazone, may even be cardioprotective. Throughout 2.5 to 5 years of treatment, empagliflozin and liraglutide reduce cardiovascular and all-cause mortality in patients at high risk of cardiovascular disease. (13)

Regardless of BMI, weight management should be a top priority for all patients to prevent comorbidities and problems linked to obesity. A shift in lifestyle, the use of weight-loss-promoting diabetes medications, the incorporation of obesity pharmacotherapy, or in some cases, bariatric surgery, can all aid in weight loss.

When the estimated glomerular filtration rate drops below 45 mL/min/1.73 m2, the risk of cardiovascular disease rises significantly. Although microalbuminuria is a sign of inflammation, vascular leakage, and elevated cardiovascular risk, it is not always caused by diabetic nephropathy. Indicators of diabetic nephropathy, such as albuminuria, have been utilised for three decades. Patients can return to normal albuminuria without treatment as it is a treatable situation.(14)

It's interesting to observe that both type 1 and type 2 diabetics share the same urinary metabolomics signature of diabetic kidney damage. Albumin excretion rate is not the only indicator of nephropathy; recently discovered biomarkers like urine adiponectin and serum tumour necrosis factor- receptor 1 may be more accurate indicators. (15)

Strict glycemic control is the only known way to prevent or delay the formation of peripheral neuropathy, and cardiac autonomic neuropathy may be even more important in relation to cardiovascular mortality.

Inflammation in Type 2 Diabetes Mellitus

Type 2 Diabetes Mellitus is a progressive condition that is becoming a global epidemic and places a significant strain on the health economies of many nations due to its micro and macrovascular consequences. Type 2 diabetes mellitus patients are more likely to develop Cardiovascular disease due to several traditional risk factors that may not thoroughly explain the condition.

There is mounting evidence from several studies that inflammation occurs alongside atherosclerosis. The whole blood count, which includes RBC and WBC counts, C-reactive protein (CRP), HbA1c, lipid profile, High density lipoprotein, Low density lipoprotein and triglycerides, are all positively correlated with an increased risk of Cardiovasculare disease in people with type 2 diabetes mellitus. (16)

The local defensive reaction to tissue injury is inflammation. Celsus identified the four primary symptoms of redness, swelling, heat, and pain; Galen added the additional symptom of loss of function (130– 200 A.D.) Microscopically, these characteristics result from vasodilation, leukocyte buildup, enhanced capillary permeability, interstitial fluid production, and mediator activation of nerve endings, such as substance P. (17)

Potential epidemiological studies have found elevated basal levels of some of these mediators to be associated with an increased risk of cardiovascular events. Inflammatory mediators like cytokines and chemokines are released by cells like monocytes, macrophages, T-cells, endothelial cells, and vascular

smooth muscle cells when a plaque forms, causing an inflammatory reaction in the vessel.

These mediators include cytokines that have been shown to be able to predict the risk of cardiovascular events, such as interleukin (IL)-6 or tumour necrosis factor (TNF-), soluble adhesion molecules, and downstream acute phase reactants like C- reactive protein (CRP), fibrinogen, and serum amyloid A (SAA). (18)

According to one theory, the inflammatory cytokines released by adipose tissue have an endocrine effect that causes insulin resistance in the liver, skeletal muscles, and vascular endothelial tissue, leading to the clinical manifestation of both T2DM and CVD.

Tumor necrosis factor (TNF-) and interleukin-6 (IL-6) in particular, which are produced at higher levels by adipocytes, cause an acute phase response that increases the synthesis of C-reactive protein (CRP), a sensitive indicator of low-grade systemic inflammation.

In the capillary and arteriolar endothelium, the adhesion molecules E-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular adhesion molecule-1 (VCAM-1) are crucial mediators of endothelial dysfunction. Additionally, insulin resistance is facilitated by TNF, IL-6, and CRP, which also stimulates endothelial production of these molecules. (18)

An important proinflammatory cytokine called interleukin 6 is produced by tissues such as activated leukocytes, adipocytes, and endothelial cells. The primary IL-6-dependent hepatic biosynthesis pathway is the source of C-reactive protein, which is the primary downstream mediator of the acute phase response.

In rodent models of glucose metabolism, IL-6 has been found to stimulate the production of gluconeogenesis, which leads to hyperglycemia and compensatory insulinemia. Humans that received recombinant IL-6 subcutaneously showed similar metabolic reactions.

Adipocytes, activated leukocytes, and endothelial cells all release interleukin 6, a potent proinflammatory cytokine. The primary IL-6-dependent hepatic biosynthesis pathway is the source of C- reactive protein, which is the primary downstream mediator of the acute phase response.

In rodent models of glucose metabolism, IL-6 has been shown to cause gluconeogenesis, followed by hyperglycemia and compensatory insulinemia. Humans that received recombinant IL-6 subcutaneously showed similar metabolic reactions.

Cross-sectional studies have revealed that higher levels of IL-6 and CRP have been seen in people with T2DM, as well as that inflammation plays a significant role in the etiology of the disease. In cross-sectional investigations, inflammatory markers have been linked to T2DM and the characteristics of the metabolic syndrome.(19)

Acute-phase reactants like C Reactive Protien are positively correlated with measures of insulin resistance and plasma insulin concentration (and sporadically the cytokines IL-6 and TNF-). BMI/waist circumference, circulating triglycerides, and negatively correlated with HDL cholesterol concentration in non-T2DM persons, the general population, or people with impaired glucose tolerance (IGT)/impaired fasting glucose (IFG).

Higher levels of inflammatory biomarkers are typically associated with individuals who exhibit greater symptoms of the metabolic syndrome. In contrast to people with normal glucose tolerance, persons with IGT or IFG appear to have higher levels of IL6, and in one study, inflammatory markers were linked to insulin resistance but not to insulin secretion. (20)

Further cross-sectional research on individuals with newly discovered or pre-existing T2DM discovered an increase in acute-phase indicators including CRP and IL-6 in these individuals compared to non-diabetic control individuals. Studies have demonstrated a relationship between inflammatory indicators of inflammation, including CRP, serum amyloid A, secretory phospholipase A2, IL-6, and endothelial dysfunction (soluble cell adhesion molecules), and insulin resistance as assessed by the homeostasis model.(20)

HbA1c

In diabetes patients, HBA1c is a metric of total glycaemic exposure over two to three months. Around 30 years ago, the first clinically accepted technique for determining the levels of hyperglycemia in T2DM patients was glycated hemoglobin measurement. The weighted mean glucose levels during the previous three months are reflected in the HbA1c values for the patients.(21)

Since elevated HbA1c is used to monitor adequate glycaemic levels, it is significantly related with ongoing microvascular problems. Numerous studies have recently looked at the significance of HbA1c as a measure of total glycemic exposure in assessing the risk of diabetes and cardiovascular disease. Numerous research have looked into the significance of HbA1c in predicting T2DM in those with high-risk pre-diabetes.

HbA1c may potentially be utilised to predict cardiovascular risk in T2DM patients, according to recent studies. Elevated HbA1c has been linked for the past three decades to a lifetime risk of microvascular problems, and now, HbA1c testing is routinely used as a cornerstone of diabetes therapy to monitor effective glycaemic control. (21)

Full blood count

The values of many haematological indices, including haemoglobin, RBC, WBC, and glucose concentration with diabetics, are analysed and compared in this study.Several studies have indicated substantial relationships of regular haematological parameters with T2DM and CVD. It has been proven that the insulin resistance syndrome and cardiovascular illnesses are closely related. Elevated RBC counts are strong independent predictors of acute cardiovascular events, including myocardial infarction and stroke.(22)

Patients with T2DM frequently have abnormal hematological markers, such as hematocrit, plasma proteins, erythrocyte aggregation, and erythrocyte deformability. Both plasma and whole blood viscosity(WBV). rise due to these abnormalities One of the hematological factors that are altered in T2DM patients is the deformability of RBCs. RBCs in T2DM patients tend to congregate more readily than those in healthy individuals. One of the most significant characteristics of T2DM patients with poor glycemic control is excessive RBC aggregation. This directly impacts the whole blood viscosity WBV. (22)

Lipid profiles

Serum lipids are abnormal in a significant portion of T2DM patients. Recent research has shown that several additional illnesses linked to lipoprotein concentrations, in addition to hyperglycemia, are also affected by insulin resistance.

Elevated levels of total and VLDL cholesterol, triglycerides, low levels of HDL, and a high concentration of dense LDL particles are characteristic abnormalities in the lipid profile frequently seen in T2DM patients. It is generally known that metabolic syndrome's primary identifier, diabetic dyslipidemia, also plays a significant role in the etiology of CVD. Additionally, it has emerged as the primary factor causing cardiovascular morbidity and mortality in T2DM patients.(23)

T2DM patients and non-T2DM people with triglyceridemia have been shown to have an elevated risk of coronary heart disease. Although the concentration of LDL cholesterol is not considerably different from non-diabetic persons, a high triglyceride level, particularly triglyceride-rich VLDL, and decreased HDL cholesterol levels are the main features of dyslipidemia in T2DM patients. (23)

Diabetic dyslipidemia, also known as atherogenic dyslipidemia, is a specific lipid trio that is more common in T2DM patients and raises the risk of CVD. In adults with early CAD, it is frequently observed. The American Diabetes Association (ADA) states that the most accurate indicators of CVD in T2DM patients are elevated triglyceride levels and reduced HDL values. (1)

C- reactive protein (CRP)

The risk factors for cardiovascular disease often impact several organs and organ systems, including the kidneys, brain, heart, and peripheral arteries. Two critical choices linked to an increased risk of Cardiovascular disease and other organ damage are T2DM and hypertension. C-reactive protein is one of these variables (CRP). The typical acute-phase protein, or C Reactive protein , can predict cardiovascular morbidity and death in the general population and high-risk patient populations such as Type diabetes mellitus. A sensitive indicator of inflammation is C Reactive Protein .(24)

The atherosclerotic process that causes damage to the vascular end organs or affects many vascular beds may be accompanied by inflammation, either systemically or locally. Slight elevations in blood CRP levels are linked to a higher risk of vascular disease.

Studies show that C Reactive protein is not a standalone risk factor for cardiovascular disease. In the pathophysiology of T2DM, C reactive Protein , an acute phase biomarker of systemic inflammation, plays a significant role. It can be utilized as a newly emerging independent risk factors for cardiovascular disease.(24)

CRP is an oligomeric protein member of the pentraxin family and is well known for its role in innate immunity and pattern recognition. CRP actively contributes to complement fixation, platelet activation modulation, leukocyte activity increase, and the removal of cellular debris from active inflammatory areas.

Through the stimulation of additional cytokines like Interleukin 1 and 6, as well as tumor necrosis factor, the liver produces CRP. According to numerous recent prospective studies, CRP carries an increased risk for the development of T2DM. Multiple cross-sectional investigations have linked high serum CRP levels to obesity, insulin resistance, and glucose intolerance.(25)

The risk of thrombotic events and the later onset of diabetes have both been associated with greater levels of C-reactive protein. Insulin resistance and CRP have a known causal link. The inflammatory component of the development of atherosclerosis in the arterial artery wall is thought to be represented by CRP, according to general consensus. (25)

SERUM FERRITIN

French researcher Laufberger first identified a novel protein from horse spleen that contained up to 23% of iron by dry weight in 1937. This protein was later identified as ferritin. A few years later, it was discovered that human serum contained ferritin. In 1972, Addison and associates used an immunoradiometric assay to successfully demonstrate the accurate ferritin detection in human serum.(26)

The authors tested serum ferritin in members of the general population, those with iron shortage, and those with iron excess to ascertain the association between serum ferritin level and total body iron storage. They showed that patients with iron overload had elevated blood ferritin levels, while those with iron deficient illnesses had decreased levels.(26)

A serum ferritin assay may provide a "useful and practical means of measuring the state of iron storage," according to a 1975 hypothesis made by Jacobs and Worwood. (26)

THE BASIC BIOLOGY OF SERUM FERRITIN

A cytosolic protein called ferritin is present in the majority of tissues, but a mitochondrial version has recently been discovered, and nuclear localization and functions have been suggested. Ferritin, a 24-subunit protein, contains two distinct subunit types: H and L. (27)

H may refer to either the heavier electrophoretic migration of the two subunits or the initial isolation of H-rich ferritin isoforms from the human heart. L stands for ferritin, which was extracted from human liver and is high in a lighter subunit.

The generated ferritin protein has varying ratios of H to L subunits depending on the kind of tissue and developmental stage. Human ferritin's H and L subunits are encoded for by genes on chromosomes 11q and 19q, respectively. Both H and L ferritin have a number of pseudogenes.(28)

This free iron correlates with and is the cause of disease since the ferritin protein portion is regarded to be nontoxic. The substance known as "serum ferritin" is derived from injured cells (and so represents cellular damage), includes some iron, but has lost the majority of its normal concentration.

Iron is absorbed in the gut as ferrous ions, then transported in the serum bound to transferrin (in the ferric form). It can enter peripheral tissues through appropriate receptors and be re-reduced. Importantly, ferritin is not produced in serum but cells, including intestinal cells. (28)

Serum ferritin levels would then represent the body's iron stores in healthy people. Numerous cellular processes, such as oxidation-reduction reactions, cellular proliferation, DNA synthesis, oxygen transport, and cell development, all depend on iron. However, too much iron is toxic and, through generating reactive oxygen species, excessive iron in the body causes organ failure.(29)

Several factors, including oxidative damage to the pancreatic beta cells, changes in the liver’s ability to produce insulin, disruptions in the way insulin works, and an increase in insulin resistance, can result in diabetes when iron levels are elevated. Numerous studies have shown the connection between iron excess and oxidative stress as a cause of diabetes and its consequences.

IRON METABOLISM

Iron has numerous physiological functions in the human body, making it a necessary mineral. It is vital to our life despite making up only 0.008% of the body's mass. Iron is present in the heme group of cytochromes, responsible for producing energy in the mitochondria and in hemoglobin and myoglobin, which carry oxygen.(30)

It is also necessary to synthesize DNA by oligodendrocytes, which are found in the brain, for the upkeep of the immune system, the development of connective tissue, and the growth of brain tissue. The duodenum serves as a source of iron absorption.

Heme iron and non-heme iron are the two types of dietary iron. For the absorption of heme and non-heme iron, various processes exist. The gut absorbs 10% of the dietary iron that is consumed. Since there are no efficient methods for iron excretion, dietary iron absorption from the duodenum primarily controls iron metabolism.

The daily need is 10 mg for men and 15 mg for women. One to two milligrammes of iron are consumed dietary per day. Menstruation, other minute blood losses, and loss of iron from sloughed intestinal mucosal cells counteract this (30)

IRON UPTAKE BY CELLS

The liver and reticuloendothelial system are primarily responsible for absorbing the iron bound to transferrin in plasma. Cells utilize transferrin receptors 1 and 2 to absorb blood-borne iron bound to transferrin (Tfr1 & 2). Tfr1 is downregulated when the body has too much iron in it. Mainly found in the liver, Tfr 2 is expressed. (31)

Plasma iron concentration does not regulate it (due to lack of iron-responsive element). Transferrin iron saturation controls Tfr2. Tfr2 receptors are upregulated by increased transferrin saturation. Hence Hepatic iron overload in Hereditary Hemochromatosis is significantly influenced by Tfr 2.

The iron that is not bound to transferrin (NTBI) is particularly toxic, and the liver clears it from plasma quickly. A protein resembling DMT1 in the duodenum reduces NTBI to Fe2+ and transports it across the hepatocyte membrane. Tranferrin bound iron (Fe3+) is now transported inside the cell and delivered to the low pH endosomes where ferric iron is released. Ferric iron (Fe+) is reduced to ferrous iron (Fe2+) via an NADPH-dependent oxidase.(31)

The iron storage protein ferritin is responsible for extra-binding iron in the cytosol. Additionally, FP1 can remove free iron from hepatocytes after it has been oxidized by ceruloplasmin and re-bound to transferrin.

EXTRACELLULAR FERRITIN :

The fundamental function of ferritin is to store iron in the cytoplasm. Ferritin is known to be secreted into plasma by hepatocytes, macrophages, and kuppfer cells. Contrarily, due to its bigger size, hemosiderin is never seen outside the cell. Most serum ferritin is L ferritin. It has little iron. (26)

Serum Transferrin, a crucial physiological protein for the transfer of iron, can bind two iron atoms per molecule. However, each ferritin molecule can hold as much as 4500 iron atoms. Because of this, serum ferritin may have the ability to transfer iron to tissues effectively. In addition, ferritin plays a part in coagulation, angiogenesis, inflammation, and the immune system. It interacts with bradykinin and HMW kininogen (interaction with fibrinogen).(26)

HEPCIDIN

Hepatic Kupffer's cells secrete a 25 amino acid peptide known as hepcidin. DMT1 expression is downregulated by hepcidin, which also decreases duodenal iron absorption. Hepcidin causes inflammation and has antibacterial effects. This results in chronic anaemia (32)

HbA1c and serum ferritin association in type 2 diabetics

Iron overload, in which the liver accumulates excessive iron, can lead to insulin resistance by impairing insulin's ability to reduce hepatic glucose synthesis. Additionally, oxidative stress can cause hyperglycemia by disrupting the glucose metabolism. Conversely, through enhanced transferrin receptor externalisation, insulin promotes cellular iron uptake. Ferritin levels can also rise as a result of insulin resistance and inadequate glycemic management. Thus, insulin and iron levels can mutually affect each others effects leading to a vicious cycle of insulin resistance and diabetes mellitus. (33)

Iron is stored in ferritin, a complex globular protein, as a soluble and non-toxic component. When there is oxidative stress, Fe2+ enters the cells, transforms to Fe3+, is attached to ferritin, and then protects the cells. Increased levels of iron and ferritin in cells may result in insulin resistance and pancreatic islet dysfunction. Serum ferritin may have increased due to hyperinsulinemia brought on by insulin resistance. The disruption of iron metabolism has been linked to insulin resistance, hyperinsulinemia, dyslipidemia, heart disease, and central obesity.

By reducing insulin's capacity to reduce hepatic glucose production, iron accumulation in the liver may contribute to insulin resistance. Iron undergoes autooxidation, forming iron-oxygen compounds. These free radicals have the ability to harm tissue and change membrane properties. Additionally, by interfering with glucose metabolism, oxidative stress can lead to hyperglycemia.This study looked for a relationship between serum ferritin

and diabetes mellitus (DM) as well as HbA1c as a measure for blood glucose management in diabetic individuals.

An imbalance of pro-oxidants, glucose auto-oxidation, protein glycation, the polyol pathway, and an excess generation of superoxide radicals are all factors in oxidative stress brought on by chronic hyperglycemia in type 2 diabetes. This oxidative stress leads to complications in type 2 DM.

Type 2 diabetes's chronic hyperglycemia causes oxidative stress, characterized by an imbalance of pro-oxidants, glucose auto-oxidation, protein glycation, the polyol pathway, and excessive production of superoxide radicals. This oxidative damage brings on complications in type 2 DM.(34)

Long-term hyperglycemia encourages glycation processes that result in the production of advanced glycated end products (AGE). Collagen gets cross-linked as a result, resulting in tissue injury. Glycemic management is therefore necessary for preventing complications in type 2 DM. Nearly all of the body's cells contain iron. Hemoglobin (Hb) has about 75% of the body's total iron, 5% of myoglobin, and 15% of ferritin. Iron is stored by the ubiquitous intracellular protein ferritin, which releases it gradually over time.About 75% of total iron is hemoglobin (Hb), 5% is in myoglobin and 15% in ferritin. (34)

Type 2 diabetes mellitus and iron metabolism are linked bi-directional. Even in the absence of severe iron excess, iron affects glucose metabolism. Iron is

a potent pre-oxidant that causes cells to experience more oxidative stress, which inhibits insulin's activities and internalization, leading to hyperinsulinemia and insulin resistance.(34)

The synthesis of ferritin is positively influenced by free iron, while the release of iron from ferritin is accelerated by oxidative stress. A possible fundamental cause of hyperferritinemia in type 2 DM is anomalies in ferritin metabolism following glycation in hyperglycemic conditions. The half-life of glycated ferritin is longer. Transferrin's ability to bind ferrous ions is reduced by glycation, which also increases the amount of free iron and promotes ferritin synthesis.(34)

Therefore, type 2 diabetes mellitus is linked to anomalies in ferritin metabolism, which cause a concomitant rise in blood ferritin levels. In this study, patients with type 2 diabetes mellitus will have their serum ferritin levels evaluated, and an association between these values and glycated hemoglobin will be investigated. Therefore, we are looking at the feasibility of screening those at high risk for diabetic complications using serum ferritin.

The ease with which iron is reversibly oxidized and reduced results in iron's central significance in the pathophysiology of the illness. Now that it has been discovered that oxidants can release catalytic iron, which interacts with a vicious cycle to create more reactive species, free radical generation may play a role by interfering with insulin function and total body glucose elimination. Possible mechanisms for iron's impact are suggested by the fact that oxidative stress is enhanced in glucose intolerance.

The half-life of glycosylated ferritin in serum is longer. Serum ferritin levels are influenced by glycemic control itself. Patients with poorly controlled diabetes mellitus usually have abnormal serum iron metabolism characteristics. Patients with elevated serum ferritin have poor glycemic control and vascular damage, and those with elevated ferritin levels have a higher chance of developing atherosclerosis.(35)

Iron is a catalyst in the creation of hydroxyl radicals, which are potent pro-oxidants that attack the lipids, proteins, and nucleic acids in cellular membranes. Type 2 diabetes eventually develops as a result of this process, which first contributes to insulin resistance. Atherosclerosis has been thought to be primarily caused by insulin resistance. (35)

It has been proven that type 2 DM development to nephropathy and iron overload are related. The finding that either an iron-deficient diet or iron chelators can stop the progression of DM to DN points to the important role that iron overload plays in the pathophysiology of nephropathy in type 2 DM patients. (35)

DIABETES PATHOGENESIS AND ITS COMPLICATIONS: THE IMPACT OF IRON

Iron exists in two different states: ferrous (Fe2+) and ferric (Fe3+). Iron is a potentially hazardous metal because of how readily it can be reduced to ferrous ions or oxidized to ferric ions for its metabolic functions.In a typical situation, oxygen receives four electrons and turns into water. But under physiological circumstances, partial oxygen reduction frequently occurs, producing superoxide anion, hydroxyl radical and hydrogen peroxide.(36)

Reactive oxygen species (ROS) are produced within the cell and organelles such as the mitochondria, endoplasmic reticulum and peroxisomes, during numerous metabolic activities. Reactive oxygen species are produced due to the electron transport pathway in mitochondria. Superoxide radicals play a crucial role as signaling molecules in numerous biochemical and metabolic processes. However, excessive ROS production also results in DNA damage, lipid peroxidation, protein oxidation, and the production of advanced glycation end products (AGEs). As a result, cells create an effective antioxidant system to eliminate these excess ROS.(36)

Molecular oxygen and iron can react to ROS or RNS because iron can exist in multivalent forms (Fe2+ or Fe3+). Oxidants release catalytic iron, which starts a chain reaction that produces an increasing amount of ROS. A reliable indicator of bodily iron stores is serum ferritin. The poisonous substance in ferritin is the released free iron; the protein portion of ferritin, or apoferritin, is not toxic.(37)

MECHANISM OF IRON INDUCED DIABETES

The mitochondrial content of pancreatic islet beta cells is high. The sole mechanism by which beta cells produce insulin is through the mitochondrial metabolism of glucose. As beta cells have high levels of Divalent Metal Transporter (DMT) expression and low amounts of antioxidant enzymes, they are particularly susceptible to iron-induced damage via Fenton and Haber-Weiss reactions.

Insulin resistance can also be brought on by iron excess. Hepatic malfunction or direct interference with insulin signaling pathways can both be the cause of insulin resistance. Insulin resistance is caused by inhibitory serine phosphorylation of IRSs 1 and 2, which is caused by ROS generated by iron-catalyzed activities.(38)

The observations listed below point to a potential involvement for iron in Diabetes mellitus and associated complications.

DIABETES MELLITUS WITH IRON OVERLOAD STATES:

First, iron's role in diabetes was foreseen using observations from instances of Classic Hereditary Hemochromatosis. Phlebotomy-assisted iron overload reduction and iron chelation therapy helped patients with advanced disease maintain better glycemic control. In about 65% of patients with advanced illness, diabetes mellitus was developed. (39)

Studies have shown that even a mild increase in body iron levels below those associated with hereditary hemochromatosis and iron overload was linked to diabetes.

acquired iron overload, which calls for frequent blood transfusions. Early in life's second decade, impaired glucose tolerance is seen. In this instance, insulin resistance brought on by hepatic dysfunction and iron deposition in the interstitial cells of the pancreas are the causes of type 2 diabetes. (39)

Additionally, mitochondrial iron overload diseases like Friedreich's ataxia have a high incidence of diabetes. The Frataxin protein, which is specifically associated with the mitochondrial inner 33 membranes and is necessary for the formation of Fe-S clusters, is produced by the Friedreich's ataxia gene (FRDA). Mutations in the FRDA gene have been linked to type 2 diabetes, pancreatic beta cell mitochondrial DNA damage, and mitochondrial iron accumulation. (40)

1. IRON'S IMPACT ON DIABETES WITHOUT OVERT IRON OVERLOAD: High levels of oxidative stress are associated with high amounts of body iron, and because iron is a potent pro-oxidant, this association may increase the risk of type 2 diabetes. Increased risks of type 2 diabetes, the metabolic syndrome, gestational diabetes, and polycystic ovarian syndrome have been associated with high body iron stores, as measured by the amount of circulating ferritin. Additionally, increasing dietary consumption of iron, especially heme iron, is connected to an increased risk of type 2 diabetes among individuals who appear to be healthy. (41)

2. DIABETES AND BLOOD DONATION: In persons who appeared to be in good health, blood donation that reduced body iron storage was associated with a lower risk of diabetes. Insulin

sensitivity has been observed to be higher among regular blood donors. (42)

3. GESTATIONAL DIABETES AND IRON: Women with gestational diabetes mellitus had higher serum iron and ferritin levels prior to diagnosis and therapy. They had significantly higher postpartum Hb levels than normal mothers. These results raise the possibility that maternal iron reserves contribute to the development of glucose intolerance. Additionally, anaemic mothers have a lower incidence of gestational diabetes, supporting the iron hypothesis of diabetes once more (43)

4. ANEMIA AND DIABETES: An increased risk of diabetes was linked to higher serum ferritin and haemoglobin levels. (44)

FIGURE 3

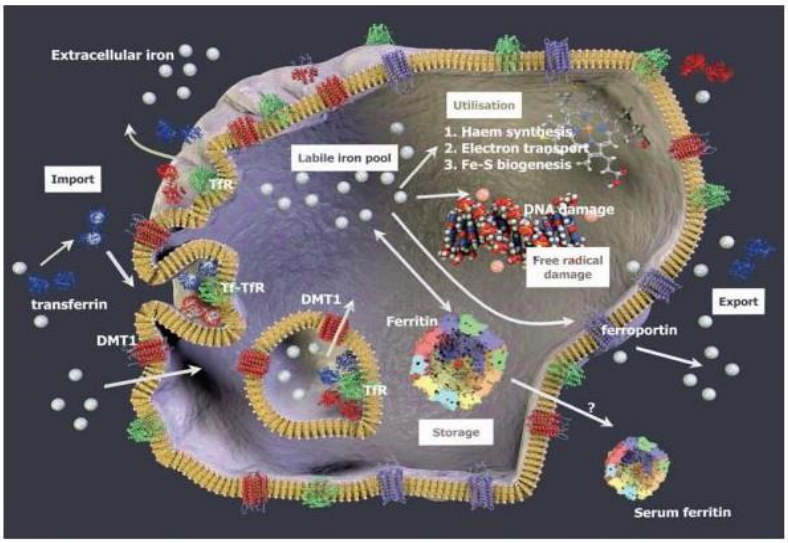


Fig. 3 Some relevant aspects of cellular iron metabolism, including ferritin and its possible loss to serum. The figure is not to scale, and is based in part on.[67] Membrane protein concentrations shown are lower (for clarity) than those in real cell membranes.[458] Diagram rendered by Dr Steve O'Hagan.

FIGURE 4

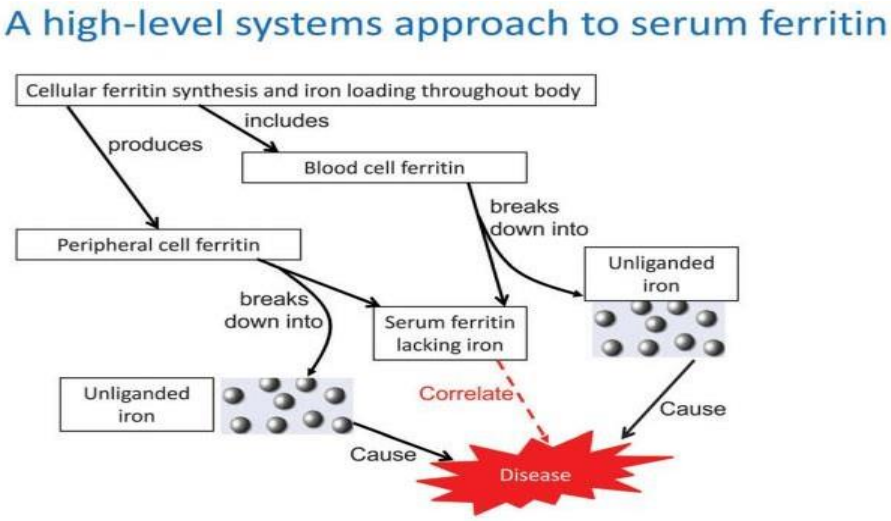


Fig. 6 A high-level systems approach to serum ferritin. The diagram serves to illustrate why there tend to be correlations between the amount of ferritin in cells, the rate of its excretion by cell damage (involving liberation of unliganded iron) and the levels of serum ferritin. The serum ferritin correlates with disease but the cause is iron, with which it too can correlate. As with any systems biology network, multiple differences in different elements of the network can lead to the same overall effects, explaining the lack of a perfect correlation with any individual process. Thus a first order rate of efflux of ferritin is the product of (and thus contains contributions from) both the internal ferritin concentration and the rate constant for efflux, which may vary independently. For these purposes we do not discriminate the many individual iron species.

C-REACTIVE PROTIEN

Acute inflammatory proteins like C-reactive protein (CRP), which are created at the sites of infection or inflammation. At the areas of infection and inflammation, monomeric C Reactive Protein , also known as native CRP (nCRP), a homopentameric protein that makes up CRP, can permanently split into five distinct monomers (mCRP). The primary sources of C Reactive Protien are the liver's hepatocytes, which also include smooth muscle cells, macrophages, endothelial cells, lymphocytes, and adipocytes.(45)

The complement cascade, apoptosis, phagocytosis, the release of nitric oxide (NO), and the creation of cytokines, specifically interleukin-6 and tumour necrosis factor, are few of the mechanisms that CRP plays a crucial role during inflammatory processes and host responses to infection. (45)

A homopentameric acute-phase inflammatory protein known as C-reactive protein was found in the sera of patients with acute pneumococcus infection by Tillet and Francis in 1930. This protein's name is derived from the way it interacts with the capsular (C)-polysaccharide of pneumococcus. (46)

When calcium is present, CRP activates C1q, which starts the conventional complement pathway of innate immunity. Phosphocholine (PCh), for example, is a polysaccharide on bacteria that C1q binds to and bonds with. Both vertebrates and some invertebrates have several homologs of CRP. It belongs to the pentraxin family, which also consists of chemical substances with similar structural characteristics, such as serum amyloid A. (47)

The protein structure of CRP is composed of five identical 23-kDa protomers stacked symmetrically and not covalently linked around a central pore. The term "pentraxins" has been used to describe the family of related proteins with this structure. According to research using x-ray crystallography, each protomer is folded into two antiparallel sheets with a flattened jellyroll structure, exactly like lectins like concanavalin A. (48)

The native CRP (nCRP), also known as the pentameric protein, is composed of five identical non-covalently bound subunits that each measure 206 amino acids in length and have a molecular weight of about 23 kDa. The pentameric protein gets its name from this arrangement. These five subunits are all oriented in the same direction around a central pore and are arranged in a recognisable "lectin fold" with a two-layered beta-sheet. (49)

Each subunit is positioned so that the PCh binding site is facing the nCRP molecule’s "recognition" face. The molecule has a face that binds ligands and is distinguished by having two calcium ions per protomer. The stability and binding of ligands depend on the calcium ions. The “opposite” face interacts with Fc receptors and the C1q component of the complement system.(50)

When the body is at rest, CRP is gradually released from the endoplasmic reticulum (in a non-inflammatory state). CRP's capacity to bind to carboxylesterases declines and it is secreted more quickly as inflammatory cytokine levels rise. The synthesis of CRP is predominantly

boosted in response to pro-inflammatory cytokines, particularly IL-6 and, to a lesser extent, Interleukin-1 and tumour necrosis factor-alpha (TNF-alpha). (51)

Complement is activated by C reactive Protein , which enhances phagocytosis. C Reactive Protein increases the release of Interleukin-1, Interleukin-6, Interleukin-18, and tumour necrosis factor as well as the creation and activity of plasminogen activator inhibitor-1. Furthermore, it induces a range of cell types to release IL-8.Additionally, it suppresses the expression of aortic endothelial nitric-oxide synthase and raises the expression of adhesion molecules in endothelial cells. (51)

Rheumatoid arthritis, a number of cardiovascular conditions, and infections with elevated c-reactive protein expression are all examples of inflammatory disorders. During inflammatory illnesses, the acute-phase protein CRP's plasma concentration fluctuates by at least 25%.(52) CRP levels are highest in the serum and can increase by a factor of 1,000 when bacterial infections are present. (53)

The levels of CRP in plasma increase from 1 g/mL to over 500 g/mL within 24 to 72 hours of substantial tissue damage, such as trauma or the onset of cancer. (54)

CRP IN DISEASE PATHOLOGY

Elevated serum levels of C reactive protein are a reliable, independent predictor of cardiovascular disease in asymptomatic patients, which are utilised as a clinical measure of inflammation. In patients with atherosclerotic disease, , myocarditis, aortic valve disease atrial fibrillation, congestive heart failure and heart transplantation, C reactive protein levels have been linked to prognosis, demonstrating a critical role for this protein in the pathogenesis of cardiovascular disease. (55)

Patients at risk for cardiovascular disease are identified by high sensitivity assays, such as nephelometric assays. A person with a C reactive protein level of more than 3 mg/L has an elevated risk of coronary heart disease, and those with type 2 diabetes mellitus have an even higher risk.(55)

During rest, the body gradually releases C reactive protein from the endoplasmic reticulum (in a non-inflammatory state). C reactive protein's capacity to bind to carboxylesterases, however, reduces when inflammatory cytokine levels rise and it is released more quickly. The main pro-inflammatory cytokines that increase C Reactive Protein synthesis are tumour necrosis factor alpha (TNF-), IL-6, and IL-1. (51)

CRP AND INFLAMMATION

The activation of the C1q molecule in the complement pathway, which results in the opsonization of pathogens, is believed to be one of C Reactive Protein's primary functions in inflammation. In addition to starting host defence responses in the fluid phase by activating the complement system, C Reactive Protein can also start cell-mediated pathways by binding to IgG Fc receptors. (56)

Additionally, it has been demonstrated that C Reactive Protein contributes to atherogenesis by activating the complement system and facilitating the uptake of low-density lipoprotein by macrophages. Atherosclerotic plaques undergo apoptosis, and more cells undergo this process as lesions progress. Growth arrest and the expression of the DNA damage-inducible gene 153 (GADD153)are brought on by apoptotic cells breaking up plaques .(57)

According to research, C Reactive Protien can cause the death of human coronary vascular smooth muscle cells by a caspase-mediated mechanism, mainly through enhanced caspase-3 activity.Numerous cancer cell types have been demonstrated to experience G1 arrest or apoptosis when GADD153 is overexpressed. Atherosclerotic lesions were shown to have C reactive protein localised to the GADD153 gene product, indicating that C reactive protein promotes the expression of the GADD153 gene to initiate the caspase cascade and apoptosis.(57)

Risk of Developing Type 2 Diabetes Mellitus and C-Reactive Protein

Type 2 diabetes mellitus has been associated with high levels of inflammatory protein synthesis and persistent low-grade inflammation. The inflammatory mediators interleukin 6 (IL-6) and TNF-, which are produced by adipocytes, regulate the inflammatory marker of Type 2 diabetes mellitus known as C-reactive protein (CRP), which is produced by liver cells.(58)

Obesity, hypertension, binge drinking, smoking, and insufficient exercise have all been linked to chronic inflammation with high CRP levels. Numerous cohort studies that found higher CRP levels in male and female individuals suggested that CRP is a risk factor for the development of T2DM.(58)

Body mass index and insulin resistance have little bearing on the association between CRP and Type 2 diabetes mellitus . The association between CRP level and incidence of T2DM remained statistically significant even after adjusting for BMI, according to a number of research that have shed light on the part CRP plays in the development of T2DM.(59)

It is believed that increased CRP causes insulin resistance by activating the complement cascade, promoting the generation of thrombogenic

agents, increasing the expression of endothelial adhesion molecules, and decreasing endothelial nitric oxide synthase (eNOS).(58)

Evidence points to CRP's role as an essential inflammatory process regulator, not merely as an indicator of infection or inflammation. Participants' blood is drawn after a 10- to 12-hour fast in order to conduct the following tests, including complete blood count, fasting lipid profile, PPBS, HbA1c, serum ferritin, and C reactive protein.

Liver produces the acute-phase reactant C-reactive protein, a highly sensitive indicator of systemic inflammation. High-sensitivity C-reactive protein (hsCRP) levels suggest chronic low-grade inflammation, which potentially underlies the genesis and expression of type 2 diabetes (T2DM)

Subjects with high levels of inflammatory markers have been found to have an elevated incidence of Type 2 diabetes mellitus vascular problems. The assessment of the vascular risk in Type 2 diabetes mellitus patients may benefit from the measurement of inflammation-related markers. Type 2 diabetes mellitus' etiology is associated with inflammation. This may suggest a relationship between diabetes mellitus and the onset of atherosclerosis because insulin resistance and hyperglycemia both enhance oxidative stress while also promoting inflammation.(60)

FIGURE 5

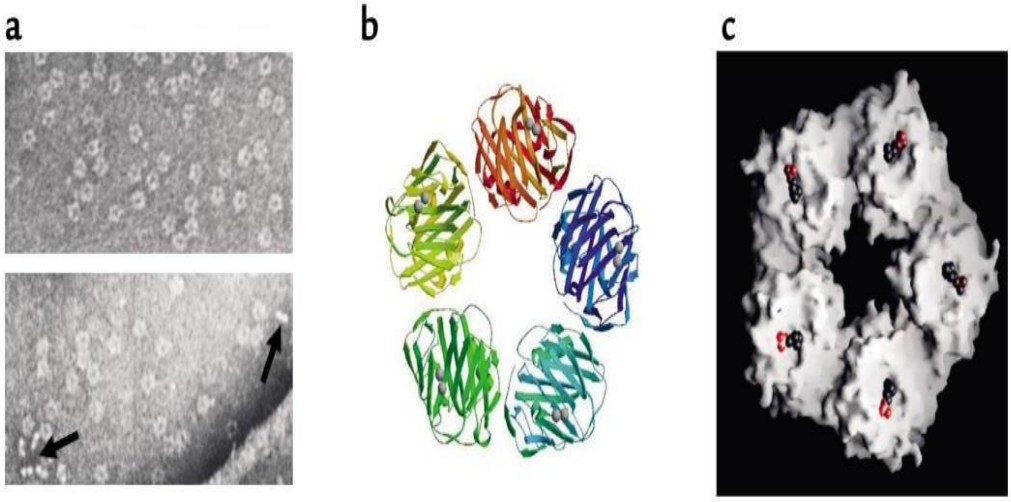


Figure 1

Molecular structure and morphology of human CRP. (**a**) Negatively stained electron micrograph showing the typical pentameric disc-like structure face-on and side-on (arrows). (**b**) Ribbon diagram of the crystal structure, showing the lectin fold and the two calcium atoms (spheres) in the ligand-binding site of each protomer (6). (**c**) Space-filling model of the CRP molecule, showing a single phosphocholine molecule located in the ligand-binding site of each protomer (6).

FIGURE 6

CRP responses in disease

Major CRP acute-phase response	
Infections	Bacterial
	Systemic/Severe fungal, mycobacterial, viral
Allergic complications of infection	Rheumatic fever
	Erythema nodosum
Inflammatory disease	Rheumatoid arthritis
	Juvenile chronic arthritis
	Ankylosing spondylitis
	Psoriatic arthritis
	Systemic vasculitis
	Polymyalgia rheumatica
	Reiter disease
	Crohn disease
	Familial Mediterranean fever
Necrosis	Myocardial infarction
	Tumor embolization
	Acute pancreatitis
Trauma	Surgery
	Burns
	Fractures
Malignancy	Lymphoma
	Carcinoma
	Sarcoma
Modest or absent CRP acute-phase response	
	Systemic lupus erythematosus
	Scleroderma
	Dermatomyositis
	Ulcerative colitis
	Leukemia
	Graft-versus-host disease

MATERIAL AND METHODS

METHODOLOGY

1. SOURCE OF DATA:

The information for the study is collected from TYPE 2 DIABETES MELLITUS patients, including OPD and IPD in B.L.D.E. (DU) Shri B.M.Patil medical college and research centre, vijaypura 583106, Karnataka from DECEMBER 2020 TO JUNE 2022

2. METHOD OF COLLECTION OF DATA:

Each patient with TYPE 2 DIABETES MELLITUS admitted to the medical wards and the outside patient department of medicine provided information using a prepared proforma.

the sociodemographic information gathered through face-to-face interviewing.

Participants' heights were measured using a stadiometer (in centimetres), weights were calculated using a weighing scale (in kilogrammes), and blood pressure was determined using a mercury sphygmomanometer by a single operator.

Body Mass Index (BMI) values for the patients were determined using the formula of weight (kg) / height (m2), and they were categorised as follows:

18 underweight,

18 to 24.9% of the normal weight,

25 to 29.9% overweight,

and 29.9% obese.

Participants' blood is drawn after a 10- to 12-hour fast in order to conduct the following tests, including complete blood count, fasting lipid profile, PPBS, HbA1c, serum ferritin, and C reactive protein.

Inclusion Criteria:

1. Patients with current therapies (i.e., OHA'S, insulin, OHA'S combined with insulin)
2. Newly diagnosed type 2 DM

Exclusion Criteria:

1. Males and females having haemoglobin (Hb) levels of at least 13 mg/dl and below 12 mg/dl, respectively
2. People who have undergone anaemia treatment in the previous two months
3. Individuals with recent hepatitis or coronary artery disease
4. Patients undergoing chemotherapy or radiation,
5. Individuals suffering from a haematological illness, such as hemochromatosis, porphyria, leukemia, or Hodgkin lymphoma.
6. Inflammatory diseases like rheumatoid arthritis and infections like pneumonia

TYPE OF STUDY: Cross- Sectional study

SAMPLE SIZE

The standard normal deviate for $\alpha = Z_\alpha = 2.0537$

The standard normal deviate for $\beta = Z_\beta = 0.8416$

$C = 0.5 * \ln[(1+r)/(1-r)] = 0.2855$

Sample size= 106

With Anticipated correlation between Serum ferritin levels and HbA1c r=0.278 (ref), at 95%confidence level and 80 power in the study, the sample size worked out is 106.

Formula used is

$$N=\left[\left(\frac{Z_\alpha+Z_\beta}{C}\right)\right]^2+3$$

The standard normal deviate for $\alpha = Z_\alpha = 2.0537$

The standard normal deviate for $\beta = Z_\beta = 0.8416$

$$C=0.5*\ln\left[\frac{1+r}{1-r}\right]=0.2855$$

N=106

Statistical Analysis

- Using the statistical software for the social sciences, the data will be analysed statistically after being entered into a Microsoft Excel sheet (Version 20).
- The results will be shown as counts, percentages, graphs, and mean (median) SD.
- Two groups' categorical variables will be compared using the Chi square test.
- The correlation between quantitative variables will be determined using the correlation coefficient. .$p<0.05$ will be considered statistically significant. All statistical tests will performed two tailed.

RESULTS

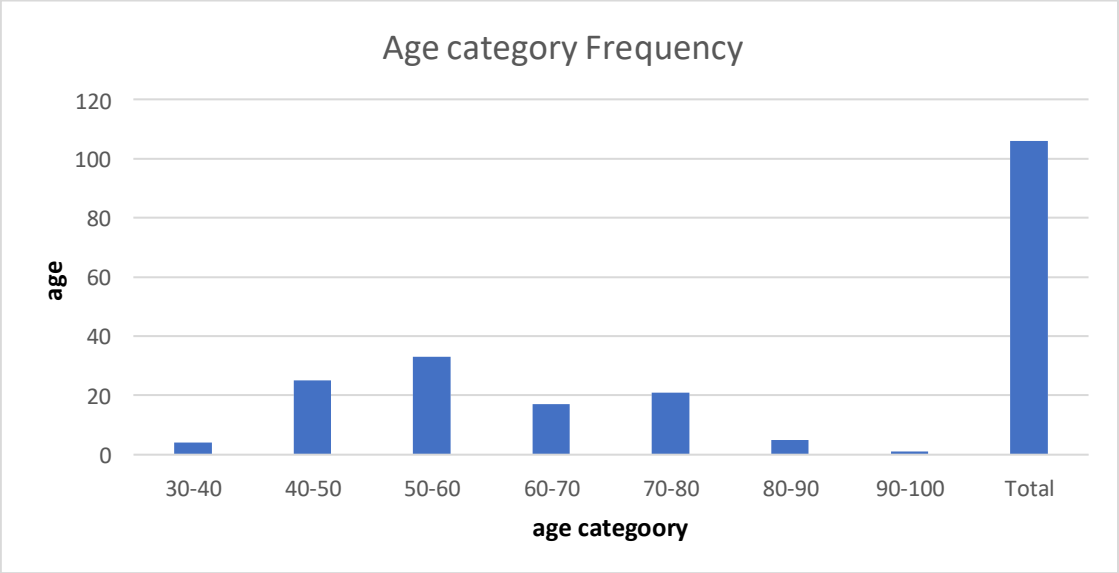
RESULTS

In this study , DIABETIC PATIENTS were distributed among age group, we found that, out of 106 pt , 31.1% were in 50-60 age group, followed by 40-50 age group having 23.6%,least was in 30-40 age group.

TABLE 5

Age category	Frequency	Percent
30-40	4	3.9
40-50	25	23.6
50-60	33	31.1
60-70	17	16.0
70-80	21	19.8
80-90	5	4.7
90-100	1	.9
Total	106	100.0

FIGURE 7

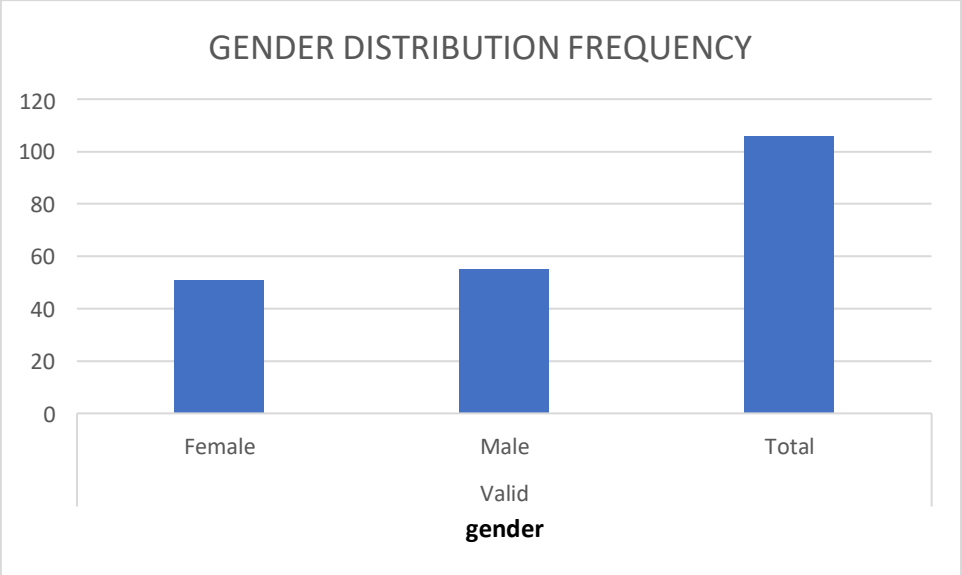


In this study among 106 pts , 51.9%were males, 48.1% were females.

TABLE 6

SEX		Frequency	Percent
Valid	Female	51	48.1
	Male	55	51.9
	Total	106	100

FIGURE 8



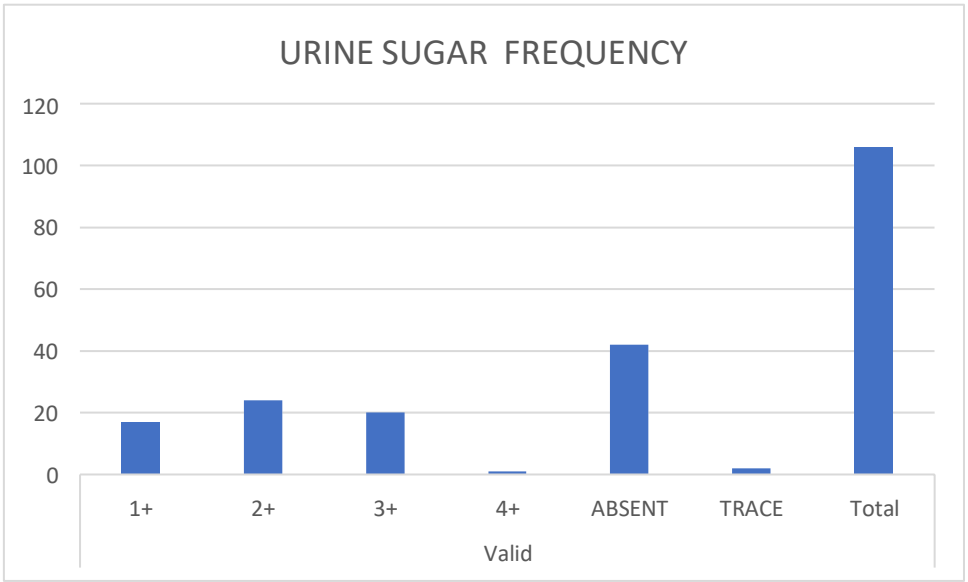
Among 106 pts , 39.6% had absent urine sugar, 22.6 % had 2 + urine sugar, 18.9% had 3+, 16% had 1+.

TABLE 7

URINE SUGAR

		Frequency	Percent
Valid	1+	17	16
	2+	24	22.6
	3+	20	18.9
	4+	1	0.9
	ABSENT	42	39.6
	TRACE	2	1.9
	Total	106	100

FIGURE 9

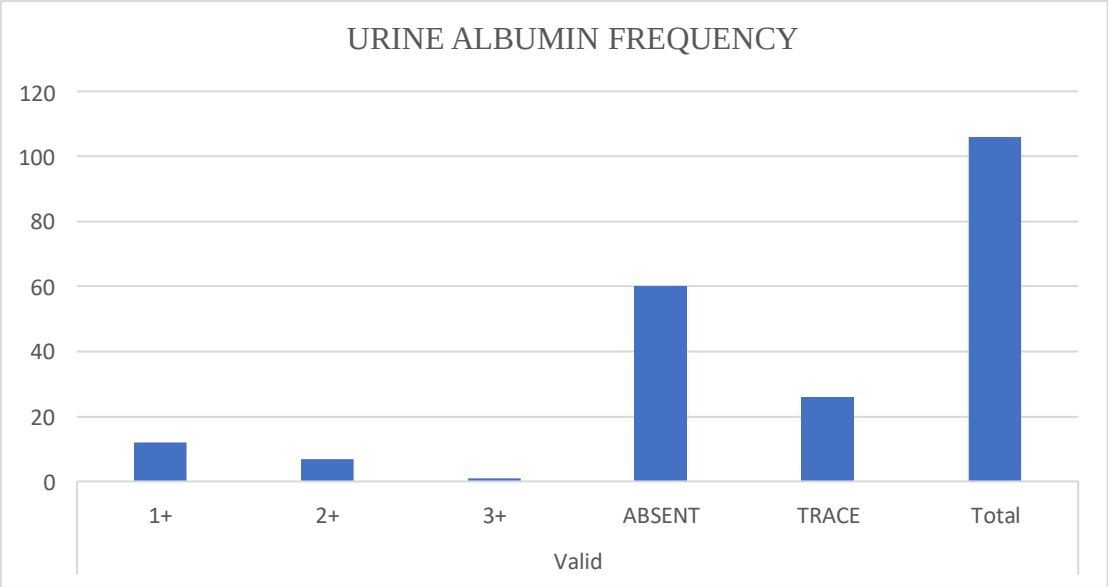


Among 106 diabetic patients, 56.6% had absent urine albumin , 24.5 % had trace albumin, 11.3% had 1+ albumin, 6.6% had 2+ albumin.

TABLE 8

URINE ALBUMIN		Frequency	Percent
Valid	1+	12	11.3
	2+	7	6.6
	3+	1	0.9
	ABSENT	60	56.6
	TRACE	26	24.5
	Total	106	100

FIGURE 10

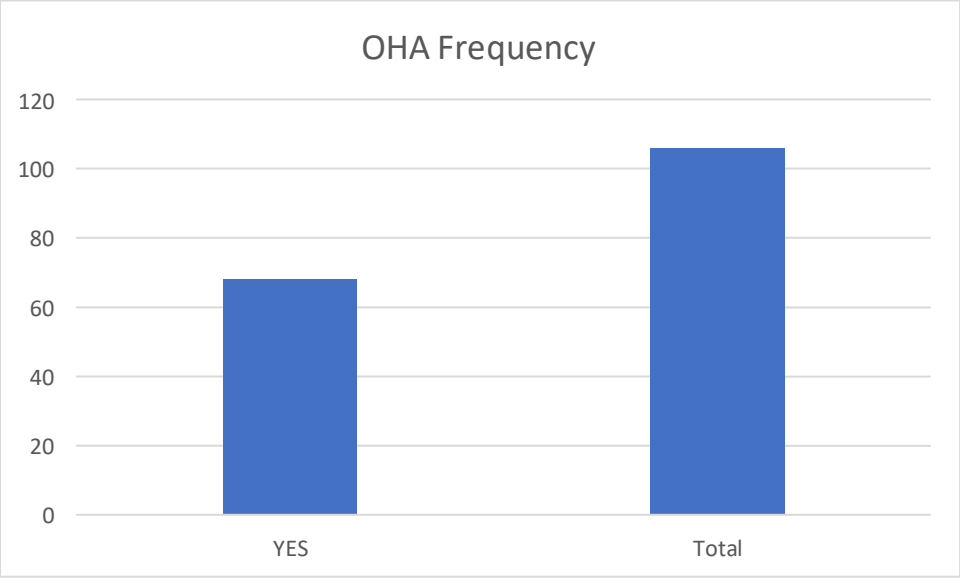


In our study, among 106 patients, 68 were using oral hypoglycaemic drugs, constituting 64.2 %

TABLE 9

OHA		Frequency	Percent
Valid		38	35.8
	YES	68	64.2
	Total	106	100

FIGURE 11

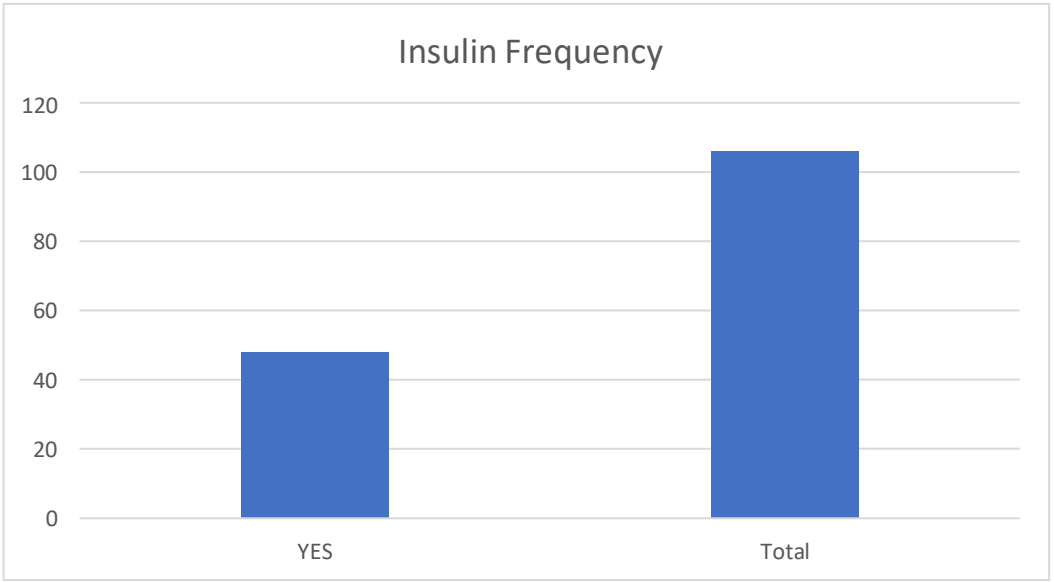


Among 106 patients in our study, 48 were on insulin, constituting 45.3%

TABLE 10

INSUILN		Frequency	Percent
Valid		58	54.7
	YES	48	45.3
	Total	106	100

FIGURE 12



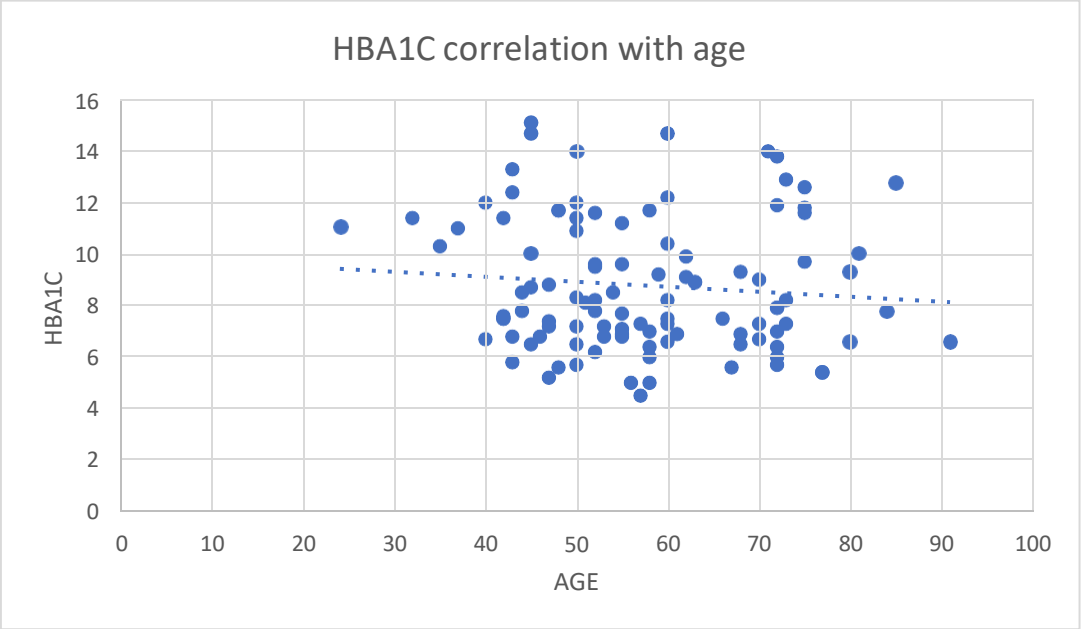
CORRELATION BETWEEN AGE AND HbA1c

TABLE 11

	r value	p value
Pearson Correlation between AGE & HbA1c	-0.098	0.317

negative correlation with HBA1c

FIGURE 13



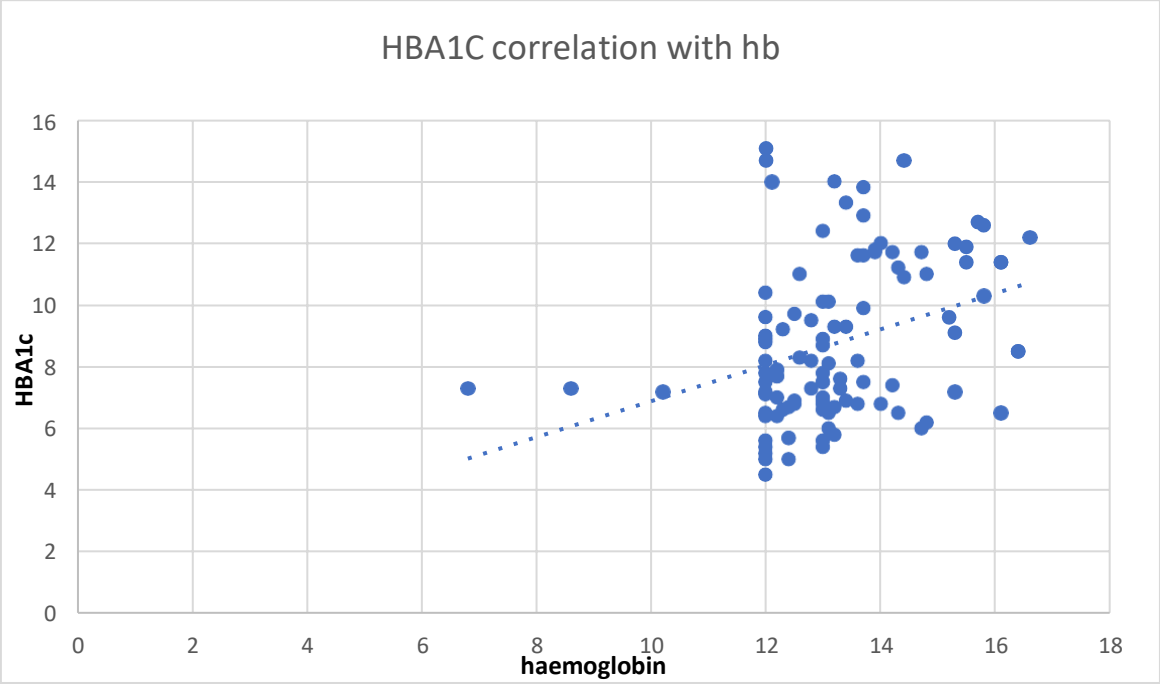
CORRELATION BETWEEN Hb AND HbA1c

TABLE 12

	r value	p value
Pearson Correlation between Hb & HbA1c	0.377	0

Positive correlation is found with haemoglobin and Hba1c

FIGURE 14



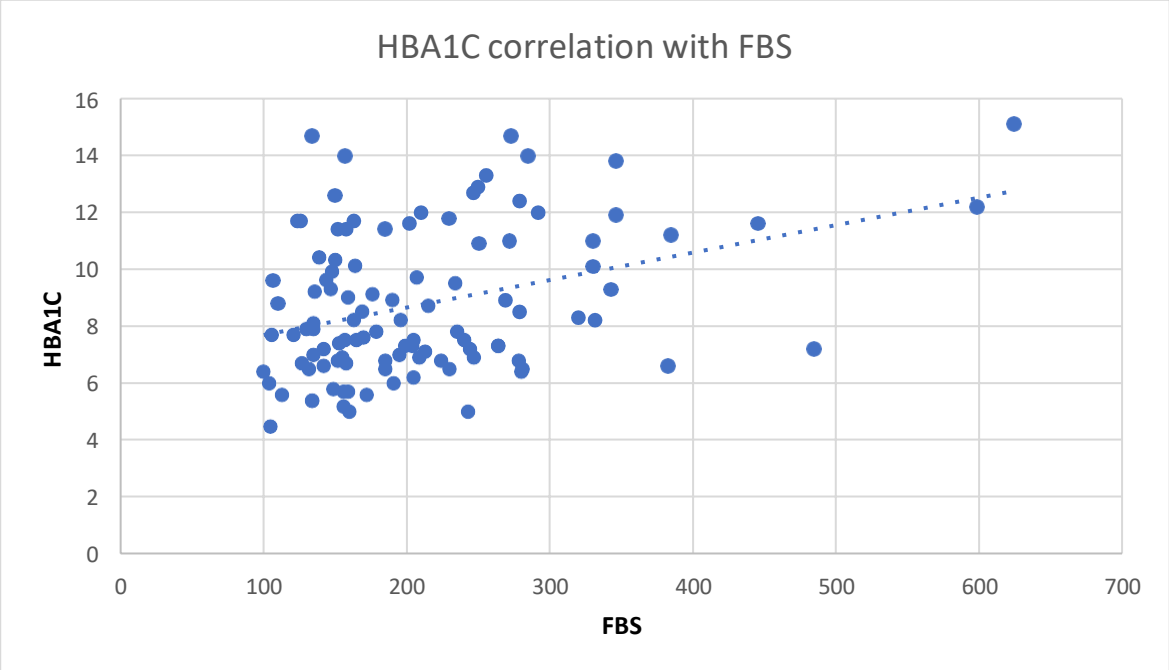
CORRELATION BETWEEN FBS AND HbA1c

TABLE 13

	r value	p value
Pearson Correlation between FBS & HbA1c	0.357	0

POSITIVE CORRELATION WITH HBA1c

FIGURE 15



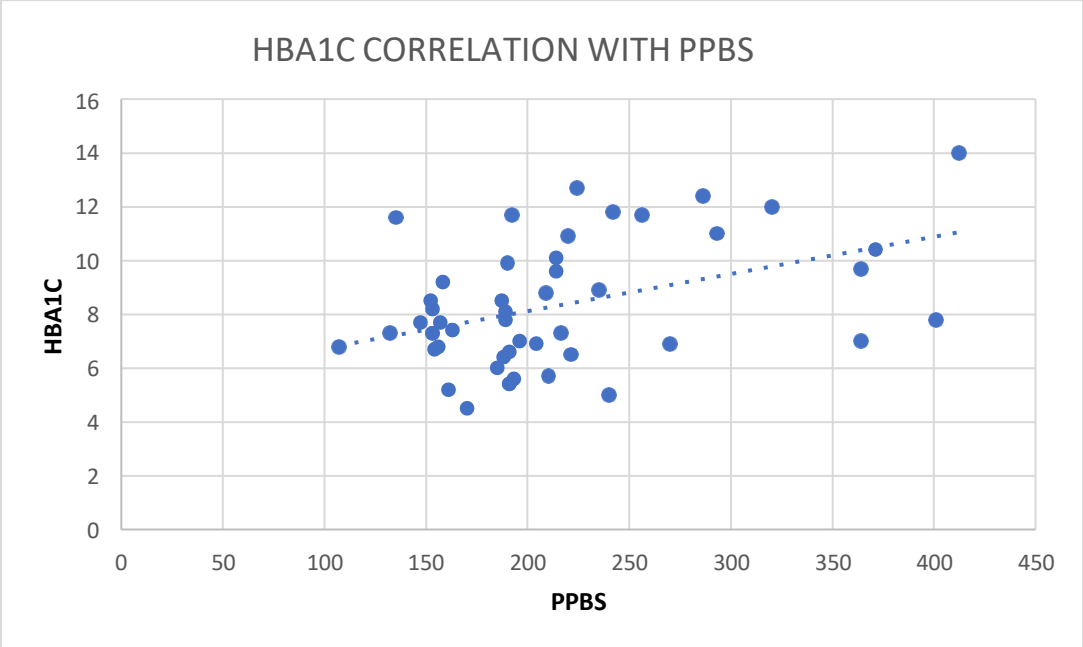
CORRELATION BETWEEN PPBS AND HbA1c

TABLE 14

	r value	p value
Pearson Correlation between PPBS & HbA1c	0.425	0.002

POSITIVE CORRELATION WITH HBA1c

FIGURE 16



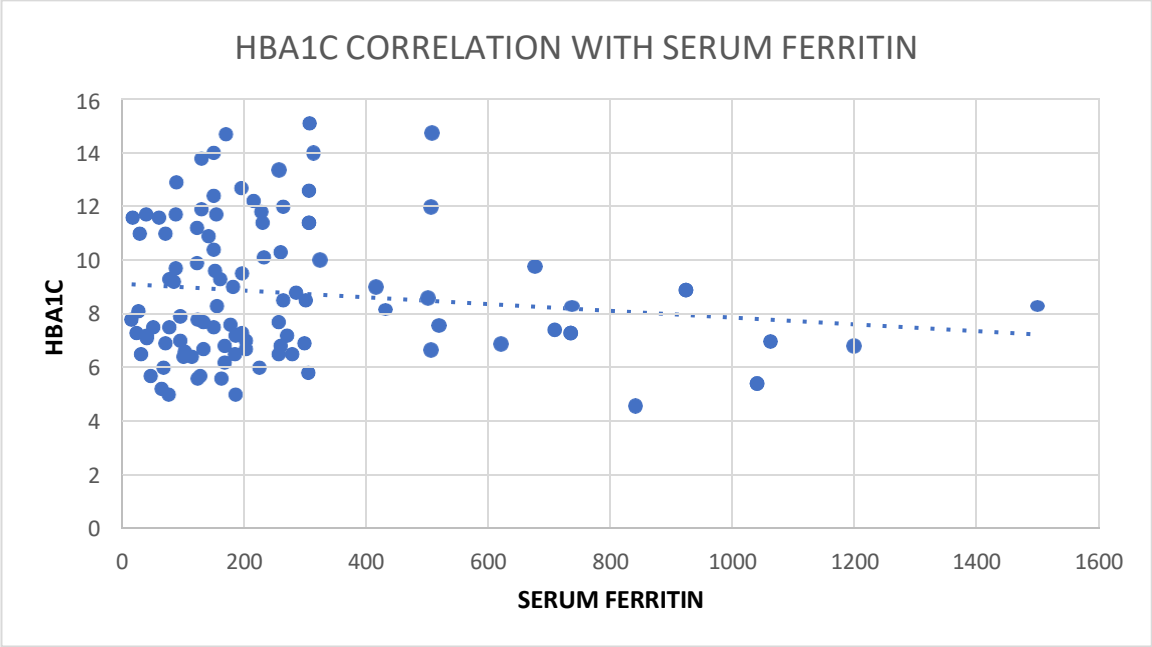
CORRELATION BETWEEN SERUM FERRITIN AND HbA1c

TABLE 15

	r value	p value
Pearson Correlation between PPBS & HbA1c	0.011	0.911

POSITIVE CORRELATION IS FOUND BETWEEN SERUM FERRITIN AND HBA1c

FIGURE 17



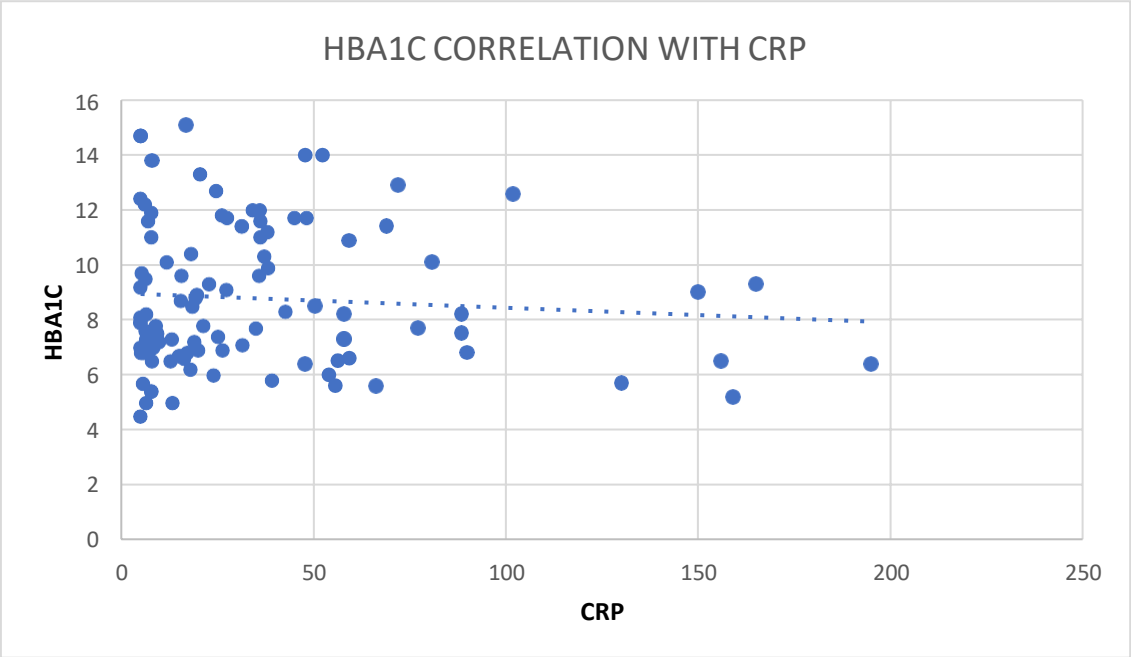
CORRELATION BETWEEN CRP AND HbA1c

TABLE 16

	r value	p value
Pearson Correlation between CRP & HbA1c	0.017	0.865

POSITIVE CORRELATION IS FOUND BETWEEN CRP AND HBA1c

FIGURE 18



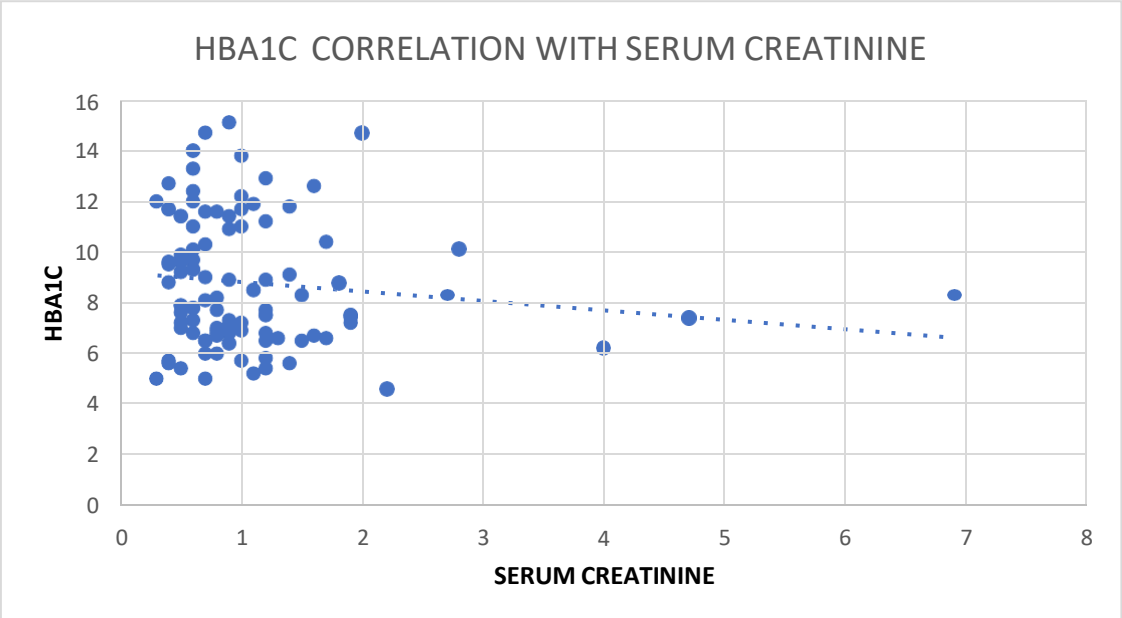
CORRELATION BETWEEN SERUM CREATININE AND HbA1c

TABLE 17

	r value	p value
Pearson Correlation between SERUM CREATININE& HbA1c	-0.166	0.09

NEGATIVE CORRELATION IS FOUND BETWEEN SERUM CREATININE AND HBA1c

FIGURE 19



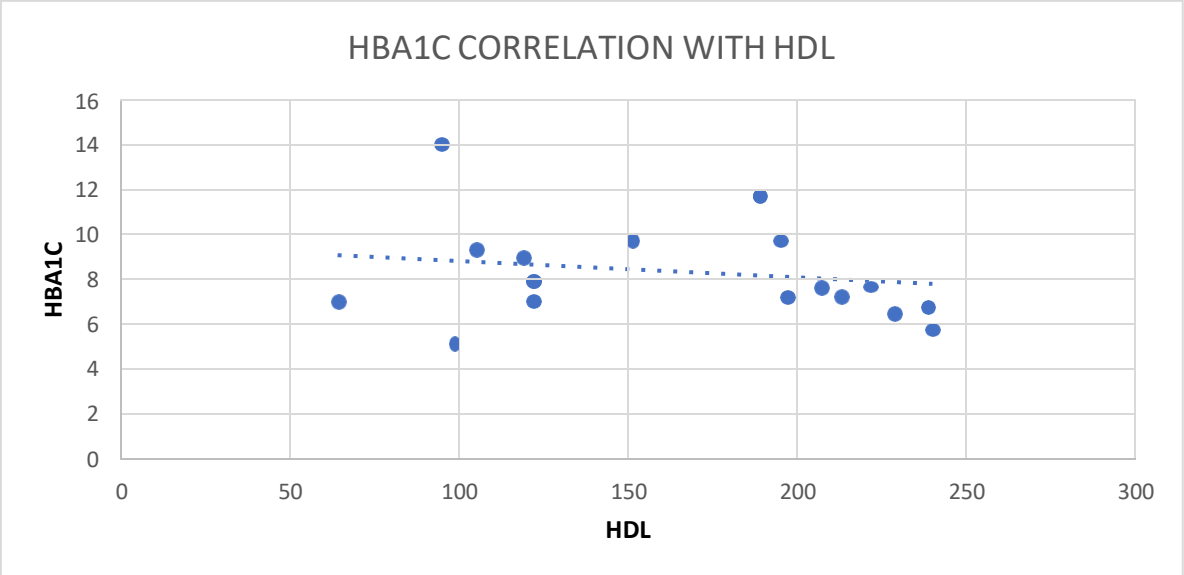
CORRELATION BETWEEN HDL AND HbA1c

TABLE 18

	r value	p value
Pearson Correlation between HDL & HbA1c	-0.166	0.09

NEGATIVE CORELATION WITH HBA1C

FIGURE 20



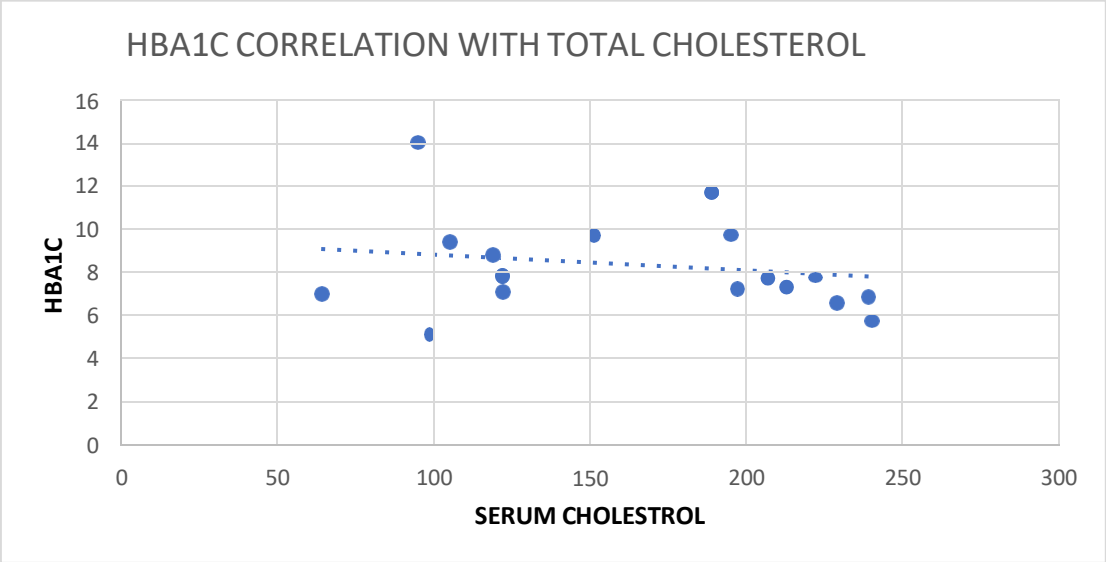
CORRELATION BETWEEN LDL AND HbA1c

TABLE 19

	r value	p value
Pearson Correlation between LDL & HbA1c	-0.018	0.457

NEGATIVE CORRELATION WITH HBA1c

FIGURE 21



DISCUSSION

DISCUSSION

Diabetes mellitus is being one of the most prevalent disease in developing countries. Genetic , environmental factors play a major role in pathophysiology of disease status. Increase in insulin resistance , decrease in insulin production, and eventual beta cell failure produces a chronic inflammatory condition in our body.These conditions can be measured by inflammatory markers such as serum ferritin and c -reactive protein. Although parameters such as HBA1c , FBS and ,PPBS are used to diagnose and screen for diabetes mellitus, inflammatory markers would help us to know the severity and complications of disease state.

This present cross sectional study was conducted in BLDE's (Deemed to be University) Shri B M Patil Medical College and Research Centre over a period of 2 years, on 106 T2DM patients. In 106 patients, HbA1c levels were correlated with serum ferritin and c-reactive protein levels, which were obtained after proper blood sampling and laboratory processes. Obtained parameters are tabulated and by statistical analysis an association of serum ferritin ,c-reactive protein and HbA1c is drawn.

In this present study on T2DM patients, it is found that 31.1% of study sample were 50-60years of age, 23.6 % were in 40-50 age group, 19.8% were in 70-80 age group. And it is understandable that type 2 diabetes mellitus is disease most often seen in elderly, T2DM prevalence in the elderly in this study is in accordance with the literature. In this study group 51.9% of patients were males and 48.1% were females.

In this study, urine sugars were present in majority of patients , urine albumin was absent in 56.6 % patients

Oral hypoglycemics were used by 68 patients, 48 used insulin , among these 10 used a combination therapy of OHA'S and insulin.

According to statistical analysis, mean of HBA1c,serum ferritin, c-reactive protein are 8.7, 279.8, 35.4 respectively.

According to this study group, positive correlation was found between serum ferritin and HBA1c ,positive correlation between c reactive protein and HBA1c

40% of Type 2 DM patients in a research by Elisabeth Svensson et al. had higher crp levels; modifiable risk factors included inactivity and central adiposity (61)

Relationships between CRP and incidence T2DM were more significant in the elderly group (>50 years old), according to research by Suganya Kanmani et al. CRP, hypertension, and obesity were all associated with an increased risk of T2DM. They came to the conclusion that there were positive correlations between CRP and incident Type 2 diabetes mellitus in a significant population-based Korean cohort. (62)

Low-grade systemic inflammation was linked to a higher risk of type 2 diabetes mellitus in middle-aged males, according to a cohort research by Barbara Thorand et al. One mechanism through which well-known risk factors for diabetes mellitus, like obesity, smoking, and hypertension, encourage the onset of diabetes mellitus is inflammation. (63)

In Type 2 diabetes mellitus with and without nephropathy, Hs-CRP was found to be substantially correlated with the metabolic characteristics and predictors of cardiovascular risk, according to research by Abid K. Shaheer1 et al. The development of nephropathy and cardiovascular risk in Type 2 diabetes patients may be predicted or indicated by the hs-CRP. (64)

According to Rui Zhang et al., T2DM subjects had higher blood ferritin levels and an iron problem. Reduced liver TFR2 levels were seen in diabetic rats along with elevated serum ferritin levels. (65)

Serum ferritin and type 2 diabetes are closely related, according to F Khondker et al., and may be a significant and independent predictor of the development of diabetes mellitus. (66)

In a study, Tanveer Ahmed used serum ferritin as a measure to explain how type 2 diabetes mellitus causes oxidative stress. This important information would aid in appropriate medical intervention. (67)

Though positive correlation between serum ferritin ,crp levels and HbA1c values which are in accordance with the above mention studies, in this study we did not find any statistically any significant correlation, which could be due to not taking duration of diabetes into consideration and due to smaller sample size.

With increase in levels of serumferritin and c reactive protein , mean HbA1c values are increasing with positive correlation, which are

statistically not significant (p value > 0.05 A Back ground history medications for T2DM and co morbid conditions was taken and were grouped into groups taking insulin, OHAs, On analyzing no significant association is found between any group of drugs with serum ferritin and crp levels with HbA1c values.

In this cross sectional study, the acute and chronic dynamic changes in serum ferritin and crp levels with HbA1c and their association could not be ascertained with confidence. Therefore it is advisable that larger study sample with a prospective study design aiming at studying of dynamic changes in inflammatory markers would lead to significant correlation with HBA1c

CONCLUSION

In this study, there is a positive correlation between inflammatory markers such as serum ferritin ,crp levels with HbA1c values though statistically not significant, showing higher HbA1c values with higher serum ferritin ,crp levels. Raised inflammatory markers suggestive of a chronic inflammatory process which occurs in a condition or disease process such as diabetes mellitus Measuring these values gives us valuable information on screening, duration of diabetes, and prevention of complications.

SUMMARY

Diabetes mellitus is a non communicable disease which is increasing in prevalence in global epidemic proportions putting stress on health care expenditure To study the association between diabetes and inflammatory markers, in this study serum ferritin CRP and HbA1c levels were assessed in T2DM patients and their correlation was studied.

Data for the study was collected from patients admitted to BLDE'S (Deemed to be University) Shri B M Patil Medical College Hospital and Research Centre, Vijayapura from November 2020 to June 2022. Patients were screened and who met inclusion criteria was included in the study. A cross sectional study was done on 106 patients, and HbA1c levels with serum ferritin and crp levels were obtained and were analyzed for association and correlation.

In our study majority of patients with 31.1% were in 50-60 age group . Majority of them were males, urine albumin was present in approximately 20% of them.

In this study standard deviation of HBA1c IS 2.5, SERUM FERRITIN is 284.64, CRP being 38.57 The Spearman's rho correlation between serum ferritin and HbA1c, the r value is 0.011 and p value is 0.911

The Spearman rho's correlation between C reactive protein and HbA1c, the r value is 0.017 and p value is 0.865

There was no association between age, gender, and with both inflammatory marker levels and HbA1c levels.

In type 2 diabetes mellitus patients, the mean HbA1c levels were found to be higher with serum ferritin and CRP levels values being high when compared to patients with normal value of inflammatory markers. There is a positive correlation between serum ferritin , crp and HbA1c

LIMITATIONS OF THE STUDY

1. Sample size is relatively small

2. Any chronic inflammatory condition would raise values of inflammatory markers which is not specific to diabetes mellitus.

3. Study design is cross sectional which could be confounding in a casual relation between serum ferritin, crp and HbA1c.

4. Duration of diabetes is not considered in the study

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ANNEXURE I

B.L.D.E. (DEEMED TO BE UNIVERSITY) IEC/NO-09/2021
(Declared vide notification No. F.9-37/2007-U.3 (A) Dated. 29-2-2008 of the MHRD, Government of India under Section 3 of the UGC Act, 1956) Date-22/01/2021
The Constituent College
SHRI. B. M. PATIL MEDICAL COLLEGE, HOSPITAL AND RESEARCH CENTRE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Institutional ethical committee of this college met on 11-01-2021 at 11am to scrutinize the synopsis of Postgraduate students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected and revised version synopsis of the Thesis has been accorded Ethical Clearance

Title: A study on serum ferritin and CRP levels in association with HbA1cIN Type 2 diabetes mellitus

Name of PG student: Dr Nikitha R, Department of Medicine

Name of Guide/Co-investigator: Dr Sanjeev Kumar N Bentoor, Professor of Medicine

DR .S.V.PATIL
CHAIRMAN
Institutional Ethical Committee
B L D E (Deemed to be University)
Shri B.M. Patil Medical College,
VIJAYAPUR-586103 (Karnataka)

Following documents were placed before Ethical Committee for Scrutinization:

1. Copy of Synopsis / Research project
2. Copy of informed consent form
3. Any other relevant documents.

15

ANNEXURE II

CONSENT FORM

BLDEDU'S SHRI B. M. PATIL MEDICAL COLLEGE HOSPITAL AND

RESEARCH CENTRE, VIJAYAPUR- 586103

TITLE OF THE PROJECT - : A STUDY ON SERUM FERRITIN, CRP LEVELS AND ITS CORRELATION WITH HbA1c IN TYPE 2 DIABETES MELLITUS

PRINCIPAL INVESTIGATOR - Dr. NIKITHA.R

+91 9880405411

P.G.GUIDE NAME - Dr. SANJEEVKUMAR N. BENTOOR

PROFESSOR OF MEDICINE

08352-, Ext-2148

All aspects of this consent form are explained to the patient in the language understood by him/her.

INFORMED PART

PURPOSE OF RESEARCH:

I have been informed about this study. I have also been given a free choice of participation in this study.

PROCEDURE:

I am aware that in addition to routine care received I will be asked series of questions by the investigator. I have been asked to undergo the necessary investigations and treatment, which will help the investigator in this study.

RISK AND DISCOMFORTS:

I understand that I may experience some pain and discomfort during the examination or during my treatment. This is mainly the result of my condition and the procedure of this study is not expected to exaggerate these feelings that are associated with the usual course of treatment.

BENEFITS:

I understand that my participation in this study will help to patient's survival and better outcome.

CONFIDENTIALITY:

I understand that the medical information produced by this study will become a part of Hospital records and will be subject to the confidentiality and privacy regulation. Information of a sensitive personal nature will not be a part of the medical records, but will be stored in the investigator's research file and identified only by code number. The code-key connecting name to numbers will be kept in a separate location.

If the data are used for publication in the medical literature or for teaching purpose, no name will be used and other identifiers such as photographs and audio or videotapes will be used only with my special written permission. I understand that I may see the photographs and videotapes and hear the audiotapes before giving this permission.

REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at anytime.

Dr. NIKITHA.R is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of the study, which might influence my continued participation.

If during the study, or later, I wish to discuss my participation in or concerns regarding this study with a person not directly involved, I am aware that the social worker of the hospital is available to talk with me. A copy of this consent form will be given to me to keep for careful reading.

REFUSAL OR WITHDRAWAL OF PARTICIPATION:

I understand that my participation is voluntary and that I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice to my present or future care at this hospital. I also understand that Dr. NIKITHA.R may terminate my participation in the study after she has explained the reasons for doing so and has helped arrange for my continued care by my own physician or physical therapist, if this is appropriate

INJURY STATEMENT:

I understand that in the unlikely event of injury to me resulting directly from my participation in this study, if such injury were reported promptly, the appropriate treatment would be available to me, but no further compensation would be provided. Iunderstand that by my agreement to participate in this study I am not waiving any of my legal rights.

I have explained to the purpose of the research, the procedures required and the possible risks and benefits to the best of my ability in patient's own language.

_____ _____

Dr.NIKITHA.R Date

(Investigator)

STUDY SUBJECT CONSENT STATEMENT:

I confirm that Dr. NIKITHA.R has explained to me the purpose of research, the study procedures that I will undergo, and the possible risks and discomforts as well as benefits that I may experience in my own language. I have read and I understand this consent form. Therefore, I agree to give consent to participate as a subject in this research project.

_____ _____

Participant / Guardian Date

_____ _____

Witness to signature Date

ANNEXURE – III

CASE PROFORMA

Name: CASE NO:

Age: IP NO:

Sex: DOA:

Religion: DOD:

Occupation:

Residence:

Presenting complaints with duration:

History of present complaints:

Past History:

Family History

Personal History:

Diet/appetite Sleep

Bladder and bowel habits: Addictions

Drug allergy

Treatment History:

General Physical Examination

Height: Weight:

Body Mass Index: Vitals

PR:

BP:

RR:

Temp

Neck:

Upper Limbs: Chest:
Abdomen: Lower Limbs:
Skin:

SYSTEMIC EXAMINATION.

Respiratory System

Cardiovascular System

Central Nervous System

Per abdomen

FINAL DIAGNOSIS:

INVESTIGATIONS

Complete blood count

FBS,

PPBS

HbA1c,

Serum ferritin,

CRP,

Fasting lipid profile

LFT

RFT

USG

2DECHO ,ECG

ANNEXURE IV MASTERCHART

NAME	AGE	SEX	IPNO	HB	FBS	PPBS	HBA1C	SERUM FERRITIN	CRP	S. CREAT	HDL	LDL	T.CHOL	URINE SUGAR	URINE ALBUMIN	OHA
SHIVANAND	45	M	162098	13	164	214	10.1	324	80.7	0.6				2+	ABSENT	YES
SHARANAPPA	44	M	66298	16.4	169	152	8.5	300	50.4	1.1				3+	ABSENT	
ANASUBAI	55	F	223090	12.2	121	157	7.7	256	35	1.2	57	183	207	ABSENT	ABSENT	YES
KAMALA	62	F	208707	13.7	148	190	9.9	123	38.2	0.5				2+	1+	
GURUSIDAPPA	73	M	70358	13.6	196	153	8.2	736.7	57.9	6.9				ABSENT	ABSENT	
KASTURI	72	F	218062	12.4	159	210	5.7	128	130	0.4	56	172	240	ABSENT	ABSENT	YES
ADIVEPPA	71	M	149508	13.2	285	412	14	150	52.3	0.6	31		95	3+	TRACE	YES
KAMALABAI	58	F	178431	13	195	196	7	202.6	8.4	0.8				2+	TRACE	YES
SHANTA	48	F	113555	14.2	124	256	11.7	154	45	0.4	31	31	189	ABSENT	ABSENT	YES
KAVERI	40	F	213144	14	292	320	12	506	36	0.3				ABSENT	ABSENT	
PRAKASH	55	M	178219	12	213		7.1	41.5	31.5	0.9	42	19	197	1+	TRACE	YES
DATEPPA	55	M	137562	14.3	385		11.2	123	38	1.2				3+	TRACE	
MAHADEVI SHINDE	60	F	116157	12	157		7.5	150	88.4	1.9				2+	ABSENT	YES
RAINAVVA	91	F	190613	12	230		6.5	31.9	12.8	0.7	42	162	229	1+	ABSENT	YES
SHATTEPPA	45	M	209434	13	215		8.7	502	15.6	1.8				ABSENT	ABSENT	
BAPU	43	M	145051	13.4	256		13.3	256	20.5	0.6				ABSENT	ABSENT	YES
SONABAI	70	F	185297	12.8	204	132	7.3	24.81	6.5	0.6	47	155	213	1+	1+	YES
KHADARBE	58	F	225875	12	280		6.4	100.6	47.9	0.9				ABSENT	ABSENT	
B.L.RATHOD	72	M	179922	13.7	346		13.8	130	7.9	1				ABSENT	ABSENT	YES
VASHANT	75	M	190702	13.7	446		11.6	60.7	36.1	0.7				3+	TRACE	
SUNITA	44	F	213391	12	235	401	7.8	15.88	9.1	0.6	53	147	222	ABSENT	TRACE	YES
CHANDRAKALA	70	F	35434	12.4	127	154	6.7	203	15.3	0.8				3+	1+	YES
BASAMMA	55	F	204725	12	107		9.6	152	35.8	0.4	37	76	151	2+	1+	
RAMAKRISHNA	45	M	164250	14.3	281	221	6.5	256	8	1.2				1+	1+	YES
YALLAPPA	53	M	179063	13	152		6.8	259	90	0.9				ABSENT	TRACE	
SUMITRA	47	F	131593	12	110	209	8.8	285	19.4	0.4				ABSENT	ABSENT	
SURESH	50	M	116210	15.3	142		7.2	270	19	1				2+	ABSENT	YES
ANNARAY	60	M	189323	14.4	273		14.7	170	5	0.7				2+	ABSENT	YES
RAMANNA	52	M	213764	15.2	144	214	9.6	676	15.7	0.5				1+	TRACE	
GANSHYAM	52	M	117710	14.8	205		6.2	168	18	4				1+	3+	
MAHADEVI	53	F	180178	12	244		7.2	41.05	9.9	1.9				2+	TRACE	YES
SHANTA. S	48	F	113555	13.9	163		11.7	40.3	48.2	0.4	31	31	189	ABSENT	1+	YES
SHRIMANTH	50	M	178949	16.1	132		6.5	185	156	0.7				ABSENT	ABSENT	YES
MALASIDAPPA	46	M	225035	13.6	185	107	6.8	620.1	5.2	1.2	44	52	239	ABSENT	ABSENT	YES
SHRIMANTH	67	M	190098	13	113	193	5.6	163	55.6	1.4				ABSENT	TRACE	YES
ANASUYA	77	F	186165	13	134	191	5.4	1041	7.9	0.5				1+	ABSENT	YES
SIDDAMMA	59	F	205517	12.3	136	158	9.2	84.8	5	0.5				2+	TRACE	
SURESH	35	M	181792	15.8	150		10.3	259	37.2	0.7				1+	TRACE	YES
SURESH G LORI	50	M	116210	15.3	210		12	264	34.2	0.6				2+	ABSENT	
GANAPATI	75	M	117437	15.8	150		12.6	306	102	1.6				2+	TRACE	
MUTTAVVA	45	F	143800	12	134		14.7	507	5	2				3+	TRACE	YES
HANAMANTH	60	M	228068	16.6	599		12.2	215	6.2	1				1+	TRACE	YES
JYOTHI	37	F	144942	12.6	272	293	11	29.1	7.9	1				3+	ABSENT	
SHIVAPPA	50	F	168677	15.5	158		11.4	230	69	0.9				2+	1+	
HUVANNA	75	M	222874	13.9	230	242	11.8	227.4	26.2	1.4				2+	1+	
MOHAMMED KALLAYYA	50	F	188881	12.1	157		14	313.8	47.9	0.6				2+	2+	YES
JAYAWANT	24	M	138165	14.8	330		11	71.8	36.2	0.6				3+	TRACE	
SHANTAMMA	60	F	99539	12	139	371	10.4	150	18.2	1.7				ABSENT	ABSENT	YES
RAJU	50	M	286335	14.4	251	220	10.9	142	59.2	0.9				1+	ABSENT	YES
MALIK	68	M	50898	13.4	155	204	6.9	71.9	5.4	0.9				ABSENT	ABSENT	YES
SAVITA	47	F	135105	12	156	161	5.2	65.2	159	1.1				ABSENT	ABSENT	YES
HANAMANTAPPA	60	M	140648	13	142		6.6	506	59.3	1.7				ABSENT	ABSENT	YES
RUSHAB	42	M	114649	16.1	185		11.4	306	31.3	0.5				2+	TRACE	
BANU BASHA	52	M	228077	12	332		8.2	433	6.5	2.7				TRACE	ABSENT	
SHARANAPPA	54	M	66298	16.4	279	187	8.5	264	18.6	1.1				3+	ABSENT	
SHIVANAND	47	M	152870	14.2	153	163	7.4	709	25.2	1.9				ABSENT	ABSENT	YES
BABUROA	66	M	153085	13	165		7.5	78		1.9				ABSENT	ABSENT	YES
RIYAZ	42	M	225852	13.3	170		7.6	178	6.3	0.5				ABSENT	ABSENT	YES
B.L.RATHOD	72	M	179922	15.5	346		11.9	130	7.9	1.1				2+	1+	YES
BHIMARAY	58	M	196952	14.7	104		6	225	54	0.7				ABSENT	ABSENT	YES
RENUKA	48	F	158015	12	172		5.6	124	66.3	0.4				ABSENT	TRACE	
SAVITRIBAI	72	F	112319	12.2	130		7.9	95.7	5	0.5	39	70	122	1+	ABSENT	YES
SUVARNA	57	F	186337	12	105	170	4.5	841	5	2.2				ABSENT	2+	YES
DEVAKMMA	50	F	126516	12.4	156		5.7	47.3	5.7	1				ABSENT	ABSENT	YES
BHAGIRATHI	70	F	124171	12	159		9	182	150	0.7				2+	TRACE	YES
VITHAL	52	M	187545	13.6	202	135	11.6	17.6	7	0.8				ABSENT	ABSENT	
ANASUYA	77	F	186165	12	134	191	5.4	1041	7.9	1.2				1+	ABSENT	YES
MUTHEPPA	72	M	217745	13.1	191	185	6	68.2	24	0.8				1+	ABSENT	
SAVITRIBAI	72	F	112319	12.2	135		7.9	95.7	5	0.5	39	70	122	1+	TRACE	YES
RANUBAI	63	F	107857	12	269	235	8.9	925	19.7	1.2	16	66	119	ABSENT	ABSENT	YES
SHANTA KANI	56	F	135868	12	243		5	77	6.6	0.7	36	42	99	ABSENT	ABSENT	YES
HANAMANTH	42	M	147121	13	205		7.5	519	9.3	1.2				ABSENT	ABSENT	YES
BASAVARAY	58	M	45285	14.7	126	192	11.7	88	27.5	1				2+	ABSENT	YES
ARVAIND ROPPAD	52	M	169349	13	179	189	7.8	124	21.3	0.6				ABSENT	TRACE	YES
RUSHAB ASHOK	32	M	12601	16.1	152		11.4	306	31.3	0.5				2+	TRACE	
VITHOBA	61	M	168637	13	209	270	6.9	298	20	0.8				3+	ABSENT	YES
MAHADEVI	60	F	116157	12.8	163		8.2	1500	88.4	0.8				2+	TRACE	
GANGODHAR	73	M	107857	13.7	250		12.9	89.17	71.9	1.2				3+	ABSENT	YES
APPASAHEB	55	M	164801	14	278		6.8	168	5.9	0.8				ABSENT	ABSENT	YES
RANUBAI	63	F	107857	13	190		8.9	925	19.7	0.9				ABSENT	1+	YES
KRISHNAJ	68	M	212513	13.1	185		6.5	278	56.3	1.5				ABSENT	ABSENT	YES
TARASINGH	85	M	143401	15.7	247	224	12.7	195	24.7	0.4				3+	ABSENT	
RAJMA	43	F	225418	13	279	286	12.4	150	5	0.6				3+	ABSENT	
SHANKARAWWA	84	F	282277	12.2	106	147	7.7	134	77.1	0.8				ABSENT	ABSENT	
RAMESH	43	F	290810	13.2	149		5.8	304	39.1	1.2				2+	ABSENT	
BILYANI	81	M	290810	13.1	330		10.1	232	11.9	2.8				3+	ABSENT	
PRAMILA	51	F	302560	13.1	135	189	8.1	27.82	5	0.7				2+	2+	YES
NANDINI	43	F	290474	12.5	224	156	6.8	1200	17.2	0.6				1+	TRACE	YES
KHAJABEE	50	F	318785	12.6	320		8.3	155	42.6	1.5				3+	ABSENT	
YANKAPPA	62	M	318692	15.3	176		9.1	417	27.4	1.4				ABSENT	ABSENT	YES
YAMANAWWA	80	F	28330	12.3	383	191	6.6	102.7	16.4	1.3				2+	2+	
HASAKABAI	72	F	19164	12.2	100	188	6.4	114.2	195	0.9				3+	TRACE	YES
BANKABAI	55	F	18472	12.5	247		6.9	1062.1	26.3	1	28		64	2+	TRACE	YES
MAHADEV	68	F	27497	13.2	343		9.3	161	22.9	0.6				3+	ABSENT	YES
KAMALABAI	47	M	34148	10.2	485		7.2	186	9.7	0.5				3+	ABSENT	YES
KASTURI	52	F	37012	12.8	234		9.5	196	6.3	0.4				TRACE	ABSENT	YES
VIJAYAKUMAR	80	M	46357	13.4	147		9.3	77.9	165	0.6			105	ABSENT	1+	YES
SANIVAROA	60	M	55143	13.3	199	216	7.3	196	13.2	0.9				ABSENT	ABSENT	YES
GURUSIDAPPA	73	M	70358	8.6	264	153	7.3	736	57.9	4.7				ABSENT	2+	YES
SUVARNA	57	F	186337	6.8	264	153	7.3	736	57.9	4.7				ABSENT	2+	
HANAMANTH	42	M	147121	13.7	240		7.5	51.9	9.3	1.2				ABSENT	ABSENT	YES
SIDAPPA	40	M	135072	13.2	158		6.7	134	15.1	1.6				3+	2+	