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"EVALUATION OF INFLAMMATORY MARKERS - IL-6, FERRITIN, HS-CRP IN TYPE 2 DIABETIC PATIENTS AND ITS CORRELATION WITH GLYCATED HEMOGLOBIN"

By

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Dissertation submitted to the

BLDE (DEEMED TO BE UNIVERSITY)

Vijayapura, Karnataka

In partial fulfilment of the requirements for the award of the degree of

DOCTOR OF MEDICINE

IN

PATHOLOGY

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LIST OF ABBREVIATIONS

ABBREVIATION	PARAMETER
T2DM	Type 2 Diabetes Mellitus
MODY	Maturity onset of diabetes of young
IL-6	Interleukin 6
TNF α	Tumor necrosis factor-alpha
CRP	C – reactive protein
hs-CRP	High-sensitive C-reactive protein
HbA1c	Glycated haemoglobin
FBS	Fasting blood sugar
PPBS	Post-prandial blood sugar
SPSS	Statistical package for social sciences
NSAIDS	Non-steroidal anti-inflammatory drugs
OGTT	Oral glucose tolerance test
EDTA	Ethylenediamine tetraacetic acid
CLIA	Chemiluminescence Immunoassay
ADA	American diabetes association
ROS	Reactive oxygen species
NF-κB	Nuclear factor-kappa B
FFA	Free fatty acid
BMI	Body mass index
AGE	Advanced glycation end products
IDF	International Diabetes Federation

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ABBREVIATION	PARAMETER
GGT	Gamma glutamyl transferase
ALT	Alanine transaminase
GLUT	Glucose transporter
SGLT	Sodium-glucose co-transporter
CD	Cluster of differentiation
DCCT	Diabetic control and complication trial
NGSP	National glycohemoglobin standardization program
WHO	World health organisation
GLP	Glucagon-like peptide

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ABSTRACT

INTRODUCTION

Diabetes mellitus has evolved from a metabolic disorder to a condition closely linked with inflammation, influenced by cytokines such as TNF-alpha, IL-6, and CRP. Measuring the levels of inflammatory markers like IL-6, hs-CRP, and ferritin can reveal subclinical inflammation and help assess the risk of microvascular and macrovascular complications along with the disease progression.

OBJECTIVES

1) To study the serum level of the inflammatory biomarkers (IL-6, Serum ferritin and hs-CRP) in type 2 Diabetic patients and a group of healthy controls.
2) To assess the correlation between glycemic control (HbA1c, FBS and PPBS) and inflammatory markers.

MATERIALS AND METHODS

The study included 80 participants, 60 clinically diagnosed type 2 diabetic patients as cases and 20 healthy controls from the Medicine department, enrolled between May 1, 2023, to December 31, 2024. FBS, PPBS, glycated haemoglobin, ferritin, hs-CRP, and IL-6 levels were measured in both groups.

RESULTS

1) Type 2 Diabetic patients have significantly higher inflammatory markers (ferritin, hs-CRP and IL-6) than healthy controls.

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2) 51.6% of type 2 diabetic patients having poorer glycemic control (HbA1C > 7) exhibit significantly higher inflammatory markers than those with better glycemic control (HbA1C ≤ 7)

3) Serum ferritin, hs-CRP, and IL-6 are positively correlated with HbA1c, with statistically significant correlations observed in the higher HbA1c group.

CONCLUSION

Our study confirms that Type 2 Diabetes Mellitus (T2DM) is associated with significantly elevated levels of inflammatory markers, including ferritin, hs-CRP, and IL-6, compared to healthy individuals. Moreover, patients with poor glycemic control (HbA1c > 7) exhibit even higher levels of these markers, reinforcing the link between hyperglycemia and systemic inflammation. The significant positive association observed among ferritin, hs-CRP, IL-6, and HbA1c emphasizes how inflammation plays a role in glycemic dysregulation and aids as a tool in the risk assessment of micro and macrovascular complications. These findings emphasize the need to monitor inflammatory markers in T2DM management and suggest that addressing inflammation could be a valuable approach to improving glycemic control and reducing diabetes-related complications.

KEYWORDS – inflammatory markers, glycemic control, diabetes

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INTRODUCTION

Diabetes mellitus (DM) is a chronic inflammatory, non-communicable disease with a complex aetiology that is characterised by hyperglycemia brought on by deficiencies in insulin action or secretion[1]. The World Health Organization estimates that 422 million people worldwide have diabetes, with China and India accounting for the most significant proportion of those with the disease [2].

Type 1 diabetes and Type 2 diabetes are the two main categories of diabetes that comprise the majority of cases. An autoimmune condition caused by the destruction of pancreatic beta cells is type 1 diabetes, formerly known as insulin-dependent diabetes, most frequently observed in patients under 20 [3]. Peripheral resistance to insulin action and impaired secretion by pancreatic beta cells that are insufficient to overcome insulin resistance combine to form type 2 diabetes, formerly known as insulin-independent diabetes [3].

Sedentary lifestyle, genetic factors, central obesity, and insufficient physical activity are the risk factors for type 2 diabetes mellitus [2]. Acute phase reactants are released, lipolysis increases, protein catabolism increases, and advanced glycation end products (AGE) are formed due to tissues using glucose less effectively, which is caused by either insulin resistance or insufficiency [3].

A subclinical inflammatory state and oxidative stress are caused by elevated plasma levels of inflammatory mediators like CRP, TNF-α, and IL-6, which are brought on by high glucose levels and macronutrient intake [3]. While other factors like infections, smoking, and stress can also cause inflammation in genetically predisposed individuals, obesity causes an increase in free fatty acids, leptin, and reactive oxygen species [4]. Thus, one of the main contributing factors to the

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etiopathogenesis of type 2 diabetes has recently been identified as chronic systemic subclinical inflammation [2,3].

The buildup of glycation products in tissue proteins is associated with the emergence of complications. Diabetic nephropathy, peripheral neuropathy, and retinopathy are examples of microvascular complications with diabetes, while myocardial infarction, cerebrovascular events, and peripheral vascular disease are examples of macrovascular complications [3]. The covalent binding of glucose to haemoglobin, known as glycation, produces glycated haemoglobin (HbA1c), a tiny haemoglobin derivative [1-3].

A patient's average three-month glycemic control is reflected in their HbA1c levels [5]. Consequently, the primary therapeutic goal for managing and preventing micro and macrovascular complications from diabetes that may affect quality of life is optimal glycemic control [6]. Due to the effects of pro- and anti-inflammatory cytokines such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF alpha), type 2 diabetes mellitus shifted from a metabolic disease to an inflammatory condition [7].

Chronic hyperglycemia causes the liver to secrete acute-phase reactants and release various inflammatory cytokines, including IL-6 [8]. The subclinical inflammatory state and the advancement of diabetes are indicated by ferritin, which measures the levels of inflammatory markers such as interleukin 6 and hs-CRP. Because it indirectly affects adipocytes and the pancreatic beta cells, interleukin-6 has a significant effect on glucose homeostasis and metabolism.

Impaired glucose metabolism and elevated hepatic glucose production have been widely associated with IL-6, a cytokine involved in immune regulation [7]. CRP is a pentameric protein that the liver produces in response to inflammatory stimuli. Its function as a predictor of diabetes-related

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complications is further supported by the fact that plasma levels of hs-CRP are frequently elevated in people with poor glycemic control and serve as a sensitive indicator of increased inflammatory activity in the arterial wall [9].

Historically considered an indicator of iron storage, serum ferritin has also been identified as an inflammatory mediator linked to metabolic syndrome and insulin resistance. Elevated blood ferritin levels are a sign of inflammation [5]. Therefore, assessing inflammatory biomarker levels could help determine the risk of both macrovascular and microvascular complications [5,6].

The current study aims to measure the levels of inflammatory markers (hs-CRP, ferritin, and IL-6) and evaluate their correlations with glycemic control metrics like HbA1c.

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AIMS AND OBJECTIVES

1) To study the serum level of the inflammatory biomarkers (IL-6, Serum ferritin and hs-CRP) in type 2 Diabetic patients and a group of healthy controls.

2) To assess the correlation between glycemic control (HbA1c, FBS and PPBS) and inflammatory markers.

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REVIEW OF LITERATURE

EPIDEMIOLOGY OF DIABETES

The International Diabetes Federation announced in 2015 that 415 million adults worldwide have diabetes, which is expected to increase to 642 million by 2040 [2] (fig 1,2). The rise in sedentary lifestyles and unhealthy eating habits has fueled the concurrent increase in type 2 diabetes (T2D) and obesity, often referred to as the "diabesity" epidemic [1]. Type 2 diabetes develops gradually and is usually diagnosed years after its onset, leaving nearly half of all diabetes cases worldwide undiagnosed. Despite being undiagnosed, these individuals can still experience diabetic complications, leading to an underestimation of the actual global disease burden. Being one of the leading causes of death worldwide, diabetes is responsible for about 4.2 million mortalities or 11.3% of the total in 2019, which surpasses the total number of deaths caused by infectious diseases [10]. The rise in atherosclerotic vascular disease essentially drives premature mortality, while diabetes also causes significant morbidity through its microvascular complications, which can affect the eyes, nerves, and kidneys [10].

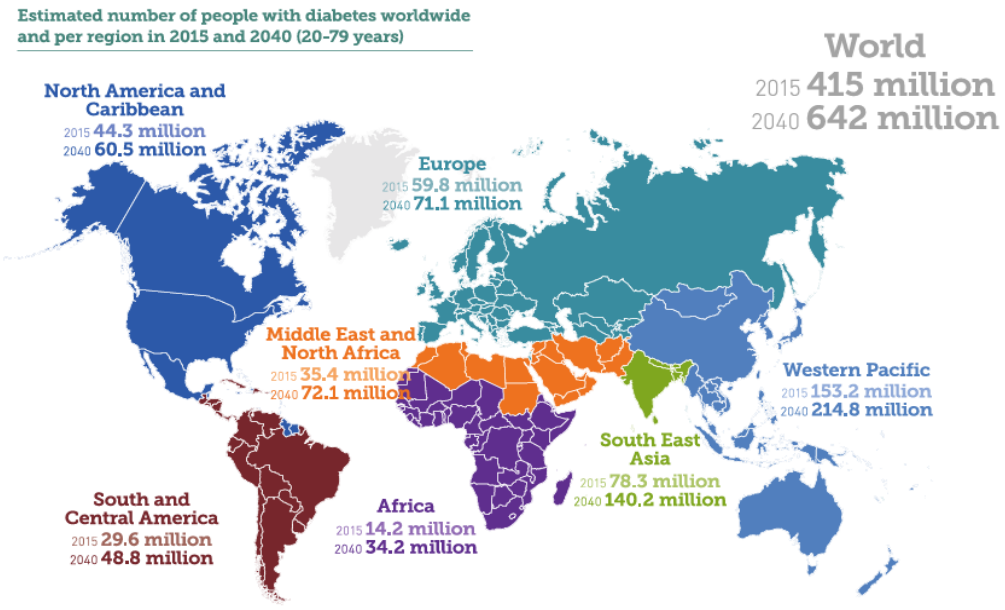

Figure 1 - Worldwide prevalence of diabetes in 2015 with projected figures in 2015 and 2040. Figures are number of people with diabetes in millions by region. Source: Modified from IDF Atlas 2019. Retrieved from: http://www.diabetesatlas.org

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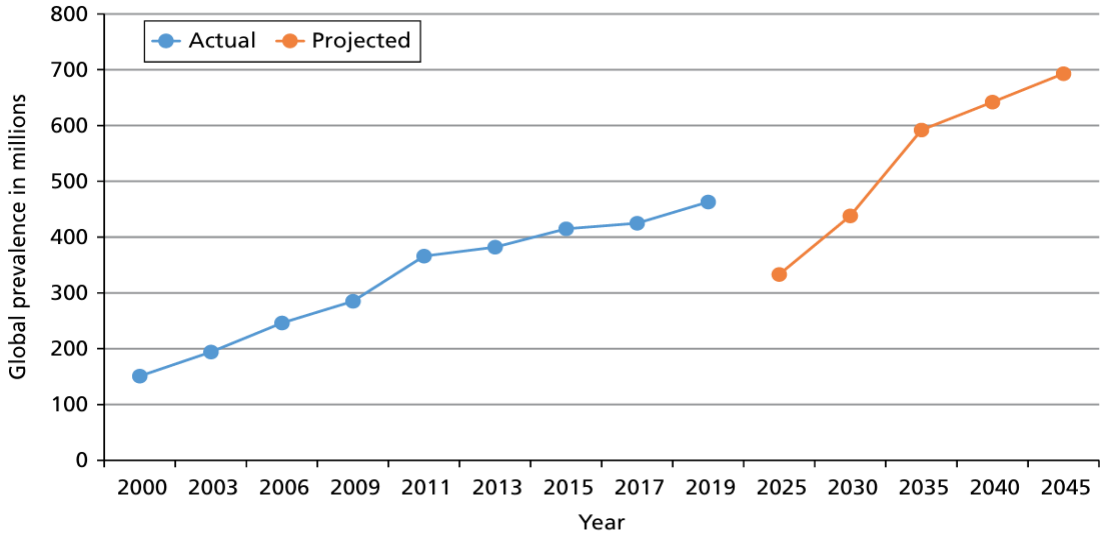

Figure 2 - International Diabetes Federation estimates of the current and projected global prevalence of diabetes. Source: Based on IDF Atlas 2019 http://www.diabetesatlas.org

ETIOLOGICAL CLASSIFICATION OF DIABETES [3] (Table – 1)

01	Type 1 Diabetes mellitus - Immune-mediated or idiopathic
02	Type 2 Diabetes mellitus
03	Other specific types A. Genetic defects in beta cell function – MODY type 1 to type 6, mitochondrial mutations B. Genetic defects in Insulin action – Type A Insulin resistance, Lipoatrophic diabetes C. Pancreatic diseases – Fibrocalcific pancreatitis, Pancreatectomy, Cystic fibrosis D. Endocrinopathies – Acromegaly, Cushing's syndrome, Pheochromocytoma, Hyperthyroidism E. Drug-induced – Glucocorticoids, Thyroid hormone, Phenytoin, Diazoxide Thiazides, Vacor, Pentamidine, Olanzapine, Rifampicin F. Infections – Congenital Rubella, Cytomegalovirus, Mumps G. Genetic syndrome association – Down's syndrome, Turner's syndrome, Klinefelter's syndrome, Myotonic dystrophy, Prader-Willi syndrome
04	Gestational diabetes

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RISK FACTORS OF TYPE 2 DIABETES

Table 2 – Risk factors of type 2 diabetes

UNMODIFIABLE FACTORS	ENVIRONMENTAL FACTORS
- Genetic polymorphisms - Positive family history - Monozygotic twins - Age - Ethnicity - History of diabetes in previous pregnancy for gestational diabetes	- Obesity - Physical inactivity - Diet - Drugs - Urbanization - Decreased sleep - Depression - Smoking

1) GENETIC RISK FACTORS

The risk of T2D is five to ten times higher for first-degree relatives than those without a family history **(1)**. Type 2 diabetes is a polygenic disorder, with no single gene fully accounting for its inheritance. Advances in modern genetic research have led to the discovery of hundreds of single-nucleotide polymorphisms (SNPs) (listed in Table 2) or genetic markers associated with an elevated risk of type 2 diabetes [(10)]. Many of these identified polymorphisms are located in introns, leaving their role in increasing diabetes risk unclear, though most appear to impact β cell function[(6-8)]. Additionally, a maternal history of diabetes poses a greater risk for type 2 diabetes in offspring compared to a paternal history. This increased risk may be linked to maternal hyperglycemia during pregnancy, which can modify the intrauterine environment and, in turn, influence the offspring's susceptibility to diabetes [(9,10)].

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Table 3 - Gene polymorphisms associated with type 2 diabetes mellitus	
CAPN10	CDKN2AI2B
SLC30A8	FTO
PPARG	TCFCB4
IGF2BP2	CDKAL1
TCF7L2	INSULIN (promoter region)
KCNJ11	HHEX

2) BEHAVIORAL AND LIFESTYLE RISK FACTORS

A lack of physical activity and sedentary behaviour are linked to a higher likelihood of developing diabetes [(10)]. The distribution of body fat plays a crucial role in obesity-related health risks; individuals with more visceral fat face a higher likelihood of developing diabetes. As shown in figure 3, the probability of diabetes increases with a rising BMI. In both the UK and USA, 80–90% of adults diagnosed with type 2 diabetes are either overweight or obese (BMI >25 kg/m2), with nearly half falling into the obese category (BMI >30 kg/m2) [(8-10)].

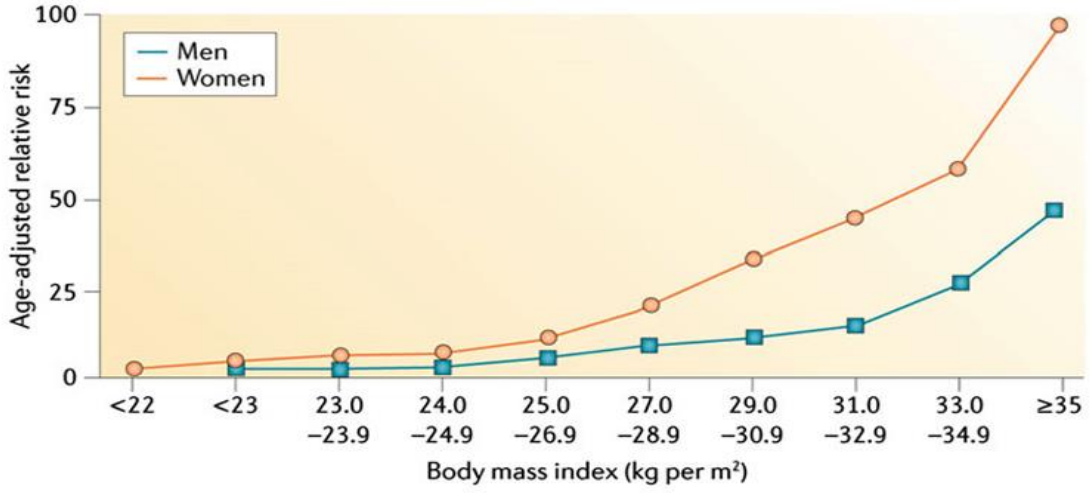

Figure 3 - Association between body mass index (BMI) and type 2 diabetes (Adapted from DeFronzo et al. (2015)

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3) METABOLIC FACTORS ASSOCIATED WITH THE RISK OF TYPE 2 DIABETES

As excess body weight increases, macrophages infiltrate adipose tissue, producing pro-inflammatory cytokines and modifying the release of adipokines, including adiponectin, which is synthesized by adipose tissue [6-8]. The liver contributes to this inflammatory process by producing C-reactive protein (CRP) and various liver enzymes. Increased concentrations of pro-inflammatory markers, including tumour necrosis factor-alpha (TNFα), interleukin-6 (IL-6), and C-reactive protein (CRP), have been associated with a heightened risk of developing type 2 diabetes [3-5]. Additionally, this inflammatory response is associated with indicators of endothelial dysfunction, liver function markers (such as GGT and ALT), and insulin-like growth factors [2-4].

PATHOGENESIS OF TYPE 2 DIABETES MELLITUS

I) GLUCOSE HOMEOSTASIS

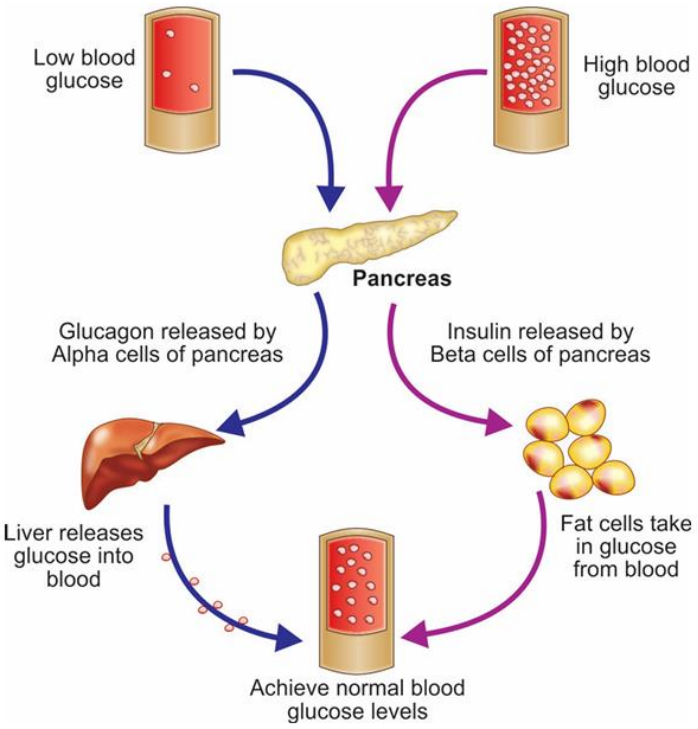

Figure 4 – Normal regulation of blood glucose [3]

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The glucose uptake into cells occurs through facilitated diffusion, mediated by a series of glucose transporters designated as GLUT 1 through GLUT 7 [3]. Specifically, GLUT 4 serves as the primary glucose transporter in muscle and adipose tissues, and its activity is enhanced by insulin. In contrast, glucose transport in the intestines and kidneys is achieved through secondary active transport mechanisms involving sodium-dependent glucose transporters, namely SGLT 1 and SGLT 2 [3]. Figure 4 illustrates how the pancreas regulates blood glucose levels through the hormones insulin and glucagon. When blood sugar is high (e.g., after eating), beta cells of the pancreas release insulin, which helps fat and body cells absorb glucose, lowering blood sugar. When blood sugar is low (e.g., during fasting), alpha cells of the pancreas release glucagon, prompting the liver to release stored glucose into the bloodstream. This cycle ensures stable blood glucose levels, maintaining energy balance and homeostasis [3].

II) METABOLIC ACTIONS OF INSULIN

Insulin is the most potent anabolic hormone, playing a key role in promoting synthesis and growth (fig 5). Its primary metabolic function is to enhance glucose transport into specific cells in the body, supplying a significant energy source and glucose-derived metabolic intermediates used for the biosynthesis of cellular components like lipids, nucleotides, and amino acids [4-6]. The primary targets of insulin's effects are striated muscle cells (including cardiomyocytes) and adipocytes [1]. The insulin receptor is a tetrameric protein consisting of two alpha and two beta subunits [3].

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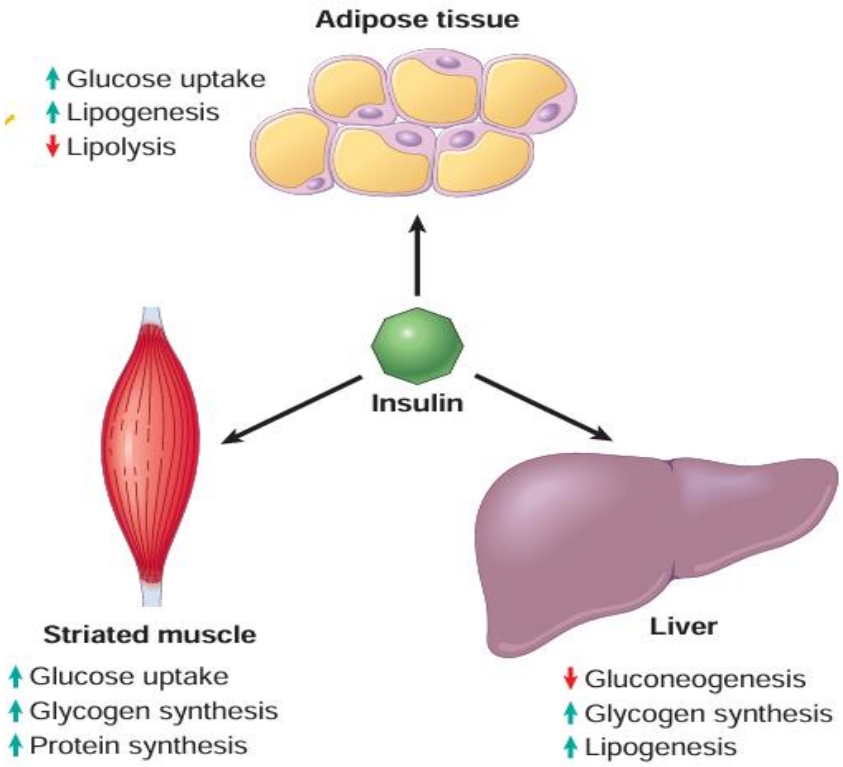

Figure 5 - Metabolic actions of insulin [1].

III) INSULIN RESISTANCE

Insulin resistance is characterized by the inadequate response of target tissues to insulin. The primary tissues affected include the liver, skeletal muscle, and adipose tissue, where insulin resistance results in compromised glucose tolerance [1]. The ramifications of insulin resistance are as follows:

- The liver's inability to suppress endogenous glucose production leads to elevated fasting blood glucose levels.
- There is a diminished capacity for glucose uptake and glycogen synthesis in skeletal muscle following meals, which contributes to increased postprandial blood glucose levels [1].

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- In adipose tissue, there is a failure to inhibit the activation of hormone-sensitive lipases, resulting in excessive triglyceride breakdown within adipocytes and heightened levels of circulating free fatty acids (FFAs).

Over time, pancreatic β cells appear to reach their limit in adapting to the sustained demands imposed by insulin resistance. Consequently, the hyperinsulinemic state transitions to a condition of relative insulin deficiency, wherein insulin levels become inadequate in relation to blood glucose levels [1-4].

IV) CONSEQUENCES OF INSULIN RESISTANCE

TABLE 4 - CARBOHYDRATE METABOLISM [3]

Metabolic defect	**Chemical abnormality**	**Clinical features**
• Decreased glucose uptake by tissue	• Hyperglycemia	• Polydipsia, polyuria polyphagia
• Increased glycogenolysis and gluconeogenesis	• Glycosuria • Osmotic diuresis	• Blurred vision • Diminished mental alterness

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TABLE 5 - PROTEIN METABOLISM [3]		
Metabolic defect	**Chemical abnormality**	**Clinical features**
• Decreased protein synthesis and uptake of amino acids • Increased proteolysis	• Negative nitrogen balance • Increased blood urea nitrogen level and potassium levels	• Weakness • Muscle wasting • Poor resistance to infection

TABLE 6 – LIPID METABOLISM [3]		
Metabolic defect	**Chemical abnormality**	**Clinical features**
• Increased lipolysis • Increased production of free fatty acids, triglycerides and ketone bodies • Decreased lipogenesis and ketone excretion	• Increased levels of plasma FFA, plasma and urine ketone • Hypertriglyceridemia	• Weight loss • Metabolic acidosis • Hyperventilation leading Kussmaul breathing • Atherosclerotic vascular disease

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Insulin resistance associated with obesity is influenced by adipokines, free fatty acids (FFAs), and persistent inflammation in adipose tissue [1]. In response to this resistance, pancreatic β-cells increase their insulin production. However, over time, this compensatory mechanism leads to β-cell dysfunction, eventually resulting in diabetes [1] (fig 6)

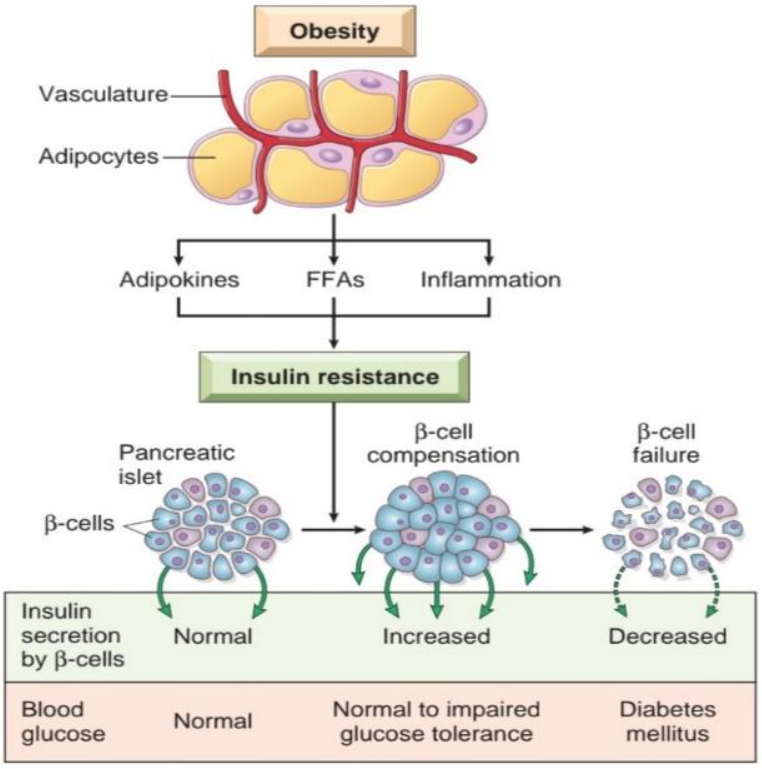

Figure 6 – Development of Type 2 Diabetes Mellitus, FFA – Free fatty acid [1]

V) ROLE OF INFLAMMATION IN TYPE 2 DIABETES MELLITUS

Inflammation is a significant factor in the onset and advancement of diabetes, functioning as both a contributing factor and a consequence of insulin resistance. This bidirectional relationship creates a cycle where inflammation exacerbates insulin resistance and insulin resistance further fuels inflammation [2-4]. Among the numerous factors contributing to insulin resistance, obesity stands out as the most significant. Insulin resistance in obesity is primarily caused by immune cells found in adipose tissue, including macrophages, CD4+ and CD8+ T

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cells [3]. These immune cells release pro-inflammatory cytokines in response to an overabundance of nutrients, including free fatty acids (FFAs) and glucose. This inflammatory response impairs insulin signalling and contributes to β-cell dysfunction, a hallmark of diabetes [3-6].

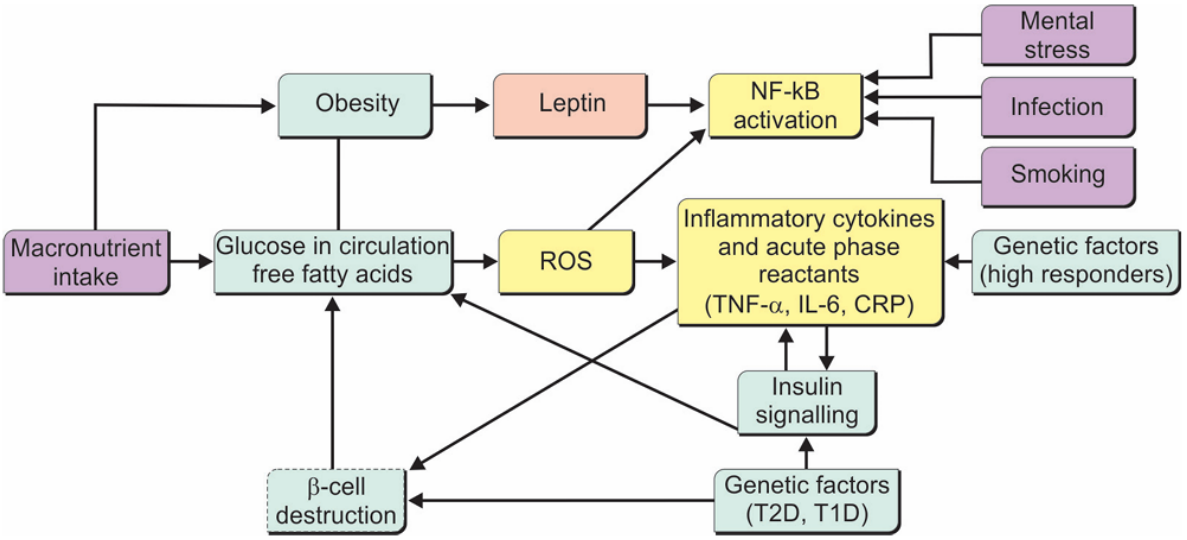

Figure 7 – Role of genetic factors, obesity and inflammation in diabetes. Source: Dandona P, Aljada A, Bandyopadhyay A. Inflammation: the link between insulin resistance, obesity and diabetes. Trends Immunol. 2004;25:4-7

(ROS: Reactive oxygen species; NF-κB: Nuclear factor-kappa B; CRP: C-reactive protein; TNF: Tumor necrosis factor; IL: Interleukin; T1D: Type 1 diabetes; T2D: Type 2 diabetes).

Excess FFAs, in particular, have a profound effect, as they activate the inflammasome, a cytoplasmic multiprotein complex within macrophages and β cells. This activation initiates the release of interleukin-1β (IL-1β), which is a significant pro-inflammatory cytokine [3]. Subsequently, IL-1β promotes the synthesis of further pro-inflammatory cytokines from various cells, including macrophages and islet cells. These cytokines act on primary insulin-responsive tissues, further promoting insulin resistance [6-9]. Beyond their indirect effects, FFAs can also

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directly disrupt insulin signaling within peripheral tissues. The dual mechanism involving both direct disruption of insulin signaling and indirect facilitation of inflammation through cytokine release underscores the significant contribution of elevated free fatty acids (FFAs) and inflammation to the development of diabetes [(10)].

DIAGNOSIS OF TYPE 2 DIABETES MELLITUS

The diagnosis of diabetes mellitus is primarily determined by the assessment of plasma glucose concentrations. The 75 g oral glucose tolerance test (OGTT) demonstrates greater sensitivity and a modest increase in specificity compared to fasting plasma glucose (FBS) for the diagnosis of diabetes; however, it exhibits limited reproducibility [(10-13)]. The measurement of fasting blood sugar (FBS) is preferred as a diagnostic test for identifying diabetes, in conjunction with haemoglobin A1c (HbA1c), owing to its straightforward nature, high patient acceptability, and cost-effectiveness [(11)].

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Table 2.1—Criteria for the diagnosis of diabetes in nonpregnant individuals

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
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 the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
In an individual with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (≥11.1 mmol/L). Random is any time of the day without regard to time since previous meal.

DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; NGSP, National Glycohemoglobin Standardization Program; WHO, World Health Organization; 2-h PG, 2-h plasma glucose. *In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal results from different tests which may be obtained at the same time (e.g., A1C and FPG), or the same test at two different time points.

Figure 8 – Criteria for diagnosis of Type 2 diabetes mellitus - Source – ADA, Diabetes Care Volume 48, Supplement 1, January 2025

- In a study conducted by Gauda et al. [5], involving 64 patients, it was observed that elevated levels of inflammatory markers, specifically high-sensitivity C-reactive protein (hs-CRP) and ferritin, are associated with poor glycemic control (HbA1c > 7) in individuals with type 2 diabetes, thereby serving as predictors for cardiovascular complications.
- Similarly, Bashir et al. [7] examined a cohort of 340, type 2 diabetic patients and found that fluctuations in cytokine levels, including tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP), not only contribute significantly to the pathogenesis of type 2 diabetes but also exhibit a positive correlation with glycemic control.
- Elimam et al. [9] conducted a study involving 90 subjects, demonstrating a robust

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correlation between inflammation and glycemic control in patients with type 2 diabetes.

- Patne et al. [6] analyzed a sample of 500 patients and highlighted the role of hyperglycemia in developing inflammation, emphasizing that early detection and optimal management of hyperglycemia can mitigate complications and reduce morbidity and mortality rates.
- In a study conducted by Lal V [8], 120 patients were observed to have timely screening and early detection of the increased hs-CRP, which enabled an early intervention in the course of the disease and prevented further complications.
- In their study comprising 100 patients, Shriram G and Keerthika E [12] discovered a notable positive correlation between high-sensitivity C-reactive protein (hs-CRP) levels and hemoglobin A1c (HbA1c) levels. This finding indicates that individuals exhibiting inadequate glycemic control may be at a heightened risk for inflammation.
- Jain MK and Jain G [13] conducted a study with 68 patients diagnosed with type 2 diabetes, which revealed elevated levels of tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6) among the diabetic cohort.
- Anjum Zahra et al. [14] examined 111 patients and found that increased ferritin levels, in the absence of iron overload, were significantly correlated with glycemic control, while elevated CRP levels indicated the presence of inflammatory changes.
- Alam F et al. [15] studied 111 patients and reported that heightened ferritin levels, despite the lack of apparent iron overload, may disrupt glucose homeostasis, contributing to insulin resistance and inflammatory responses, as evidenced by increased C-reactive protein levels.
- Jagannatha SB [16], in their investigation involving 100 patients, found that increased levels of high-sensitivity C-reactive protein (hs-CRP) and ferritin serve as predictors for future cardiovascular complications in individuals with type 2 diabetes mellitus. Their findings also indicated a significant association between elevated HbA1c levels and increased hs-CRP levels, thereby suggesting a noteworthy relationship between inflammation and

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glycemic control.

- Similarly, Wang et al. [17] performed a systematic review and meta-analysis that revealed a significant correlation between elevated levels of interleukin-6 (IL-6) and C-reactive protein (CRP) and an increased risk of developing type 2 diabetes mellitus (T2DM).
- Lontchi-Yimagou et al. [18] posited that the inflammatory response may play a critical role in the onset of T2DM by inducing insulin resistance, which is exacerbated by hyperglycemia and contributes to the long-term complications associated with diabetes.
- Stanimirovic J et al. [19] in their study, concluded that CRP is one of the possible targets for T2DM progression and understanding the connection between insulin and inflammation may be helpful in clinical treatment and prevention of complications of diabetes
- Calle MC [20], Fernandez ML, described the role of inflammatory cytokines such as CRP, TNF α and adiponectin in developing type 2 diabetes mellitus.

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MATERIALS AND METHODS

SOURCE OF DATA

- **Study Setting:** The research was conducted within the Department of Pathology at BLDE (Deemed to be University), specifically at the Shri B. M. Patil Medical College, Hospital and Research Centre in Vijayapura.
- **Study Period:** The duration of the study spanned from May 1st, 2023 to December 31st, 2024.
- **Study Design:** This investigation employed a hospital-based cross-sectional study design.
- **Study Population:** The study population comprised individuals who were clinically diagnosed with Type 2 Diabetes Mellitus and presented at the Medicine outpatient department of BLDE (Deemed to be University), Shri B. M. Patil Medical College, Hospital and Research Centre in Vijayapura.

SELECTION CRITERIA

- **Inclusion Criteria:** Clinically diagnosed cases of Type 2 Diabetes mellitus

without complications according to ADA criteria.

- **Exclusion Criteria**:

a) Endocrinological dysfunctions

b) Infectious disorders

c) Iron deficiency anemia

d) Patients with a past history of the cerebrovascular event or myocardial infarction

e) Malignancy or any other systemic illness.

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f) Patients on statins, thiazolidinediones, NSAIDS.

STATISTICAL DATA ANALYSIS

- The data collected were systematically recorded in a Microsoft Excel spreadsheet, and subsequent statistical analyses were conducted utilizing the Statistical Package for the Social Sciences (SPSS), Version 20.
- The results were articulated in terms of mean, standard deviation, frequency counts, percentages, and graphical representations.
- For continuous variables that exhibited a normal distribution, comparisons between the two groups were executed using an independent samples t-test.
- In contrast, the Mann-Whitney U test was employed for variables that did not conform to a normal distribution.
- Categorical variables between the two groups were analyzed using the Chi-square test or Fisher's exact test, as appropriate.
- A p-value of less than 0.05 was deemed statistically significant, and all statistical analyses were conducted as two-tailed tests.

METHODS OF DATA COLLECTION

- **Sample size:** The sample size was determined by utilizing G*Power version 3.1.9.4 software to calculate the sample size. The mean and standard deviation of HbA1c (%) for the Cases group were 4.55 and 0.58, respectively, while for the Control group, the mean and standard deviation were 7.5 and 3.23, respectively. To achieve a statistical power of 99% for detecting a difference in means between the two independent groups, a total

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sample size of 64 participants is required, with 32 individuals allocated to each group, assuming equal group sizes.

- We included a total of 80 subjects, which included 60 diabetic patients and 20 healthy controls.
- **Ethical clearance:** Institutional ethical committee approval was taken.

  Shri B. M. Patil Medical College, Hospital and Research Centre in Vijayapura.

  BLDE (DU)/IEC/938/2023-24.
- **Consent:** Written and informed consent was taken for every patient participating in the study

DATA COLLECTION PROCEDURE (fig 9)

Venous blood samples of 9 ml were obtained from all participants through phlebotomy following a minimum overnight fasting period of 8 hours. 2 ml was transferred into a vacutainer tube containing EDTA to assess HbA1c and haemoglobin levels. 5 ml of blood was placed in plain tubes and subsequently centrifuged to isolate serum, which will be utilized to measure ferritin, high-sensitivity C-reactive protein (hs-CRP), and interleukin-6 (IL-6) levels.

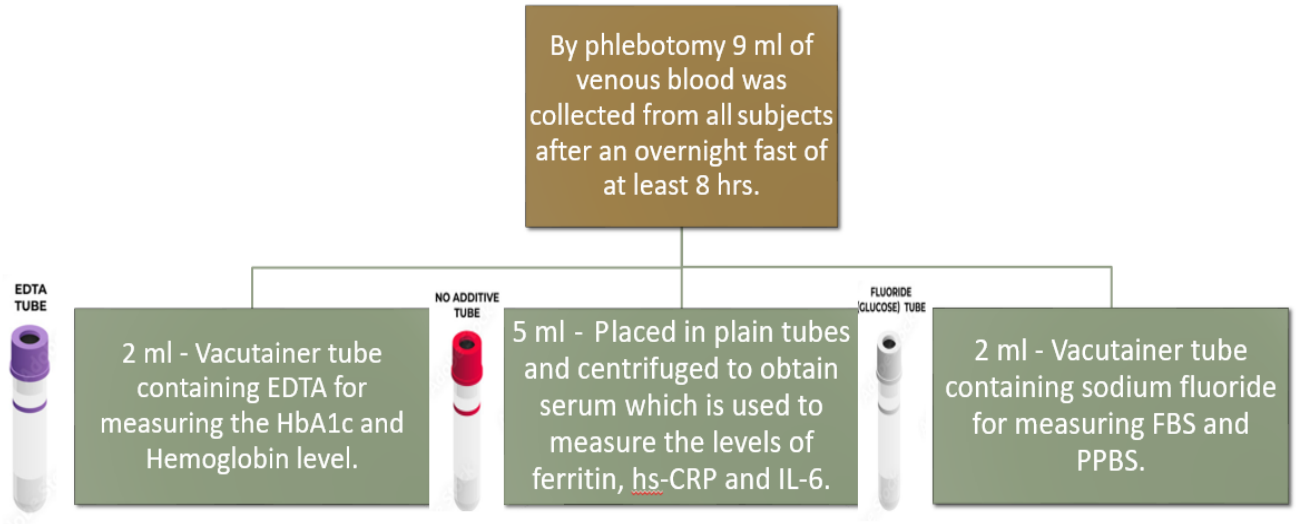

Figure 9 – Data collection procedure

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Finally, 2 ml was collected in a vacutainer tube containing sodium fluoride to determine fasting blood sugar (FBS) and postprandial blood sugar (PPBS).

The following parameters were estimated,

- HbA1c (%) by Bio-Rad D10
- Hemoglobin (g/dl) by Sysmex hematology analyser
- FBS (mg/dl) and PPBS (mg/dl) by Beckman Coulter
- Ferritin (ng/mL) and IL-6 (pg/mL) by C.L.I.A (Chemiluminescent Immunoassay)
- hsCRP (mg/L) by Immunoturbidimetry method

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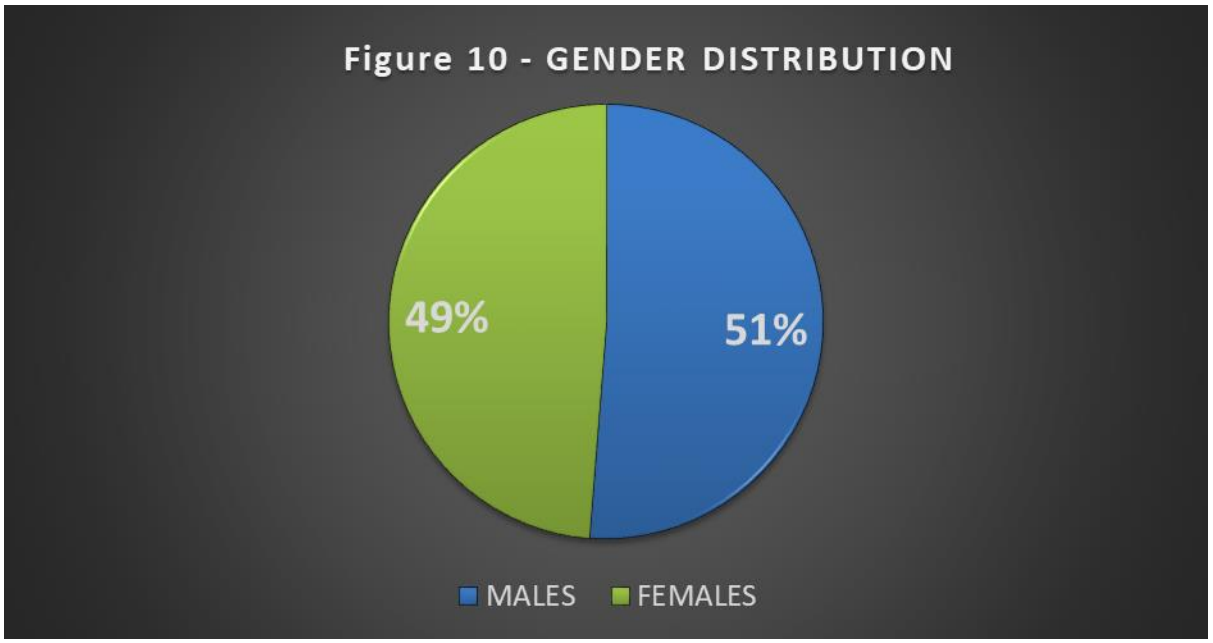
RESULTS

The study involved 60 patients with type 2 diabetes and 20 healthy controls, evaluating serum levels of inflammatory biomarkers, including IL-6, serum ferritin, and hs-CRP.

1) GENDER DISTRIBUTION (Males n = 41, Females n = 39) (Fig - 10)



2) COMPARISION OF BLOOD GLUCOSE LEVELS AND INFLAMMATORY MARKERS BETWEEN DIABETES MELLITUS PATIENTS AND HEALTHY CONTROLS

Table 7 and figure 11 compares blood glucose levels and inflammatory markers between individuals with type 2 diabetes mellitus (T2DM) and healthy controls. The results highlight significant differences between the two groups.

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Table 7 – Comparison of blood glucose levels and inflammatory markers between type 2 diabetes mellitus (n=60) and healthy controls (n=20).

	TYPE 2 DM (n = 60)	**CONTROLS (n = 20)**	**p-value**
FBS (mg/dl)	155 ± 54	88.65 ± 2.92	**0.0001**
PPBS (mg/dl)	236 ± 70	115 ± 10.3	**< 0.0001**
HbA1c (%)	8.13 ± 1.72	5.11 ± 0.15	**0.00**
Serum Ferritin (ng/ml)	77.6 ± 69.4	49.8 ± 12.0	**0.035**
hs-CRP (mg/L)	3.78 ± 3.11	1.65 ± 4.19	**0.01**
IL-6	7.6 ± 0.8	2.7 ± 0	**0.00**

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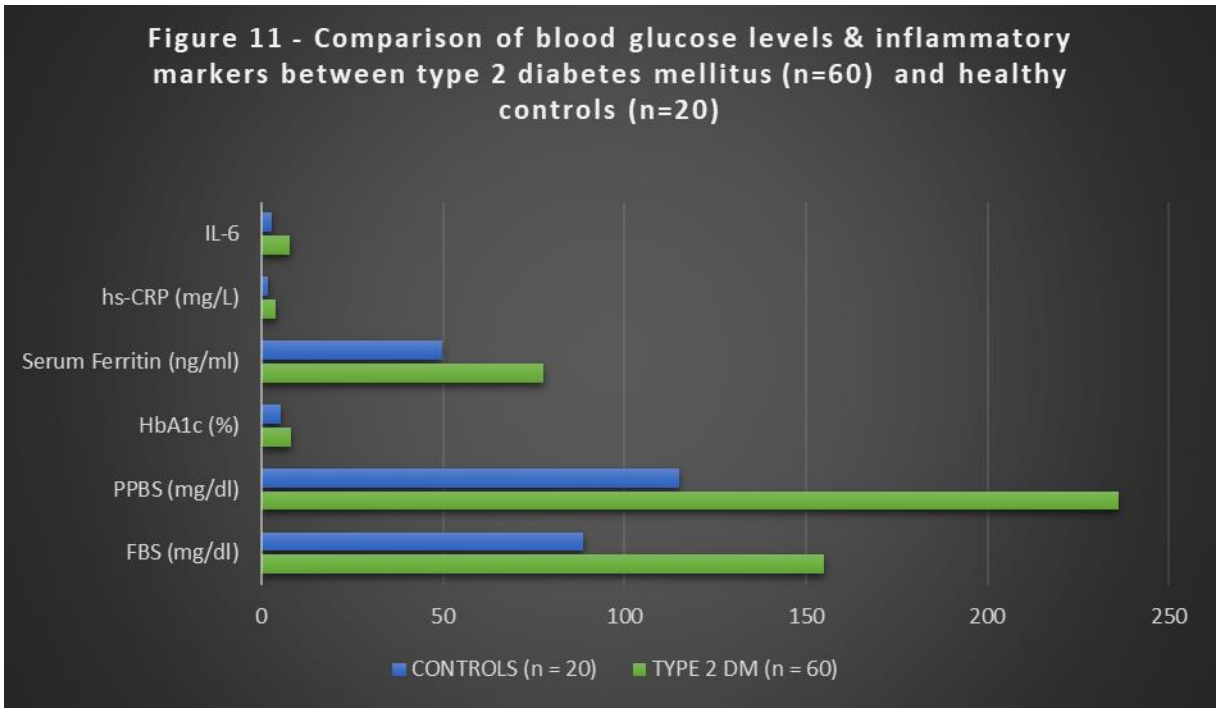

a) Blood Glucose Levels

- **Fasting Blood Sugar (FBS):** The T2DM group had a significantly higher FBS (101 to 209 mg/dl) compared to the control group (85.73 to 91.57mg/dl), with a p-value of 0.0001, indicating a statistically significant difference.

- **Postprandial Blood Sugar (PPBS):** The T2DM group had a much higher PPBS (166 to 306 mg/dl) than the controls (104.7 to 125.5 mg/dl), with a p-value of <0.0001, showing strong statistical significance.

- **HbA1c (%):** A significant difference was observed in HbA1c levels, with the T2DM group 6.41 to 9.85 %, compared to 4.96 to 5.26 % in controls (p = 0.00), indicating strong statistical significance.

b) Inflammatory Markers

- **Serum Ferritin:** Higher levels were found in the T2DM group (8.2 to 147 ng/ml) compared to controls (37.8 to 61.8 ng/ml), with a significant p-value of 0.035.

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- **High-sensitivity C-reactive protein (hs-CRP):** Levels were elevated in the T2DM group (0.67 to 6.89 mg/L) versus controls (-2.54 to 5.84 mg/L), with p = 0.01, suggesting increased inflammation in diabetes.

- **Interleukin-6 (IL-6):** IL-6 levels were significantly higher in the T2DM group (6.8 to 8.4) compared to the controls (0 to 2.7), with p = 0.00, further confirming increased inflammation in diabetic group.

This table clearly demonstrates that individuals with T2DM have significantly higher blood glucose levels and elevated inflammatory markers (Ferritin, hs-CRP, and IL-6) compared to healthy controls.

3) DISTRIBUTION OF PATIENTS AS GOOD CONTROL (HbA1c ≤ 7, n = 29) AND POOR CONTROL (HbA1c > 7, n = 31) AMONG THE TYPE 2 DIABTES MELLITUS PATIENTS (Fig 12)

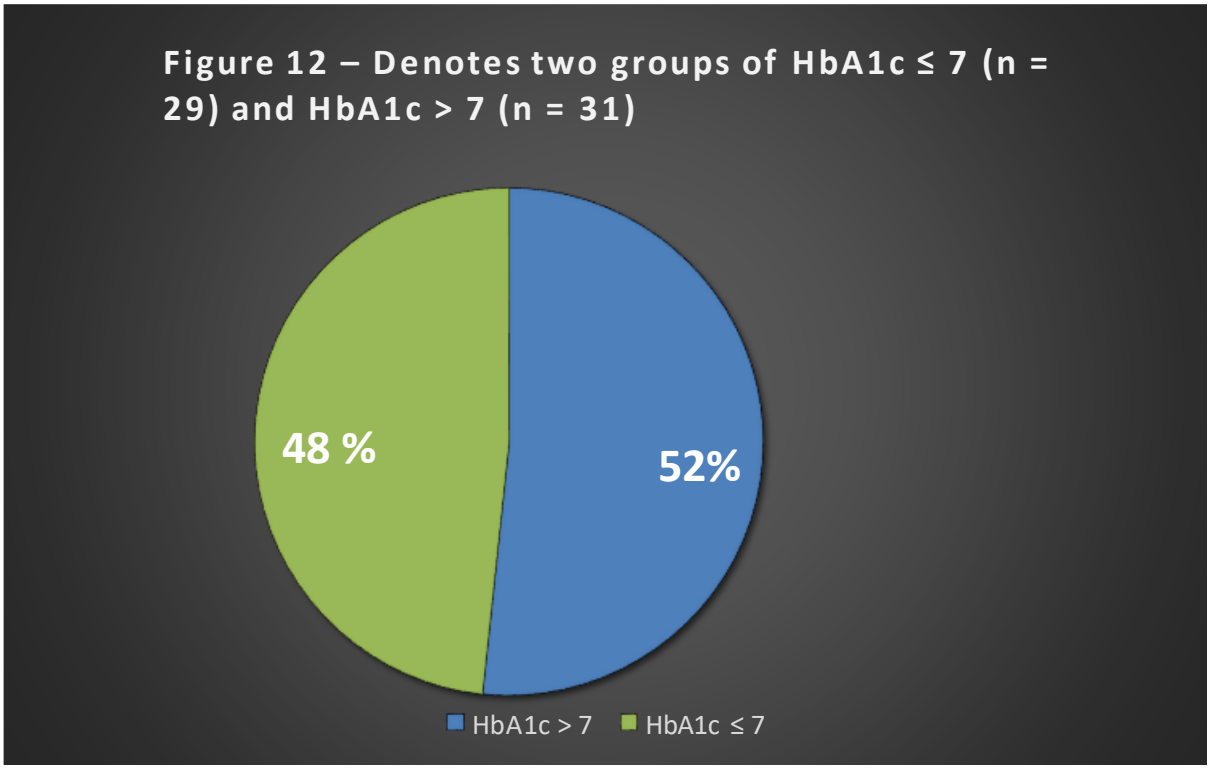

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Figure 12 represents the distribution of patients with type 2 diabetes mellitus (T2DM) based on their HbA1c levels, categorizing them into good control (HbA1c ≤ 7, 48% of patients (n = 29) and poor control (HbA1c > 7, 52% of patients (n = 31) groups.

4) COMPARISION OF THE BLOOD GLUCOSE LEVELS AND INFLAMMATORY MARKERS BETWEEN GOOD AND POOR GLYCEMIC CONTROL GROUP (Table 8)

	HbA1c ≤ 7 (n = 29)	**HbA1c > 7 (n = 31)**	**p-value**
FBS (mg/dl)	110.22 ± 27.49	183.26 ± 59.66	**0.00**
PPBS (mg/dl)	165.96 ± 60.96	270.52 ± 65.62	**0.00**
Serum Ferritin (ng/ml)	60.5 ± 40.7	89.3 ± 30.2	**0.0019**
hs-CRP (mg/L)	2.5 ± 2.3	5.1 ± 1.6	**0.00**
IL-6	10.7 ± 50.5	40.9 ± 40.4	**0.013**

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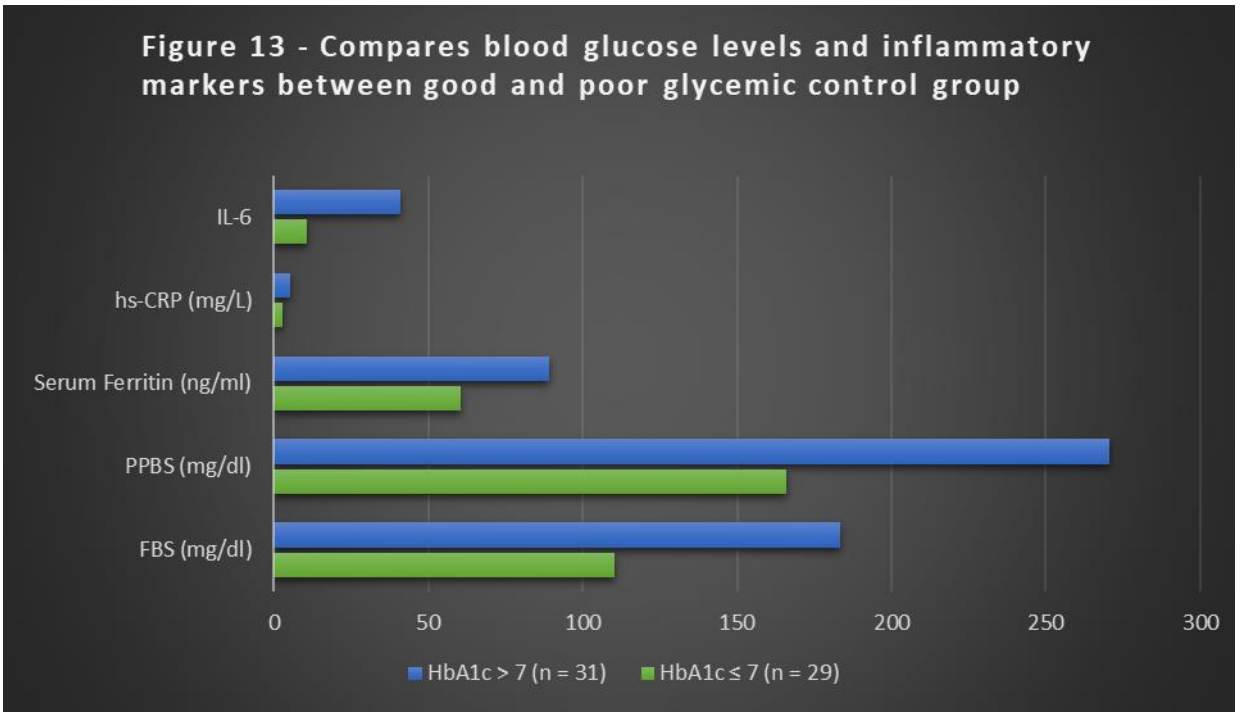

Table 8 and figure 13 compares inflammatory markers in two groups of individuals based on their HbA1c levels. HbA1c is a measure of long-term blood sugar control, with values above 7% indicating poor glycemic control. The analysis highlights significant differences in fasting and postprandial blood sugar, inflammatory markers, and ferritin levels between the two groups.

1. Fasting Blood Sugar (FBS) & Postprandial Blood Sugar (PPBS)

- Individuals with well-controlled diabetes (HbA1c ≤ 7) had fasting blood sugar ranging from 82.73 to 137.71 mg/dl, while those with poor glycemic control (HbA1c > 7) had a much higher fasting blood sugar ranging from 123.6 to 242.92 mg/dl.

- Similarly, postprandial blood sugar was significantly higher in the poorly controlled group (204.9 to 336.14 mg/dl) compared to the well-controlled group (105 to 226.95 mg/dl).

- The p-values for both parameters are 0.00, indicating that the differences are highly significant. Higher HbA1c is strongly associated with higher fasting and postprandial glucose levels, emphasizing the need for better glucose management to prevent complications.

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2. Serum Ferritin Levels

- Serum ferritin is a marker of iron storage in the body. The group with HbA1c ≤ 7 had ferritin level ranging from 19.8 to 101.2 ng/ml, while the poorly controlled group had a significantly higher value ranging from 59.1 to 119.5 ng/ml.

- A p-value of 0.0019 confirms that this difference is statistically significant. Increased serum ferritin levels in individuals with high HbA1c may indicate an ongoing inflammatory process or metabolic dysfunction. High ferritin levels have been linked to insulin resistance, oxidative stress, and chronic diseases.

3. High-sensitivity C-reactive protein (hs-CRP)

- hs-CRP is a well-known marker of inflammation. The group with good glycemic control had a relatively low hs-CRP level ranging from 0.2 to 4.8 mg/L, while the poorly controlled group had a much higher level ranging from 3.5 to 6.7 mg/L.

- The p-value of 0.00 confirms a highly significant difference between the two groups. Chronic inflammation is more prevalent in individuals with poor blood sugar control. High hs-CRP levels suggest an increased risk of cardiovascular disease, as inflammation plays a key role in heart disease and other complications of diabetes.

4. Interleukin-6 (IL-6)

- IL-6 is another important inflammatory marker. The HbA1c ≤ 7 group had an IL-6 level ranging from -39.8 to 61.2 pg/mL, whereas the poorly controlled group had a much higher level ranging from 0.5 to 81.3 pg/mL.

- The p-value of 0.013 indicates that this difference is statistically significant. IL-6 is involved in the body's immune response and inflammation. Elevated IL-6 levels in individuals with high

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HbA1c suggest that poor glycemic control contributes to systemic inflammation, which can lead to complications like cardiovascular disease, insulin resistance, and metabolic disorders.

5) PEARSON CORRELATION COEFFICIENTS (r) AND THEIR CORRESPONDING P-VALUES FOR TWO GROUPS DEFINED BY HbA1c LEVELS (Table 9)

	HbA1C ≤ 7 (n = 29)		**HbA1C > 7 (n = 31)**	
	r	**p**	**r**	**p**
FBS (mg/dl)	0.751	0.001	0.851	0.0001
PPBS (mg/dl)	0.802	0.0005	0.902	0.000
Serum Ferritin (ng/ml)	0.301	0.05	0.401	0.02
hs-CRP (mg/L)	0.401	0.02	0.502	0.005
IL-6	0.356	0.03	0.451	0.01

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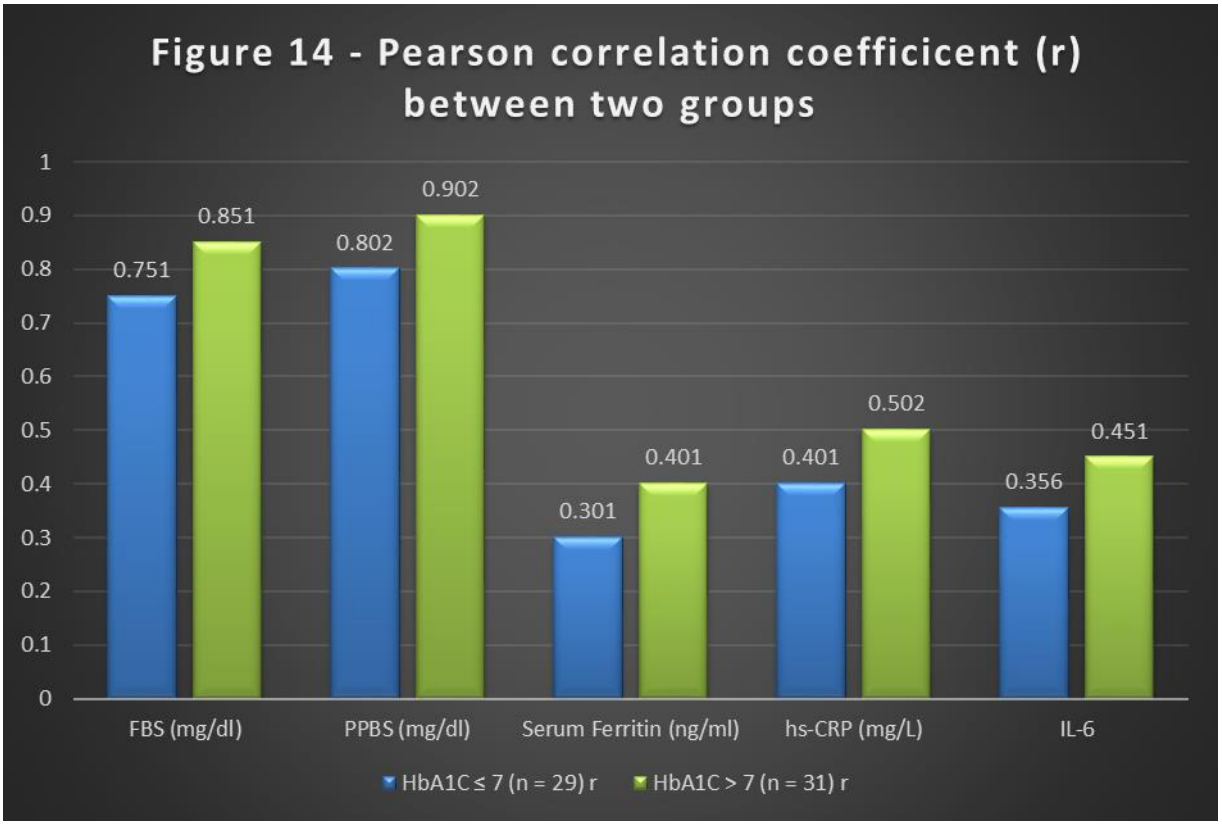

Table 9 and figure 14 presents Pearson correlation coefficients (r) and their corresponding p-values for fasting blood sugar (FBS), postprandial blood sugar (PPBS), serum ferritin, high-sensitivity C-reactive protein (hs-CRP), and interleukin-6 (IL-6) in two groups of Type 2 Diabetes Mellitus (T2DM) patients based on their HbA1c levels (≤ 7 and > 7). Stronger correlations are observed in the poor glycemic control group (HbA1c > 7), particularly for FBS ($r = 0.851$, $p = 0.0001$) and PPBS ($r = 0.902$, $p = 0.000$), compared to the good control group ($r = 0.751$ and 0.802, respectively). This suggests a stronger association between glucose levels and HbA1c in poorly controlled patients. Inflammatory markers (serum ferritin, hs-CRP, and IL-6) also show higher correlations with HbA1c in the poor control group, indicating a stronger link between inflammation and poor glycemic control. The significant p-values ($p < 0.05$) confirm that these correlations are statistically significant. Overall, the findings emphasize the role of inflammation in diabetes progression and the need for better glycemic management.

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DISCUSSION

Diabetes is an inflammatory disease, and sub-optimal glycemic control is associated with the development of microvascular and macrovascular complications. This study included a total of 60 patients with type 2 diabetes and 20 healthy controls and evaluated the serum levels of pro-inflammatory biomarkers, namely IL-6, serum ferritin, and hs-CRP. The findings concluded a substantial positive correlation between the glycemic control markers (HbA1c, FBS, and PPBS) and inflammatory markers, which reveal the contribution of chronic inflammation in diabetes pathophysiology.

Elevated levels of IL-6, hs-CRP, and serum ferritin suggest that diabetic patients are experiencing a chronic inflammatory response that could induce insulin resistance and worsening of the disease [(21)]. The strong correlation between HbA1c and inflammatory markers observed in this study further emphasizes the role of chronic hyperglycemia in inflammation. Deteriorating glycemic control increases oxidative stress and inflammatory response, leading to increased insulin resistance and a higher risk of vascular complications [(22)]. Elevated FBS and PPBS levels in diabetic patients were also strongly associated with inflammatory biomarkers, indicating that postprandial and fasting hyperglycemia contribute to systemic inflammation [(23)]. Both hyperglycemia and increased systemic inflammation may contribute to disease complications and also suggest that these inflammatory markers are associated with the disease's pathophysiology [(24)].

Our study demonstrates that Type 2 Diabetes Mellitus (T2DM) is associated with significantly elevated inflammatory markers, including ferritin, high-sensitivity C-reactive protein (hs-CRP), and interleukin-6 (IL-6), compared to healthy controls. These findings align with the existing literature of Hotamisligil, G. et al. [(25)] and Donath MY, Shoelson SE et al. [(26)] that describes chronic low-grade inflammation as a hallmark of type 2 diabetes mellitus. In the study conducted

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by King GL [27] and Shoelson SE et al. [28] revealed that elevated inflammatory markers in type 2 diabetes patients reflect ongoing metabolic disturbances and insulin resistance, both of which are linked to systemic inflammation.

A key finding of our study is that 51.6% of T2DM patients with poorer glycemic control (HbA1c > 7) exhibit significantly higher inflammatory markers than those with better glycemic control (HbA1c ≤ 7). This is consistent with Esser et al. [29] and Pradhan et al. [30], indicating that chronic hyperglycemia exacerbates oxidative stress and inflammatory responses, leading to endothelial dysfunction and increased risk of cardiovascular complications. Studies by Pickup JC [31] and Kahn SE et al. [32], have demonstrated that persistent hyperglycemia enhances pro-inflammatory cytokine production, including IL-6, which, in turn, stimulates hepatic production of acute-phase proteins such as CRP and ferritin.

Additionally, our findings indicate a positive correlation among serum ferritin, high-sensitivity C-reactive protein (hs-CRP), and interleukin-6 (IL-6) with HbA1c levels, with statistically significant associations observed in the group exhibiting elevated HbA1c levels. This corroborates findings by Fernández-Real et al. [33] and Forouhi et al. [34], who reported that ferritin, as an acute-phase reactant, is closely associated with poor glycemic control and insulin resistance. Wang et al. [17] and Schulze MB et al. [35] revealed that elevated ferritin levels had been suggested to contribute to β-cell dysfunction and reduced insulin sensitivity, primarily through iron-mediated oxidative stress mechanisms. Additionally, Van Campenhout et al. [36] found that diabetes disrupts iron metabolism, inflammation, and oxidative stress, exacerbating metabolic complications. Alexandraki et al. [37] highlighted the persistence of cytokine secretion in both T1DM and T2DM, reinforcing the systemic nature of diabetes-related inflammation.

hs-CRP, a sensitive marker of systemic inflammation, was significantly higher in patients with poor glycemic control. This supports the results of Ridker PM [38], which links elevated CRP levels with insulin resistance and cardiovascular complications in Type 2 diabetic patients. A study by

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Kant et al. [39] suggests that chronic inflammation significantly impacts T2DM progression, with elevated serum ferritin and hs-CRP levels correlating with poor glycemic control and dyslipidemia. Similarly, Liu et al. [40] identified TNF-α as a key contributor to insulin resistance and β-cell dysfunction, further increasing T2DM risk. The role of IL-6 in T2DM has been extensively studied, with evidence suggesting that it directly contributes to hepatic insulin resistance and impairs glucose homeostasis, corroborating to the studies by Mohammadi M et al. [37] and Kristiansen OP et al. [38].

The interplay between inflammation and glycemic control highlights the importance of anti-inflammatory interventions in T2DM management. Dandona P et al. [39] suggested that pharmacological and lifestyle interventions targeting inflammation, such as metformin therapy and dietary modifications, can improve both glycemic control and inflammatory status. Additionally, studies by Ridker PM et al. [40] and Larsen CM et al. [41] support that using anti-inflammatory agents such as statins and IL-1 antagonists helps reduce systemic inflammation and improve insulin sensitivity. Bellucci et al. [46] and Esser et al. [47] demonstrated that anti-inflammatory agents, including NSAIDs, show potential in managing T2DM by mitigating metabolic disturbances. Our study findings and those of Li D et al. [48], Everett BM [49] and Goldberg RB [50] reinforce the strong association between inflammation and glycemic control in T2DM, highlighting the potential benefits of inflammation-targeted therapeutic strategies.

These findings underscore the importance of a multidisciplinary approach to diabetes management, addressing both glucose regulation and inflammatory reduction. Therefore, lifestyle changes, such as diet, physical activity, weight management, and inflammatory-targeted treatment approaches, may play an essential role in glycemic control and lowering complications associated with inflammation in patients with diabetes [4,5]. Additionally, emerging pharmacological interventions, like SGLT2 inhibitors or GLP-1 receptor agonists, have demonstrated promising effects on anti-inflammation and glycemic control. Therefore, current treatment strategies for type

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2 diabetes mellitus go beyond targeting hyperglycemia towards an improved inflammatory profile [3,4].

Beyond pharmacological and lifestyle interventions, it is imperative to understand the molecular mechanisms associated with the relationship between inflammatory responses and diabetes [4-6]. Chronic hyperglycemia, resulting from oxidative stress, induces an immune imbalance that activates pro-inflammatory molecular pathways, including nuclear factor-kappa B (NF-κB) and tumour necrosis factor-alpha (TNF-α) [3]. The activation of these pathways exacerbates insulin resistance and endothelial dysfunction, thereby playing a significant role in the progression of diabetes-related complications, such as nephropathy, retinopathy, and cardiovascular disorders. Therefore, targeting these pathways could be a new molecular approach to pharmacotherapy for hyperglycemia and concomitant inflammation in diabetics [1-3].

Despite its strengths, this study has certain limitations. This study featured a relatively small sample size and did not extensively analyse other potential confounding factors, including obesity, lipid profiles, and medication use. However, future longitudinal studies with larger cohorts and comprehensive metabolic profiling will be required, including the potential effect of specific anti-inflammatory interventions on glycemic control and overall metabolic health, and may provide insights into optimising treatment strategies.

Our study reinforces the association of chronic inflammation with glycemic control in type 2 diabetes. The strong association that inflammatory biomarkers show with glycemic indices indicates the need for anti-inflammatory strategies to be included in diabetes management to counteract long-term complications and improve patient outcomes. Future research should focus on identifying individualized treatment approaches that address both hyperglycemia and inflammation, ultimately enhancing the quality of life for diabetic patients.

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SUMMARY

- Type 2 Diabetes Mellitus (T2DM) is associated with chronic inflammation, contributing to insulin resistance and disease progression.
- Inflammatory markers such as IL-6, Ferritin, and hs-CRP play a significant role in diabetes-related complications.
- This study evaluated the correlation between inflammatory markers and glycemic control using HbA1c levels.
- A hospital-based cross-sectional study was conducted with 80 participants, including 60 Type 2 Diabetic patients and 20 healthy controls. Blood samples were analyzed for fasting blood sugar (FBS), postprandial blood sugar (PPBS), glycated haemoglobin (HbA1c), Ferritin, hs-CRP, and IL-6 levels.
- Diabetic patients exhibited significantly higher levels of inflammatory markers compared to healthy individuals.
- Among the diabetic patients, 51.6% with poor glycemic control (HbA1c > 7) had notably higher inflammatory marker levels than those with better glycemic control (HbA1c ≤ 7).
- A strong positive correlation was observed between HbA1c and inflammatory markers, indicating that worsening glycemic control leads to increased systemic inflammation.
- Elevated Ferritin, hs-CRP, and IL-6 levels suggest a link between chronic hyperglycemia and inflammatory responses, which could contribute to vascular complications.
- The findings support the role of inflammation in diabetes pathophysiology and highlight the importance of monitoring inflammatory markers in diabetic patients.
- The study suggests that anti-inflammatory interventions could improve glycemic control and reduce diabetes-related complications.

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CONCLUSION

Our study confirms that Type 2 Diabetes Mellitus (T2DM) is associated with significantly elevated levels of inflammatory markers, including ferritin, hs-CRP, and IL-6, compared to healthy individuals. Moreover, patients with poor glycemic control (HbA1c > 7) exhibit even higher levels of these markers, reinforcing the link between hyperglycemia and systemic inflammation. The significant positive association observed among ferritin, hs-CRP, IL-6, and HbA1c emphasizes how inflammation plays a role in glycemic dysregulation and aids as a tool in the risk assessment of micro and macrovascular complications. These findings emphasize the need to monitor inflammatory markers in T2DM management and suggest that addressing inflammation could be a valuable approach to improving glycemic control and reducing diabetes-related complications.

RECOMMENDATIONS - To strengthen this study's findings, future research should incorporate a larger and more diverse cohort, utilize advanced metabolic profiling techniques, and explore the long-term effects of targeted anti-inflammatory treatments on glycemic regulation. Additionally, randomized controlled trials could help establish causality and refine therapeutic approaches.

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ANNEXURE - I

BLDE
(DEEMED TO BE UNIVERSITY)
Declared as Deemed to be University u/s 3 of UGC Act, 1956
Accredited with 'A' Grade by NAAC (Cycle-2)
The Constituent College
SHRI B. M. PATIL MEDICAL COLLEGE, HOSPITAL & RESEARCH CENTRE, VIJAYAPURA

BLDE (DU)/IEC/ 938/2023-24 10/4/2023

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this University met on **Saturday, 18th March, 2023 at 11.30 a.m. in the CAL Laboratory, Dept. of Pharmacology,** scrutinized the Synopsis/ Research Projects of Post Graduate Student / Under Graduate Student /Faculty members of this University /Ph.D. Student College from ethical clearance point of view. After scrutiny, the following original/ corrected and revised version synopsis of the thesis/ research projects has been accorded ethical clearance.

TITLE: "EVALUATION OF INFLAMMATORY MARKERS- IL-6, FERRITIN, hs-CRP IN TYPE 2 DIABETIC PATIENTS AND ITS CORRELATION WITH GLYCATED HEMOGLOBIN".

NAME OF THE STUDENT/PRINCIPAL INVESTIGATOR: DR.ANGELA SUSAN A.J.

NAME OF THE GUIDE: DR.MAMATHA K , ASSOCIATE PROFESSOR
DEPT. OF PATHOLOGY.

Dr. Santoshkumar Jeevangi
Chairperson
IEC, BLDE (DU),
VIJAYAPURA
Chairman,
Institutional Ethical Committee,
BLDE (Deemed to be University)
Vijayapura

Dr.Akram A. Naikwadi
Member Secretary
IEC, BLDE (DU),
VIJAYAPURA
MEMBER SECRETARY
Institutional Ethics Committee
BLDE (Deemed to be University)
Vijayapura-586103. Karnataka

Following documents were placed before Ethical Committee for Scrutinization.

- Copy of Synopsis/Research Projects
- Copy of inform consent form
- Any other relevant document

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ANNEXURE – II

B.L.D.E. (DEEMED TO BE UNIVERSITY)
SHRI B.M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTER,
VIJAYAPUR-586103

INFORMED CONSENT FOR PARTICIPATION IN DISSERTATION/RESEARCH

I, the undersigned,_____ ,S/O D/O W/O _____,aged____years, ordinarily resident of _____do hereby state/declare that Dr. _____ of _____ Hospital has examined me thoroughly on _____ at _____ (place) and it has been explained to me in my own language that I am suffering from _____ disease (condition) and this disease/condition mimic following diseases . Further Doctor informed me that he/she is conducting dissertation/research titled **"EVALUATION OF INFLAMMATORY MARKERS - IL-6, FERRITIN, HS-CRP IN TYPE 2 DIABETIC PATIENTS AND ITS CORRELATION WITH GLYCATED HEMOGLOBIN"** under the guidance of Dr.Mamatha .K requesting my participation in the study. Apart from routine treatment procedure, the pre-operative, operative, post-operative and follow-up observations will be utilized for the study as reference data.

Doctor has also informed me that during conduct of this procedure like adverse results may be encountered. Among the above complications most of them are treatable but are not anticipated hence there is chance of aggravation of my condition and in rare circumstances it may prove fatal in spite of anticipated diagnosis and best treatment made available. Further Doctor has informed me that my participation in this study help in evaluation of the results of the study which is useful reference to treatment of other similar cases in near future, and also I may be benefited in getting relieved of suffering or cure of the disease I am suffering.

The Doctor has also informed me that information given by me, observations made/ photographs/ video graphs taken upon me by the investigator will be kept secret and not assessed by the person

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other than me or my legal hirer except for academic purposes.

The Doctor did inform me that though my participation is purely voluntary, based on information given by me, I can ask any clarification during the course of treatment / study related to diagnosis, procedure of treatment, result of treatment or prognosis. At the same time I have been informed that I can withdraw from my participation in this study at any time if I want or the investigator can terminate me from the study at any time from the study but not the procedure of treatment and follow-up unless I request to be discharged.

After understanding the nature of dissertation or research, diagnosis made, mode of treatment, I the undersigned Shri/Smt _____ under my full conscious state of mind agree to participate in the said research/dissertation.

Signature of patient:

Signature of doctor:

Witness: 1.

2.

Date:

Place:

Docusign Envelope ID: AB7734B4-F0D0-4C26-B8DC-71497D6EB60C

B.L.D.E (DEEMED TO BE UNIVERSITY) ಶ್ರೀ ಬಿ.ಎಂ.ಪಟ್ಟೀಲ್ ಮೆಡಿಕಲ್ ಕಾಲೇಜು, ಆಸ್ಪತ್ರೆ ಮತ್ತು ಸಂಶೋಧನಾ ಕೇಂದ್ರ, ವಿಜಯಪುರ-586103

ಪ್ರಬಂಧ/ಸಂಶೋಧನೆಯಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳಲು ಮಾಹಿತಿ ಪಡೆದ ಸಮ್ಮತಿ

ನಾನು, ಕೆಳಗಿನವರು_____ ಸಹಿಯಿಟ್ಟವರು, ಮಗ/ಮಗಳು/ಪತ್ನಿಯ _____ ವಯಸ್ಸು _____ವರ್ಷಗಳು, ಸಾಮಾನ್ಯವಾಗಿ ನಿವಾಸಿಸುವ ಸ್ಥಳದ ಹೆಸರು_____, ಇಲ್ಲಿ ಹೇಳಿದ್ದೇನೆ/ಘೋಷಿಸುತ್ತೇನೆ ಡಾಕ್ಟರ್ ಹೆಸರು_____ ಅವರು ಆಸ್ಪತ್ರೆ ಹೆಸರು_____ ಅವರು ನನ್ನನ್ನು ಪೂರ್ಣವಾಗಿ ಪರೀಕ್ಷಿಸಿದರು ದಿನಾಂಕದಲ್ಲಿ_____ ಸ್ಥಳ ಹೆಸರು_____ ಮತ್ತು ನನಗೆ ನನ್ನ ಭಾಷೆಯಲ್ಲಿ ವಿವರಿಸಲಾಗಿದೆ ನಾನು ಒಂದು ರೋಗ (ಸ್ಥಿತಿ) ಅನುಭವಿಸುತ್ತಿದ್ದೇನೆ. ಮುಂದುವರಿದು ಡಾಕ್ಟರ್ ನನಗೆ ತಿಳಿಸಿದ್ದಾರೆ ಅವರು ಒಂದು ಪದ್ಧತಿ/ಸಂಶೋಧನೆ ನಡೆಸುತ್ತಿದ್ದಾರೆ ಶೀರ್ಷಿಕೆಯುಳ್ಳ "EVALUATION OF INFLAMMATORY MARKERS - IL-6, FERRITIN, HS-CRP IN TYPE 2 DIABETIC PATIENTS AND ITS CORRELATION WITH GLYCATED HEMOGLOBIN" ಡಾಕ್ಟರ್ Dr.Mamatha.K ಮಾರ್ಗದರ್ಶನದಲ್ಲಿ ನನ್ನ ಪಾಲ್ಗೊಳ್ಳುವಿಕೆಯನ್ನು ಕೇಳಿದ್ದಾರೆ ಅಧ್ಯಯನದಲ್ಲಿ.

ಡಾಕ್ಟರ್ ನನಗೆ ಇದನ್ನು ಕೂಡಾ ತಿಳಿಸಿದ್ದಾರೆ ಈ ಕ್ರಮದ ನಡುವಲ್ಲಿ ಪ್ರತಿಕೂಲ ಫಲಿತಾಂಶಗಳನ್ನು ಎದುರಿಸಬಹುದು. ಮೇಲೆ ಹೇಳಿದ ಪ್ರಕಟಣೆಗಳಲ್ಲಿ, ಅಧಿಕಾಂಶವು ಚಿಕಿತ್ಸಿಸಬಹುದಾದರೂ ಅದನ್ನು ನಿರೀಕ್ಷಿಸಲಾಗುತ್ತಿಲ್ಲ ಆದ್ದರಿಂದ ನನ್ನ ಸ್ಥಿತಿಯ ಹಿರಿದಾಗುವ ಅವಕಾಶವಿದೆ ಮತ್ತು ಅಪರೂಪದ ಸಂದರ್ಭಗಳಲ್ಲಿ ಅದು ಮರಣಕಾರಕವಾಗಿ ಪರಿಣಮಿಸಬಹುದು ಹೊಂದಿದ ರೋಗನಿರ್ಧಾರ ಮತ್ತು ಯಥಾಶಕ್ತಿ ಚಿಕಿತ್ಸೆ ಮಾಡಲು ಹೊಂದಿದರೂ, ಮುಂದುವರಿದು ಡಾಕ್ಟರ್ ನನಗೆ ತಿಳಿಸಿದ್ದಾರೆ ನನ್ನ ಪಾಲ್ಗೊಳ್ಳುವಿಕೆ ಈ ಅಧ್ಯಯನದ ಫಲಿತಾಂಶಗಳ ಮೌಲ್ಯಮಾಪನದಲ್ಲಿ ಸಹಾಯಕವಾಗುತ್ತದೆ ಇತರ ಸಮಾನ ಪ್ರಕರಣಗಳ ಚಿಕಿತ್ಸೆಗೆ ಉಪಯುಕ್ತ ಉಲ್ಲೇಖವಾಗಿದೆ, ಮತ್ತು ನಾನು ಅನುಭವಿಸುವ ರೋಗದಿಂದ ವಿಮುಕ್ತಿ ಅಥವಾ ಗುಣಮುಖಗೊಳ್ಳುವಲ್ಲಿ ನನಗೆ ಪ್ರಯೋಜನವಾಗಬಹುದು.

ಡಾಕ್ಟರ್ ನನಗೆ ಇದನ್ನು ಕೂಡಾ ತಿಳಿಸಿದ್ದಾರೆ ನನ್ನಿಂದ ನೀಡಿದ ಮಾಹಿತಿ, ಮಾಡಿದ ಪರಿಶೀಲನೆಗಳು / ಫೋಟೋಗ್ರಾಫ್‌ಗಳು / ವೀಡಿಯೋ ಗ್ರಾಫ್‌ಗಳು ನನ್ನ ಮೇಲೆ ತೆಗೆದುಕೊಳ್ಳಲಾಗುವ ಅನ್ವೇಷಕರು ರಹಸ್ಯವಾಗಿ ಇಡುವರು ಮತ್ತು ನಾನು ಅಥವಾ ನನಗೆ ಕಾನೂನು ದೃಷ್ಟಿಯಲ್ಲಿ ಸಂಬಂಧಿತರನ್ನು ಹೊರತುಪಡಿಸಿ ಇತರ ವ್ಯಕ್ತಿಯಿಂದ ಮೌಲ್ಯಮಾಪನ ಮಾಡಲಾಗುವುದಿಲ್ಲ. ಡಾಕ್ಟರ್ ನನಗೆ ತಿಳಿಸಿದ್ದಾರೆ ನನ್ನ ಪಾಲ್ಗೊಳ್ಳುವಿಕೆ ಶುದ್ಧವಾಗಿ ಸ್ವೇಚ್ಛಾಯಿತ, ನನ್ನಿಂದ ನೀಡಿದ ಮಾಹಿತಿಯ ಆಧಾರದ ಮೇಲೆ, ಚಿಕಿತ್ಸೆ / ಅಧ್ಯಯನದ ಸಂಬಂಧದಲ್ಲಿ ರೋಗನಿರ್ಧಾರ, ಚಿಕಿತ್ಸೆಯ ವಿಧಾನ, ಚಿಕಿತ್ಸೆಯ ಫಲಿತಾಂಶ ಅಥವ ಭವಿಷ್ಯದ ಪ್ರವೃತ್ತಿಗಳು ಬಗ್ಗೆ ಯಾವುದೇ ಸ್ಪಷ್ಟತೆ ಕೇಳಬಹುದು. ಅದೇ ಸಮಯದಲ್ಲಿ ನನಗೆ ತಿಳಿಸಲಾಗಿದೆ ನಾನು ಯಾವುದೇ ಸಮಯದಲ್ಲಿ ಈ ಅಧ್ಯಯನದಲ್ಲಿ ನನ್ನ ಪಾಲ್ಗೊಳ್ಳುವಿಕೆಯನ್ನು ನಿಲ್ಲಿಸಬಹುದು ನಾನು ಬಯಸಿದರೆ ಅಥವಾ ಅನ್ವೇಷಕರು ಅಧ್ಯಯನದಿಂದ ಯಾವುದೇ ಸಮಯದಲ್ಲಿ ನನ್ನನ್ನು ನಿಲ್ಲಿಸಬಹುದು.

ಪ್ರಬಂಧ ಅಥವಾ ಸಂಶೋಧನೆಯ ಸ್ವಭಾವ, ಮಾಡಿದ ರೋಗನಿರ್ಧಾರ ಮತ್ತು ಚಿಕಿತ್ಸೆಯ ವಿಧಾನವನ್ನು ಅರ್ಥಮಾಡಿಕೊಂಡು, ನಾನು ಕೆಳಗಿನ ಶ್ರೀ / ಶ್ರೀಮತಿ_____ ನನ್ನ ಪೂರ್ಣವಾದ ಪ್ರಜ್ಞೆಯ ಸ್ಥಿತಿಯಲ್ಲಿ ಹೇಳಿದ ಸಂಶೋಧನೆ / ಪ್ರಬಂಧದಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳಲು ಒಪ್ಪುತ್ತೇನೆ.

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ರೋಗಿಯ ಡಾಕ್ಟರನ ಸಹಿ

ಸಾಕ್ಷಿಗಳು

1)

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ANNEXURE – III

PROFORMA

NAME **:** OP/IP No. **:**

AGE **:**

SEX **:** D.O.A **:**

OCCUPATION **:**

RESIDENCE **:**

Presenting Complaints :

Past history :

Personal history :

Family history :

Treatment history **:**

General physical examination:

VITALS:

PR:

BP:

RR:

TEMPERATURE:

WEIGHT:

Laboratory Investigations:

Parameters:	**Patient Values:**
Hemoglobin (g/dl)	
FBS (mg/dl)	
PPBS (mg/dl)	
Interleukin – 6 (pg/ml):	
S.ferritin (mcg/L):	
hs-CRP (mg/L):	
HbA1c (%)	

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KEY TO THE MASTER CHART

S.No	Serial Number
M	Male
F	Female
Hb (g/dl)	Hemoglobin
FBS (mg/dl)	Fasting blood sugar
PPBS (mg/dl)	Post-prandial blood sugar
HbA1c (%)	Glycated haemoglobin
hs CRP (mg/L)	High-sensitive C-Reactive Protein
IL-6 (pg/ml)	Interleukin 6

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MASTER CHART

CASES (n=60)	AGE IN YEARS	SEX	IP NO	Hb (g/dl)	FBS (mg/dl)	PPBS(mg/dl)	HbA1c (%)	FERRITIN (mcg/L)	hs CRP (mg/L)	IL 6 (pg/ ml)
1)	77	F	314431	12.3	106	156	6.6	38.2	2.2	2.7
2)	58	M	27980	14	138	363	7	80.4	3	2.7
3)	65	M	12786	15.9	156	266	8.9	135.1	0.9	2.7
4)	71	M	132741	13.2	86	170	5.9	75.6	2.32	2.7
5)	66	M	14016	14.2	109	159	6.6	79.3	3	4.3
6)	67	M	105632	13.1	108	149	7	21	4.1	2.7
7)	51	M	20675	16.9	138	229	7	383.3	3.75	7.3
8)	76	M	3119	14.2	139	164	5.8	207.8	2.94	2.7
9)	69	M	85817	13.9	107	145	6.4	59.9	0.6	2.7
10)	63	F	85818	12	123	168	6.9	10.2	1.39	2.7
11)	59	M	94322	14.7	178	348	9.5	37.5	4.1	2.7
12)	61	M	389344	13.9	82	123	6.3	169.1	14.8	10.5
13)	49	M	127957	13.8	127	202	7.7	132.5	3.1	2.7
14)	54	F	180621	12.8	137	179	8.3	44.7	2.9	2.7
15)	51	M	827	14	133	151	9.4	56	6.9	2.7
16)	51	F	187802	12.7	199	314	9.6	34.7	7.2	2.7
17)	60	M	167658	15	118	193	8.1	98	1.31	37.4
18)	53	M	85409	15.4	118	157	7	103.9	1.9	4.1
19)	57	F	15490	12.5	179	191	10.3	26.2	2.5	2.7
20)	63	M	40754	13.5	91	144	7	20.5	2.9	2.7

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CASES (n=60)	AGE IN YEARS	SEX	IP NO	Hb (g/dl)	FBS (mg/dl)	PPBS(mg/dl)	HbA1c (%)	FERRITIN (mcg/L)	hs CRP (mg/L)	IL 6 (pg/ml)
21)	56	F	14622	13.4	194	312	9.4	70.5	2.2	2.7
22)	88	F	335840	13	354	397	10.8	164.6	2.1	2.7
23)	62	F	176928	13.5	169	153	6.1	100.7	2.1	2.7
24)	63	M	204658	12.4	94	210	11.1	102.7	1.2	2.7
25)	59	F	299376	13.4	181	223	9.9	69.8	3.1	2.7
26)	49	F	438798	13.2	188	252	8.7	117.5	2.5	2.7
27)	44	M	42160	14.6	233	331	10.4	267.4	4.3	3.3
28)	66	M	25982	13.8	90	171	7	61.8	13.3	2.7
29)	51	M	829	13.4	147	157	10.4	63.5	4.5	2.7
30)	51	F	438273	13.5	276	356	12.5	42.5	4.9	2.7
31)	70	M	42158	13	145	298	10.4	136.5	14.4	2.7
32)	58	M	438272	13.4	239	360	11.9	50.3	5.2	2.7
33)	72	F	299612	12.5	117	201	6.5	25	0.7	2.7
34)	44	F	413264	13	93	130	6.4	34.9	3.7	2.7
35)	56	F	42341	13.6	118	248	8.7	49.4	1.5	2.7
36)	78	M	184219	13.2	140	241	7.9	36.8	0.8	2.7
37)	90	F	42565	13	239	315	10.3	131.3	2	2.7
38)	48	F	248810	13.6	232	343	11.4	29.9	6.7	2.7
39)	61	M	2264	14.1	317	370	11.3	137.5	2.9	17.6
40)	64	M	288441	14.1	96	198	6.7	52.4	3.4	3.6

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CASES (n=60)	AGE IN YEARS	SEX	IP NO	Hb (g/dl)	FBS (mg/dl)	PPBS(mg/dl)	HbA1c (%)	FERRITIN (mcg/L)	hs CRP (mg/L)	IL 6 (pg/ml)
41)	62	F	176928	13.5	169	153	6.1	266.2	11.3	4.9
42)	40	M	322324	16.8	150	253	7.8	73.5	2.9	437.6
43)	47	M	133048	14.8	143	248	7	17.7	1.7	189.9
44)	51	F	390010	13.2	155	239	7.6	26.3	2.3	16.7
45)	61	F	203751	12.2	110	204	6.5	51.6	2.1	636
46)	73	M	389926	13.6	166	262	7	29.8	2.4	15.4
47)	40	F	194578	12.8	241	320	10	18.1	0.7	5.9
48)	64	M	85908	14.3	153	259	7	72.3	5.6	2.7
49)	63	F	231752	13.1	149	261	7	54.3	4	2.7
50)	51	F	239181	12.7	189	229	9.4	49.5	5.2	2.7
51)	67	F	134551	13	108	206	6.4	17.9	3.1	3
52)	67	M	8189	15	138	258	8.1	68.6	5.8	5.1
53)	55	F	14322	13.5	150	262	7.6	26.5	2.2	16.5
54)	38	M	87011	14	112	220	6.9	10.2	1.39	2.7
55)	40	F	38557	12.9	145	270	8.2	50.1	1.5	2.7
56)	36	F	12556	12.6	157	245	7	72.4	5.6	2.7
57)	45	M	15548	13.4	149	265	7	71.3	5.2	2.7
58)	39	F	18755	13.2	152	272	7	26.3	2.2	16.7
59)	50	M	16345	13.9	189	298	8.2	49.4	1.5	2.7
60)	39	M	14785	14	150	254	7	70.3	5.4	2.7

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CONTROLS (n=20)	AGE IN YEARS	SEX	Hb (g/dl)	FBS (mg/ dl)	PPBS (mg/dl)	HbA1c (%)	FERRITIN (mcg/L)	hs CRP (mg/L)	IL 6 (pg/ml)
1)	27	F	12.4	80	100	4.9	35.3	1	2.7
2)	23	M	15.9	84	90	5.5	88.9	19	2.7
3)	29	F	12.2	86	86	5.5	24.5	0.3	2.7
4)	28	M	14	90	120	5	50.5	0.5	2.7
5)	30	F	13.5	88	118	5.1	45.3	0.4	2.7
6)	45	M	14.5	92	122	5.2	55.4	0.6	2.7
7)	49	F	13.8	89	119	5	52.2	0.5	2.7
8)	50	F	13.9	91	121	5.1	47.5	0.4	2.7
9)	27	M	14.1	90	120	5	53.1	0.5	2.7
10)	33	F	13.7	87	117	5	48.2	0.4	2.7
11)	33	F	13.6	89	119	5.1	49.5	0.5	2.7
12)	42	M	14.2	88	118	5	51.3	0.6	2.7
13)	26	F	13.8	90	120	5	50.2	0.5	2.7
14)	28	F	13.5	91	121	5.1	46.3	0.4	2.7
15)	45	M	14.4	92	122	5.2	54.6	0.6	2.7
16)	55	M	13.6	88	118	5	47.2	0.4	2.7
17)	28	F	13.7	89	119	5.1	50.3	0.5	2.7
18)	38	M	14	87	117	5	52.2	0.5	2.7
19)	25	F	13.1	90	120	5.2	59.2	0.6	2.7
20)	29	F	12	92	116	5.2	36.2	4.8	2.7

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angela susan

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