"A Study of Highly Sensitive C-Reactive Protein (hs-CRP) in Type 2 Diabetes Mellitus and its Correlation with Glycosylated Hemoglobin (HbA1C) at Tertiary Care Centre. A One Year Cross Sectional Study."

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ENDORSEMENT

This is to certify that the dissertation entitled **"A Study of Highly Sensitive C-Reactive Protein (hs-CRP) in Type 2 Diabetes Mellitus and its Correlation with Glycosylated Hemoglobin (HbA1C) at Tertiary Care Centre. A One Year Cross Sectional Study.**" is a bonafide research work done by **REG NO. BG0115009.**

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LIST OF ABBREVIATIONS

%	Percentage
ALP	Alkaline Phosphatate
BMI	Basal Mass Index
BP	Blood pressure
BPM	Beats per minute
CBC	Complete Blood Count
DB	Direct Bilirubin
DM	Diabetes mellitus
ECG	Electrocardiogram
ESR	Erythrocyte Sedimentation Rate
f	Female
Fbs	Fasting Blood Sugars
Hb	Hemoglobin
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
hr	Hour
hs-CRP	Highly Sensitive C – Reactive Protein
HTN	Hypertension
IHD	Ischemic Heart Disease
LFT	Liver Function Test
m	Male
mg/dL	Milligram per Deciliter
mg/ltr	Milligram per Liter

OPD	Outpatient Department
Plt	Platelets
PS	Peripheral Smear
RA	Rheumatoid Arthiritis
RFT	Renal Function Test
RHD	Rheumatic Heart Disease
RR	Respiratory rate
SGOT	Serum Glutamic-Oxaloacetic Transaminase (AST)
SGPT	Serum Glutamic Pyruvic Transaminase (ALT)
SLE	Systemic Lupus Erythematosus
T2DM	Type 2 Diabetes Mellitus
TB	Total Bilirubin
TEMP	Temperature
TLC	Total Leukocyte Count
URTI	Upper Respiratory Tract Infection
UTI	Urinary Tract Infection
WBC	Whole blood count
WHO	World Health Organization

ABSTRACT

Background and objectives

There is a rising prevalence of non –communicable diseases in developing countries like India especially Diabetes Mellitus with more than 50% percent of diabetic patients being unaware of their diabetic status in India. The rise in Diabetes in India can be attributed to genetic predisposition, the sedentary lifestyles and the changing food habits.

hs-CRP is a marker of systemic inflammation, is emerging as an independent risk factor for cardiovascular disease. High hs-CRP levels have been linked to an increased risk of thrombotic events including myocardial infarction and stroke. hs-CRP levels are higher in people with diabetes compared with those without diabetes. Less is known about whether hs-CRP in people with diabetes is related to level of HbA1C.

According to a previous study done by Dana E. King et al. Where they concluded that a higher HbA1c is significantly associated with a greater likelihood of higher CRP among adults with diabetes. The relation was significant in unadjusted comparisons of the percent of people with elevated CRP according to HbA1c level and in logistic regression models to predict elevation of CRP after controlling for age, race, sex, smoking, BMI, insulin level, and length of time with diabetes.

Type II diabetes is disease in which blood sugar level increases the shear stress contributing to inflammation and dysfunction of endothelium. The purpose of this study was to identify the relationship between serum hs-CRP and HbA1c in type II diabetic subjects.

Methods:

The present cross-sectional study was conducted on patients with T2DMin medicine OPD or admitted in KLE'S Dr.Prabhakar Kore Hospital and Medical Research Centre, Belagavi from Jan 2016 to Dec 2016.Patients were selected who had come for follow up and are known diabetics and other Patients with diabetes were identified using the question, "Has your doctor ever told you that you have diabetes?" patients who answered positively to the question regarding having diabetes were enrolled. Their relevant data was collected by a detailed interview, clinical examination and lab reports. These findings were noted on a predesigned and pretested proforma. These patients were stratified according to their age, gender, BMI, duration of diabetes and HbA1c levels and each of these variables were compared to hs-CRP levels. The comparison of categorical data was done using Chi-square test, probability value ('p' value) of less than or equal to 0.05 was considered as statistically significant.

Results:

In our study we enrolled 100 cases who were diabetic, we observed majority of cases 41% in the age group of 36-50 years. Our study male population was 72% with a male to female ratio of 2.57:1 (male preponderance). None of our cases had any other co-morbidity except for T2DM, co-morbidity were ruled out by normal ECG, CBC, RFT, LFT and URINE EXAMINATION and even any patients taking medication that could influence the level of hs-CRP. Maximum number of patients had poor glycemic control with 47% of cases had HbA1c levels more than 9.6%. We observed most of our patients had hs-CRP levels ≥ 3.0 (82%) and remaining cases had hs-CRP levels < 3.0 (12%). Most number of our cases had duration of T2DM ≤5 years of duration

58%, followed by 27% in the duration of 6-10 years and 15% who had a duration of ≥ 11 years. We also observed most of our cases had a higher BMI according to Indian standardized BMI ≥ 23kg/m² were 93% and BMI < 23 kg/m² were 7%. We observed that hs-CRP levels were affected by duration of Diabetes, BMI and HbA1c levels. We also observed hs-CRP was not influenced by the age and gender of the patient.

Conclusion:

In our study we could not elicit statistical significance between hs-CRP with AGE of our patients even though patients above 65 years all had hs-CRP levels ≥ 3.0 and gender. But we concluded hs-CRP levels ≥ 3.0 was very significant with BMI ≥ 23.0 kg/m². hs-CRP levels also was affected by duration of diabetes and poor glycemic control (HbA1c).The result we concluded that hs-CRP was affected by longer duration of diabetes, poor glycemic control and high BMI.

Keywords: Type 2 diabetes mellitus, hs-CRP, HbA1c

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INTRODUCTION

Diabetes is a metabolic -disorder with inappropriate hyperglycemia either due to an absolute or relative deficiency of insulin secretion or reduction in the biologic effectiveness of insulin or both. It is also associated with disturbances concerned with protein, carbohydrate and lipid metabolism. The decreased uptake of glucose into muscle and adipose tissue leads to chronic extra cellular hyperglycemia which results in tissue damage and chronic vascular complications in both type I and II Diabetes Mellitus.[1, 2]

Diabetes is pandemic in both developed and developing countries. In 2000, there were an estimated 175 million people with diabetes worldwide and by 2030; the projected estimate of diabetes is 354 million.[3] By the year 2030, over 85 percent of the world's diabetic patients will be in developing countries. In India alone, the prevalence of diabetes is expected to increase from 31.7 million in 2000 to 79.4 million in 2030.[3]

Diabetes mellitus is of three types, Type 1 also called insulin dependent diabetes mellitus [IDDM], type 2 also called non-insulin dependent diabetes mellitus [NIDDM] and type 3 main forms and occurs when pregnant women without a previous history of diabetes develop a high blood sugar level called gestational diabetes.

Type 2 diabetes mellitus is a heterogeneous multifactorial disorder resulting from either insulin resistance or abnormalities of insulin receptor. It usually develops after the age of 40 but can be seen in thirties in obese people[3]. The current WHO diagnostic criteria for diabetes are maintained as fasting plasma glucose ≥ 7.0mmol/l (126mg/dl) of 2–h plasma glucose ≥11.1 mmol / l (200mg/dl)[4]. In 1976 HbA1c was

first time used to assess the level of glucose in diabetic patients[5]. Glycated hemoglobin [HbA1C] is one of the well-established methods to identify the average plasma glucose level over last 120 days or 3 months of time in patient with diabetes [6].

Glycated hemoglobins, including HbA1c and other hemoglobins, constitute the HbA1 fraction of adult hemoglobin (HbA)[7]. HbA1c is the predominant hemoglobin found in HbA1 fractions. Hemoglobin A1c (HbA1c) is a glycated hemoglobin that can be used as an indicator of a patient's glycemic status over the previous 3 months [7]. According to the American Diabetes Association Guidelines published in 2007, HbA1c levels should be maintained below 7% in all diabetic patients in order to prevent the development of microvascular complications[8].

Among several markers of inflammation, hs –CRP is found to be significant in people with diabetes. C-Reactive Protein, a pentameric protein produced by the liver has emerged as the 'golden marker for inflammation'. It is a non-immunoglobin protein having five identical sub units. It is a member of pentraxin family proteins. The C-reactive protein derives from the fact that it reacts with capsule polysaccharide of streptococcus pneumoniae. It is an acute phase response protein markedly increased in both inflammatory and infectious diseases. It plays an important role in innate immunity. It assists in complement binding to foreign and damaged cells and enhances phagocytosis. It was also noticed that the elevated levels of IL18/IL18BP in plasma during active stages of disease suggest a possible role in the pathogenesis and course of idiopathic thrombocytopenia (ITP)[4]. Hyper glycemia is an associated factor to the increase of serum CRP levels, non-controlled type II diabetic subjects[5]. Several studies demonstrate that hs-CRP remained a significant predictor of diabetes risk even after adjusting with body mass index, family history of diabetes mellitus, smoking and

other factors[6]. Previous studies have suggested that serum hs-CRP levels are higher in patients with T2DM with complications than in patients without.[7, 8] A case control study of patients with DM and normal lipid profiles suggested that hs-CRP was an independent predictor of cardiovascular risk in patients with T2DM[8] and closely associated with diabetic complications.

Previous studies have shown that hs-CRP is associated with insulin resistance, type 2 diabetes and higher HbA1c levels. A recently retrospective observed the hs-CRP levels correlated with HbA1c levels. Mean HbA1c levels were significantly higher in patients who had hs-CRP levels of 1 mg/L or more[9]. In year 2015 Chinese study was also revealed through multivariate stepwise regression analysis that indicated that HbA1c correlated with hs-CRP[10]. A Turkish study reported positive correlation between serum hs-CRP and HbA1c, jointly contribute to the cardiovascular risk in T2DM men[11].

Need for the study

Chronic inflammation plays an important role in the development and progression of late complications of diabetes. C-reactive protein (CRP), an acute phase reactant, is a highly sensitive marker of inflammation. Its level rises dramatically during an inflammatory process[12]. CRP has a long half-life, affordability of estimation, and stability of its levels with no circadian variation, and therefore is one of the best markers of vascular inflammation[13]. CRP has been found to be associated with disorders like DM, cardiovascular disorders, metabolic syndrome, Rheumatoid Arthritis, renal failure, etc[14,15,16]. Serum high sensitivity CRP (hsCRP) level is higher in patients with Type 2 diabetes than in normal subjects and plays an important role in the development and progression of Type 2 DM[17].

India has the distinction of having the highest number of T2D individuals worldwide, with a prevalence of 11.6% in urban populations[18,19]. Furthermore, Asian Indians are known to be at a high risk for T2D, CVD, and metabolic syndrome[20,21]. Although elevated levels of hs-CRP have been observed in expatriate adult Indians[22]and adolescents residing in India[23], data on adult individuals residing in India are scanty. Therefore, the present study was designed to study the correlation of hs-CRP levels with HbA1c in type II subjects in Kle Dr Prabhakar Kore Hospital And Medical Research Center, Belagavi

OBJECTIVE

The purpose of the study is to investigate the correlation between hs-CRP and HbA1C in adults with type 2 diabetes mellitus in KLES Dr.Prabhakar Kore Hospital and Medical Research Centre, Belagavi.

REVIEW OF LITERATURE

Types of Diabetes and their Classification

Definition of Diabetes Mellitus:

Diabetes mellitus (DM) is characterized by a state of chronic hyperglycemia, resulting from multiple etiologies, environmental and genetic. The underlying cause of diabetes is the ineffective production or action of insulin, a hormone that controls glucose, fat, and amino acid metabolism.[24]

Incidence and prevalence of DM has significantly increased in recent decades, mainly because of an increase in type 2 diabetes, which represents almost 90% of all cases of diabetes. The WHO estimated that, by 2025, there will be 300 million diabetic patients. Older patients are most affected by diabetes, as the disease prevalence increases with age.[25] Macrovascular disease (coronary artery disease, stroke, and peripheral vascular disease) is a factor for the majority of morbidity and mortality associated with type 2 diabetes mellitus. In the UK prospective diabetes study (UKPDS),[26] the 10 year risk of all macrovascular complications was four times that of microvascular complications. Coronary artery disease is the most common cause of death among diabetic patients, and women have a higher cardiovascular risk. Diabetics have a worse prognosis after an acute coronary syndrome than non-diabetic patients. This was documented both for ST elevation and non-ST elevation acute myocardial infarction (AMI). The Framingham heart study has also shown a higher mortality rate, as well as re-infarction and heart failure rates, in diabetic patients, both during the acute phase and in the post-infarction period, even after data adjustment for other risk factors.[25]

Classificationof Diabetes Mellitus:[25]

Type 1 Diabetes:

▸ β-cell destruction which leads to absolute insulin deficiency

▸Usually mediated by immune mechanisms

▸ LADA (latent autoimmune diabetes in adults) is classified as type 1 diabetes.

Type 2 Diabetes:

▸Can range from predominant insulin resistance with relative insulin deficiency to prevailing defective secretion with insulin resistance.

▸Is frequently associated with other problems of the so-called metabolic syndrome

Other Specific Diabetes Types:

▸ Diseases of the exocrine pancreas (e. g. pancreatitis, cystic fibrosis, hemochromatosis)

▸Endocrinopathies (e. g. Cushing syndrome, acromegaly, pheochromocytoma)

▸ Drug induced (e. g. glucocorticoids, neuroleptics, alpha-interferons, pentamidine)

▸ Genetic defects of the β-cell function (e. g. MODY forms)

▸ Genetic defects of insulin action

▸Other genetic syndromes which can be associated with diabetes

▸ Infections

▸ Rare forms of auto-immune mediated diabetes

Gestational Diabetes: Glucose tolerance impairments that first appear or are first diagnosed during pregnancy.

Epidemiology of Diabetes mellitus

Diabetes is pandemic in both developed and developing countries. In the year 2000, there were an estimated 175 million people with diabetes worldwide and by the year 2030; the projected estimate of diabetes is 354 million.[27]Byyear 2030, over 85 percent of the world's diabetic patients will be in developing countries. In India alone, the prevalence of diabetes is expected to increase from 31.7 million in 2000 to 79.4 million in 2030.[27]

Worldwide Epidemiology of Diabetes Mellitus:

The WHO's definition of diabetes states that it occurs from deficiency in the body's use of insulin due to an ineffective pancreas or an ineffective body for using insulin. There are two main type of diabetes; "type 1 called insulin-dependent or juvenile-onset diabetes", which is found only 5–10% of patients with diabetes and "type 2 is known as non-insulin dependent or insulin resistance", which is found 90–95% of patients with diabetes.[28]American Diabetes Association (ADA) and the WHO recommend diagnosis in term of fasting plasma glucose (FPG), diabetes symptoms with plasma glucose concentration and oral glucose tolerance test (OGTT).[28,29]Diabetes causes serious damage to many of the body's systems especially the nerves and the blood vessels, which increases the risk of heart disease and stroke. In 2004, the WHO reported that worldwide 346 million people suffered from diabetes and 3.4 million people died from the consequences of high blood sugar. Furthermore, it is predicted by the WHO projections that deaths due to diabetes will double between 2005 and 2030. In addition, the WHO mentioned that half the people with diabetes died due to cardiovascular disease (primarily heart disease and stroke).[30] Thus, diabetes is a large and growing global health problem including an important

determinant of vascular disease.[31] Surprisingly, more than 80% of the burden of death from diabetes occurs in low- and middle- income countries such as Thailand.[31] where coronary heart disease (CHD) is also one of the first three causes of death among the Thai population.[32]

It is likely that the incidence of type 2 diabetes will rise as a consequence of lifestyle patterns contributing to obesity.[33]Cardiovascular physicians are encountering many of these patients because vascular diseases are the principal causes of death and disability in people with diabetes. The macrovascular manifestations include atherosclerosis and medial calcification. The microvascular consequences, retinopathy and nephropathy, are major causes of blindness and end-stage renal failure. Physicians must be cognizant of the salient features of diabetic vascular disease in order to treat these patients most effectively.

Worldwide Studies Related to Epidemiology of Diabetes Mellitus:

García-García E et al[34](2002) summarized that clinical, metabolic and genetic characteristics of early-onset type 2 diabetes in Mexico. Early-onset type 2 diabetes is both a clinical challenge and a public health problem. It was calculated that almost 300,000 Mexican diabetics are diagnosed between the ages of 20 and 40. The large Mexican family structure and the high prevalence of the disease provide a unique opportunity to identify the genes and the metabolic abnormalities involved in this form of the disease. The reported that mutations in the NHF-1 alpha or HNF-4 alpha genes or autoimmunity to the beta cell were found in a small proportion of cases, leaving unexplained the majority of cases. Authors also discussed that the epidemiologic and therapeutic implications of early-onset type 2 diabetes, and the possible role of genetic testing for prevention.

Alberto Goday[35](2002) studied the epidemiology of diabetes and its non-coronary complications and they reported that in Spain, the prevalence of diabetes in the 30-65 year-old population is estimated to be 6.5% and 10.3% among the 30-to-89 year-old population. The ratio of known to unknown diabetes ranges from 1:3 to 2:3. The incidence of T2DM in Spain is 8/1000 persons per year, and the incidence of type 1 is 11 to 12 cases per 100,000 persons per year. The prevalence of chronic complications varies according to type of diabetes, time since onset and degree of metabolic control: neuropathy 25%, retinopathy 32% and nephropathy 23%. Diabetes is one of the highest causes of death in Spain, occupying 3rd place for women and 7thfor men.

GoodarzDanaei et al[36] (2011) systematic analysis of health examination surveys and epidemiological studies the National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980 and observed that in 2008, global age-standardised mean FPG were 5.50 mmol/L for men and 5.42 mmol/L for women, having risen by 0.07 mmol/L and 0•09 mmol/L per decade, respectively. Age-standardised adult diabetes prevalence was 9•8% (8•6–11•2) in men and 9•2% (8•0–10•5) in women in 2008, up from 8•3% (6•5–10•4) and 7•5% (5•8–9•6) in 1980. The amount of people with diabetes increased from 153 (127–182) million in 1980, to 347 (314–382) million in 2008. They recorded almost no change in mean FPG in east and Southeast Asia and central and Eastern Europe. Oceania had the largest increase, and the highest mean FPG (6•09 mmol/L, 5•73–6•49 for men; 6•08 mmol/L, 5•72–6•46 for women) and prevalence (15•5%, 11•6–20•1 for men; and 15•9%, 12•1–20•5 for women) in 2008. Mean Fasting plasma glucose and diabetes prevalence in 2008 were high in south Asia, Latin America and the Caribbean, and central Asia, North Africa, and the Middle East. Mean FPG in 2008 was lowest in sub-Saharan Africa, east and Southeast Asia, and high-income Asia-Pacific. In high-income subregions, Western

Europe had the smallest rise, 0•07 mmol/L per decade for men and 0•03 mmol/L per decade for women; North America had the largest rise, 0•18 mmol/L per decade for men and 0•14 mmol/L per decade for women. Authors concluded that the glycaemia and diabetes are rising globally, driven both by population growth and ageing and by increasing age-specific prevalences. Effective interventions are needed, and health systems should prepare to detect and manage diabetes and its sequelae.

Andréa D Bertoldi et al[37] (2013) studied the epidemiology, management, complications and costs associated with type 2 diabetes in Brazil and observed that an approximate 20% increase in the prevalence of self-reported diabetes was observed. In 2010, it's estimated that 6.3% of Brazilians aged 18 years or over had diabetes. Diabetes was estimated to be responsible for 278,778 years of potential life lost for every 100,000 people. In 2013, it is estimated that about 7% of patients with diabetes has had one or more of the following complications: diabetic foot ulcers, amputation, kidney disease, and fundus changes. They concluded that Brazil has the capacity to address and respond to non-communicable diseases (NCDs) due to the leadership of the Ministry of Health in NCD prevention activities, including an integrated programme currently in place for diabetes. Strengthening the surveillance of NCDs is a national priority along with recognising the urgent need to invest in improving the coverage and quality of mortality data. It is also essential to conduct regular surveys of risk factors on a national scale in order to design effective preventive strategies.

Nita Gandhi Forouhi and Nicholas J. Wareham[38] (2014) studied the epidemiology of diabetes and their estimates show a global prevalence of 382 million people with diabetes in 2013, expected to rise to 592 million by 2035. The etiological classification of diabetes has now been widely accepted. Type 1 and type 2 diabetes

are the two main types, with type 2 diabetes accounting for the majority (>85%) of total diabetes prevalence. Both types of diabetes can lead to multisystem complications of microvascular endpoints, including retinopathy, nephropathy and neuropathy, and macrovascular endpoints including ischaemic heart disease, stroke and peripheral vascular disease. The premature morbidity, mortality, reduced life expectancy and financial and other costs of diabetes make it an important public health condition.

Lui PP[39](2017)studied tendinopathy in diabetes mellitus patients. His review aimed to appraise the current literature on the epidemiology and pathology of tendinopathy in diabetic patients. Systematic reviews were done to summarize the literature on (a) the association between diabetes mellitus and tendinopathy/tendon tears, (b) the pathological changes in tendon under diabetic or hyperglycemic conditions, and (c) the effects of diabetes mellitus or hyperglycemia on the outcomes of tendon healing. They reported in his review that the potential mechanisms of diabetes mellitus in causing and exacerbating tendinopathy with reference to the major non-mutually exclusive hypotheses of the pathogenesis of chronic tendinopathy as reported in the literature were also discussed. Potential strategies for the management of tendinopathy in diabetic patients were presented.

Bello-ChavollaOYet al[40](2017) reviewed epidemiology of diabetes mellitus in Mexico. The large and growing number of cases and the remarkable economic impact of the disease support this statement. The condition was expressed at an earlier age and at a lower body mass index in Mexican mestizos compared with the age and body mass index reported in Caucasians. They suggested that the Mexican health system needs major adjustments in order to prevent and treat type 2 diabetes, treatment is not

currently based on the needs and expectations of the patient. They found that close to 20% of the preventable deaths in Mexico were caused by diabetes and related metabolic diseases. Even a small decrease in this rate could result in substantial savings for the Mexican healthcare system.

Indian Epidemiology of Diabetes Mellitus:

Diabetes is fast gaining the status of a potential epidemic in India with more than 62 million diabetic individuals currently diagnosed with the disease.[41,42]In 2000, India (31.7 million) the highest number of people with diabetes mellitus in the world followed by China (20.8 million) than the United States (17.7 million) in second and third place respectively. According to Wild et al.[43] the prevalence of diabetes is predicted to double globally from 171 million in 2000 to 366 million in 2030 with a maximum increase in India. It is predicted by 2030 diabetes mellitus may afflict up to 79.4 million individuals in India, while China (42.3 million) and the United States (30.3 million) will also see significant increases in those affected by the disease.[43,44]India currently faces an uncertain future in relation to the potential burden that diabetes may impose upon the country. Many factors affect the prevalence of disease throughout a country, and identification of those factors is necessary to facilitate change when facing health challenges.

The etiology of diabetes mellitus in India is multifactorial and includes genetic factors coupled with environmental influences such as obesity associated with rising living standards, steady urban migration, and lifestyle changes. Yet despite the incidence of diabetes within India, there are no nationwide and few multi-centric studies conducted on the prevalence of diabetes and its complications. The studies have been undertaken are also prone to potential error as the heterogeneity of the Indian population with

respect to culture, ethnicity, and socio-economic conditions, mean that the extrapolation of regional results may give inaccurate estimates for the whole country.

There are, however, patterns of diabetes incidence that are related to the geographical distribution of diabetes in India. Rough figures show that the prevalence of diabetes in rural populations is one-quarter that of urban population for India and other Indian sub-continent countries such as Bangladesh, Nepal, Bhutan, and Sri Lanka.[43,45] Preliminary results from a large community study conducted by the Indian Council of Medical research (ICMR) revealed that a lower proportion of the population is affected in states of Northern India (Chandigarh 0.12 million, Jharkhand 0.96 million) as compared to Maharashtra (9.2 million) and Tamil Nadu (4.8 million).[45] The National Urban Survey conducted across the metropolitan cities of India reported similar trend: 11.7 per cent in Kolkata (Eastern India), 6.1 per cent in Kashmir Valley (Northern India),[46] 11.6 per cent in New Delhi (Northern India), and 9.3 per cent in West India (Mumbai) compared with (13.5 per cent in Chennai (South India), 16.6 per cent in Hyderabad (south India), and 12.4 per cent Bangalore (South India).[47] A suggested explanation for this difference is that the north Indians are migrant Asian populations and south Indians are the host populations,[48]however this possible cause-and-effect has not been corroborated through further research. Similar ethnographic disparities are observed in indigenous and non-indigenous populations in countries colonized by the Great Britain: indigenous people from New Zealand and Australia have been shown to suffer from diabetes and cardio-metabolic disorders more than the non-indigenous people.[49,50]

Indian Clinical Studies on Epidemiology of Diabetes Mellitus:

Ramachandran A[51] (2005) studied theepidemiology of diabetes in India--three decades of research and they reported that India has nearly 33 million diabetic subjects today, which is briefly contributed by the urban population. The scenario is changing rapidly due to socio-economic transition occurring in the rural areas also. Availability of improved modes of transport, and less strenuously as in the vicinity have resulted in decreased physical activities. Better economic conditions have produced changes in diet habits. The conditions are more favorable for expression of diabetes in the population, which already has a racial and genetic susceptibility of the disease. Prediabetic conditions like impaired glucose tolerance and impaired fasting glucose are also on the rise, indicating the possibility of further rise in the prevalence of diabetes. Metabolic syndrome, which is a constellation of cardiovascular riskfactors, of which hyperglycaemia and insulin resistance are components, is also widely prevalent. The conversion to diabetes is enhanced by the low thresholds for the risk factors, such as age, body mass index and upper body adiposity. Indians have shown a genetic phenotype characterized by low body mass index, but with high upper body adiposity, high body fat percentage and high level of insulin resistance. With a high genetic predisposition and the high susceptibility to the environmental insults, the Indian population faces a high risk for diabetes and its associated complications. Early diagnosis of high risk groups and appropriate intervention by lifestyle modification may be the solution for the disease burden.

Swapan Kumar Das[52] (2006) studied the epidemiology of adult onset type 2 diabetes in Asian Indian population and they reported that the prevalence of Type 2 Diabetes mellitus (T2DM) continue to rise in Indian populations. Despite known roles for

obesity, sedentary lifestyles and diet, genetic predisposition accounts for significant risk. The identification of the susceptibility loci for both monogenic and typical (oligogenic) diabetes have introduced novel genes, pathways and mechanisms of diabetes pathogenesis. Very little data is available on T2DM susceptibility loci in Asian Indian population. An extensive association based approach is required to identify the susceptibility locus and genes responsible for common form of familial diabetes in India. By defining the genetic susceptibility loci, such studies will eventually facilitate a direct, systematic exploration of the interactions of environmental factors, obesity, insulin resistance, and genetic predisposition in the pathogenesis of T2DM and prediabetic traits and also will open new pathways of exploration and therapy.

V. Mohan et al[53] (2007) studied the epidemiology of type 2 diabetes and reported that to certain unique clinical and biochemical abnormalities in Indians which include increased insulin resistance, greater abdominal adiposity i.e., higher waist circumference despite lower body mass index, lower adiponectin and higher high sensitive C-reactive protein levels. This phenotype makes Asian Indians more prone to diabetes and premature coronary artery disease. At least a part of this is due to genetic factors. However, the primary driver of the epidemic of diabetes is rapid epidemiological transition associated with changes in dietary patterns and decreased physical activity as evident from the higher prevalence of diabetes in the urban population. The most disturbing trend is the shift in age of onset of diabetes to a younger age in the recent years. This could have long lasting adverse effects on nation's health and economy. Early identification of at-risk individuals using simple screening tools like the Indian Diabetes Risk Score (IDRS) and appropriate lifestyle

changes would greatly help in preventing or postponing the onset of diabetes and thus reducing the burden on the community and the nation as a whole.

Rajeev Gupta and AnoopMisra[54](2007) studied the type 2 diabetes in India and they reported that the epidemiological studies in the 1960's and 1970's using random and post-load blood glucose estimations reported diabetes prevalence varying from 1–4% in urban populations and 1–2% in rural populations. More standardized epidemiological studies since the 1990's reported prevalence rates that vary from 5–15% among urban populations, 4–6% in semi-urban populations and 2–5% in rural populations with large location-based disparities within urban and rural populations. There is a significantly increasing trend in urban populations while among rural populations the prevalence is increasing at a slower rate. At the turn of this century diabetes in adult urban Indian populations varies from a low of 5.4% in a northern state to a high of 12.3–15.5% in Chennai, South India, and 12.3–16.8% in Jaipur, Central India. This scenario is similar to other South Asian countries and evolving populations in East Asia, Middle-East, Americas, Australasia and Pacific Islands. Gene-environment interactions appear to be responsible for this rapid increase. The insulin-resistant state that was meant to be protective mechanism for regulation of calorie and fat metabolism at times of famine has turned deleterious as affluence has increased among these populations leading to diabetes epidemic. Population based measures to prevent the control of a diabetes epidemic include avoidance of adiposity by enhanced physical activity and regulated calorie intake.

V. Mohan and Pradeep R[55](2009) studied the epidemiology of diabetes in different regions of India and they reported that the prevalence of diabetes in the urban metros of India is approaching the figures reported in the affluent migrant Indians. Although

in rural India the prevalence of diabetes is much lower than in the urban population, even here the prevalence of diabetes is rapidly rising, though clearly more studies are needed. Nevertheless, there is enough information to derive significant conclusions and projections that will not only help define the burden of diabetes in India but also throw some light on the causes of the diabetes epidemic. Environmental and lifestyle changes resulting from industrialization and migration to urban environment from rural settings may be responsible to a large extent, for this epidemic of Type 2 diabetes in Indians. In addition, given the large number of people with Type 2 diabetes in our country, the morbidity due complications associated with it would still be very high. Thus, effective preventive programs need to be urgently implemented to stem the tide.

Kapoor D et al[56] (2014) studied the prevalence of diabetes mellitus and its risk factors among permanently settled tribal individuals in tribal and urban areas in northern state of sub-Himalayan region of India and observed that among urban tribes the prevalence of central obesity (59.0%), overweight (29.3%), stage 1 (22.8%) and stage 2 (5.3%) hypertension, and DM (fasting: 7.8%; OGTT: 8.5%) was significantly higher than the tribes of tribal area. Based on OGTT, the prevalence of DM was found to be 9.2% among central obese tribes of urban area and 6.7% of tribal area. DM showed a significant high prevalence among urban tribes with prehypertension (urban: 8.3%; tribal: 2.9 %;), and stage 1 (urban: 14.1%; tribal: 8.7%;) and stage 2 (urban: 17.5%; tribal: 13.9%;) hypertension. They concluded that the urban environment showed a changing lifestyle and high prevalence of DM among tribal migrating urban tribes as compared to traditional tribes.

Madaan H et al[57] (2014) studied the prevalence of diabetes mellitus in rural population of district Sonepat, India and observed that gender specific prevalence for diabetes was 19.36% and 16.98% for male and female respectively. Maximum prevalence of diabetes 41.96% was found in the age group of 46-60 yrs. In this age group Mean fasting plasma glucose among males was 149.36 ± 19.51 and among female it was 147.43 ± 18.19. Mean 2 hour postprandial plasma glucose was 259.94 ± 51.36 & 259.65 ± 51.39 in male and female respectively. They concluded that the rural population remains exposed to high level of blood sugar for long time due to lack of screening facility of diabetes at PHC level, and this increases the chance of developing various complication of diabetes mellitus.

Risk Factors of Type II Diabetes Mellitus

Heritable genetic correlation.

Genetic component:

Although we have not completely elucidated thepathophysiology of T2DM so far, it is the case that thedisease has a major genetic component. Higher concordancerates are found among monozygotic (96%)than dizygotic (DZ) twins in some[58] but not all[59]twin studies, which has been a compelling evidenceof a significant genetic component in T2DM.Moreover, 40% of first-degree relatives of T2DM patientsmay develop diabetes, whereas the incident rateis only 6% in the general population.[60]

Susceptibility loci:

In addition to the number of genetic components associated withT2DM, segregation analysis also suggests the polygenicnature of T2DM. The susceptibility loci of T2DMhave been discovered by genome-wide associationstudies (GWAS) since early

2007.[61,62]Then, numerousGWAS conducted in different countries andethnic groups have reported linkage signals at thesame or different chromosomes with T2DM, and have successfully identified approximately 75 susceptibility loci related to T2DM. Examples of candidate genes are KCNJ11 (potassium inwardly rectifying channel, subfamily J, member 11), TCF7L2 (transcription factor 7–like 2, the strongest T2D locus identified to date), IRS1 (insulin receptor substrate 1), MTNR1B (melatonin-receptor gene), PPARG2 (peroxisome proliferator-activated receptor gamma 2), IGF2BP2 (insulin-like growth factor two binding protein 2), CDKN2A (cyclin-dependent kinase inhibitor 2A), HHEX (hematopoietically expressed homeobox) and FTO (fat mass and obesity associated) gene. VanExel and his group found that low IL-10 production capacity is also associated with T2DM.[63]It is worth highlighting that IL-10-1082A/G polymorphism is associated with T2DM susceptibility in Asians, but not in Europeans and Africans, which may be ascribable to various genetic background and environmental exposures.[64]

Lifestyle factor correlation.

A large number of lifestyle factors are also of great importance to the development of T2DM, such as sedentary lifestyle,[65] physical inactivity,[66] smoking[67] and alcohol consumption.[68]

Obesity:

Substantial epidemiological studies have shown that obesity is the most important risk factor for T2DM, which may influence the development of insulin resistance and disease progression.[69]Nearly 90% diabetic patients develop T2DM mostly relating to excess body weight according to the World Health Organization (WHO, 2011). Furthermore, obesity is strongly inherited.[70]Pamidi et al. demonstrated that

obstructive sleep apnea (OSA), a treatable sleep disorder that is pervasive among overweight and obese adults, has become a novel, modifiable risk factor relevant to insulin resistance and glucose intolerance, and may influence on the development of prediabetes (20%-67%) and T2DM (15%-30%), independent of shared risk factors.[71] Several studies have indicated that Obstructive sleep apnea in T2DM patients is much more prevalent (36%–60%) than in the general population.[72]

Diet:

Diet is considered as a modifiable risk factor for T2DM. Studies have shown that a low-fiber diet with a high glycemic index is positively associated with a higher risk of T2DM,[73] and specific dietary fatty acids may affect insulin resistance and the risk of diabetes in varying degrees.[74] Total and saturated fat intake is associated with an increased risk of T2DM independently of BMI, but higher intake of linoleic acid has the opposite effect, especially among leaner and younger men].[75]Frequent consumption of processed meat, but not other meats, may increase the risk of T2DM after adjustment for BMI, prior weight change, and alcohol and energy intake.[75] Soft drinks have also been bounded up with increased risk of T2DM76 and metabolic syndrome,[77]because they are directly associated with BMI.78

Gut metagenome correlation:

In some recent studies, gut metagenome was shown to be a factor for the development of T2DM.[79]Different kinds of gut bacteria may play different roles in maintaining or interacting with their environment. Two-stage metagenome-wide association study (MGWAS) suggested that Type 2 diabetes mellitus patients show a moderate degree of gut microbial dysbiosis, with various butyrate-producing bacteria being decreased (Clostridiales sp. SS3/4, Roseburia intestinalis,

Roseburiainulinivorans, Eubacteriumrectale and Faecalibacteriumprausnitzii) and some opportunistic pathogens being increased (Bacteroidescaccae, Clostridium hathewayi, Clostridium ramosum, Clostridium symbiosum, Eggerthellalenta and Escherichia coli).[80]

Vitamins and type 2 Diabetes.

Vitamin D:

Accumulating evidence supports that vitamin D may have a potential role in the control of T2DM,[81] as seasonal variation is found in glycemic status of T2DM patients, in which hypovitaminosis D frequently occurred in the winter is likely to be associated with the aggravation of T2DM. A recent research shows that vitamin D deficiency may have negative effects on glucose intolerance, insulin secretion and T2DM,[82]either directly via vitamin D receptor (VDR) activation or indirectly via calcemic hormones and also via inflammation.[83] As both 1-α-hydroxylase and VDR are present in pancreatic β cells, vitamin D has significant roles in the synthesis and release of insulin.[84] Furthermore, vitamin D has affect on the insulin sensitivity by controlling calcium flux through the membrane in both β cells and peripheral insulin-target tissues.[85] In addition, vitamin D supplementation is recognized as a promising and inexpensive therapy, which may decrease the risk of T2DM and improve glycemic parameters in T2DM patients.[86] Therefore, it is seemingly that the positive effects of vitamin D are correlated with its action on insulin secretion and sensitivity as well as on inflammation.

Vitamin K:

Vitamin K has two naturally occurring forms, including phylloquinone (vitamin K1) and menaquinones. Menaquinone-4 (vitamin K2) is considered as the active form of vitamin K in the bone tissue and functions in maintaining bone quality[87] and also as a transcriptional regulator of bone-specific genes that acts through steroid and xenobiotic receptors (SXRs) to promote expression of osteoblastic markers.[88] It plays a protective role in bone fractures, in which the substance can promote γ-carboxylation of osteocalcin and induce production and secretion of osteocalcin by osteoblasts or may stimulate bone formation through SXRs.

Besides, a recent survey indicates that vitamin K1 provides benefits in glucose homeostasis, as higher intake of vitamin K1 is correlated with greater insulin sensitivity and glycemic status.[89]Because poor glycemic control and bone quality may occur when vitamin K is deficient, it is cardinal to exclude vitamin K deficiency in T2DM patients. Several preclinical and clinical observations show that vitamin K2 has effects on bone quality and subsequent bone mechanical strength in T2DM patients independently of increasing BMD (bone mineral density).[90]

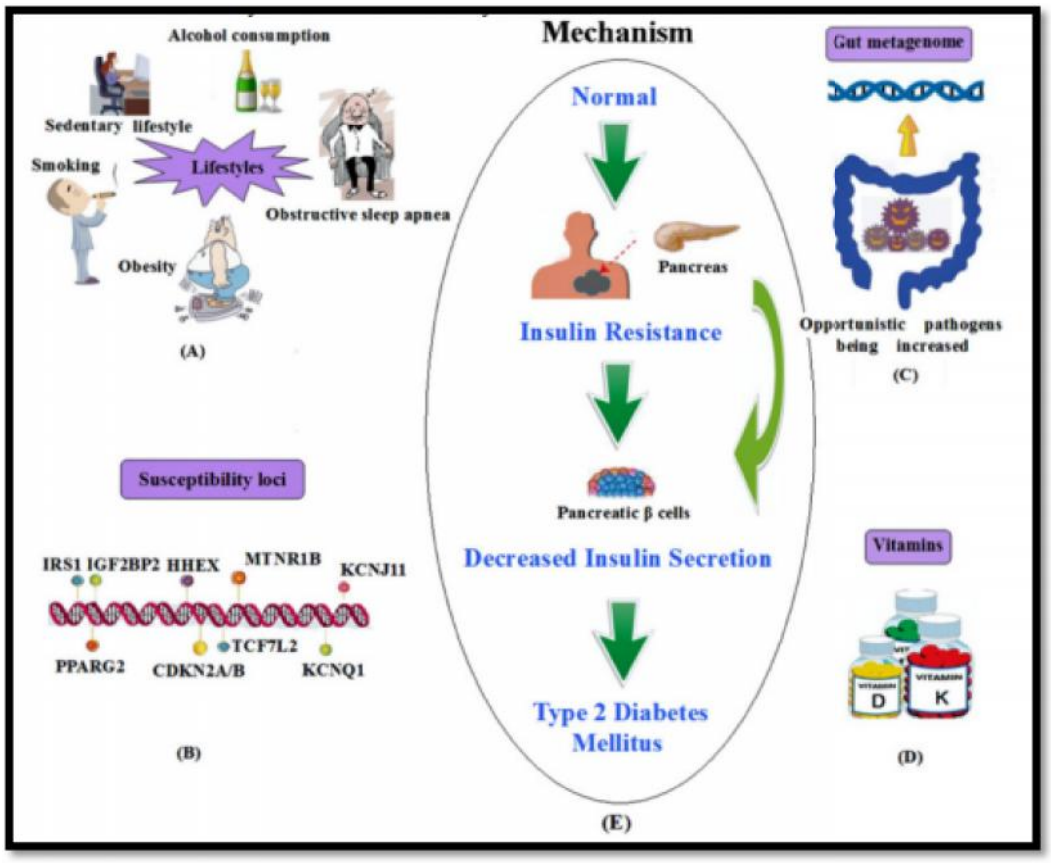


Figure 1: A summary of the influencing factors and mechanism of T2DM. (A) Lifestyles; (B) Susceptibility loci; (C) Gut metagenome association; (D) Vitamins. (E) The mechanism of T2DM.

Role of Glycosylated hemoglobin in diabetes mellitus Patients

Garlick RL et al[91]did a study on characterization of glycosylated hemoglobins. Relevance to monitoring of diabetic control and analysis of otherproteins. Authors reported that the Boronate affinity chromatography and ion exchange chromatography were used to measure the levels of glycosylated hemoglobin in normal and diabetic hemolysates, as well as the distribution of glucose adducts on alpha-NH2-valine and epsilon-NH2-lysine residues. When analyzed by ion exchange chromatography on BioRex 70 resin, the HbAlc peak comprised 4.4 +/- 0.6% of 15 normal hemolysates and 9.1 +/- 2.1% of 15 diabetic hemolysates. The "HbAlc" was rechromatographed on

GlycoGel B boronate affinity resin that binds vicinal hydroxyl groups of covalently linked sugars. Only 70 +/- 5% of the hemoglobin adhered to the resin. Analysis by the thiobarbituric acid colorimetric test confirmed that the affinity resin effectively separated glycosylated from nonglycosylated hemoglobin. When corrected for non-glycosylated contaminants, the mean level of HbAlc in normal hemolysates was 2.9 +/- 0.4%, a value considerably lower than those previously reported. In addition to HbAlc, 5.2 +/- 0.5% of the remaining hemoglobin (HbAo) were glycosylated. In diabetics, glycosylated Ao was increased in parallel with HbAlc. After reduction with [3H]borohydride and acid hydrolysis, glycosylated amino acids were first purified on Affi-Gel boronate affinity resin and then analyzed by ion exchange chromatography. The glucose adducts on HbAo were distributed as follows: alpha-chain N-terminal valine, 14%; alpha-chain lysines, 40%; beta-chain lysines, 46%. Their study has revealed several pitfalls in the analysis of nonenzymatically glycosylated proteins. Peaks isolated by ion exchange chromatography or electrophoresis are likely to be contaminated by nonglycosylated proteins. Furthermore, both the thiobarbituric acid test and [3H]borohydride reduction show variable reactivity depending upon the site of the ketoamine-linked glucose.

McFarland KF et al[92] did a study of clinical value of glycosylated serum protein and glycosylated hemoglobin levels in the diagnosis of gestational diabetes mellitus. Glycosylated serum protein and glycosylated hemoglobin levels were compared to the oral glucose tolerance test to determine their relative sensitivity in identifying women with gestational diabetes mellitus. The mean glycosylated serum protein level (0.49 +/- SD 0.07 nmol hydroxymethylfurfural per milligram protein) of 17 pregnant women with normal glucose tolerance and the mean value (0.54 +/- SD 0.06 nmol hydroxymethylfurfural per milligram protein) of eight pregnant women with

gestational diabetes mellitus were statistically different (P less than .05). However, there was such an overlap between these groups that individuals could not be categorized as normal or as having gestational diabetes mellitus on the basis of the glycosylated serum protein level. There was no difference in glycosylated hemoglobin levels between 41 women with normal glucose tolerance and 12 women with gestational diabetes mellitus. This study concluded that glycosylated serum protein and glycosylated hemoglobin determinations are not as sensitive as the glucose tolerance test in detecting gestational diabetes mellitus as it is now defined.

Li PL et al[93]did a study to find clinical significance of glycosylated serum protein in patients with diabetic nephropathy and they observed that theGSP levels were significantly higher in patients with diabetic nephropathy than in the non-diabetic patients (P<0.01). In patients with diabetic nephropathy, GSP levels were found to positively correlate to FBG (r=0.606) and HbA1c (r=0.733).Authors concluded that the patients with diabetic nephropathy show strong correlations between FBG, HbA1c and GSP. GSP detection is convenient, stable, and practical in evaluating the average FBG over a short term, which reduces the interference by FBG fluctuations in conventional blood glucose monitoring.

Goswami R K et al[94] did a study for evaluation of Serum Zinc Status and Glycated Hemoglobin of Type 2 Diabetes Mellitus Patients in a Tertiary Care Hospital of Assam. They reported that the concentrations of fasting and postprandial blood glucose were significantly higher in the diabetic group than controls (P < 0.001) and the mean HbA1c% was also higher in cases (8.32% ±1.58%). The mean serum zinc concentration in cases was found to be significantly lower than controls (79.85 ± 13.4 vs. 109.74 ± 9.72 µg/dL) and P < 0.001 with correlation coefficient r = –0.804. Their

study revealed an inverse relationship between HbA1C% and serum zinc concentration in patients with type 2 DM, substantiated by regression analysis.

Factors affecting Glycosylated hemoglobinin diabetes mellitus Patients

Factors that Interfere with HbA1c Test Results

Factors that Interfere with HbA1c Measurement: Genetic variants (e.g. HbS trait, HbC trait), elevated fetal hemoglobin (HbF) and chemically modified derivatives of hemoglobin (e.g. carbamylatedHb in patients with renal failure) can affect the relative accuracy of HbA1c measurements. The effects vary depending on the specific hemoglobin variant or derivative and the specific HbA1c method. Table 1 contains information for most of the commonly used current HbA1c methods for the four most common hemoglobin variants, elevated HbF and carbamylated Hemoglobin. Interferences from less common hemoglobin variants and derivatives are discussed in Bry, et al.[95] All entries in Tables are based on published information. In addition, if a product insert indicates clearly that there is inference from a particular factor, then the interference is entered as "yes" and the product insert is cited. When selecting an assay method, laboratories should take into consideration characteristics of the patient population served, (e.g. high prevalence of hemoglobinopathies or renal failure).

Factors that affect interpretation of HbA1c Results: Any condition that shortens erythrocyte survival or decreases mean erythrocyte age (e.g., recovery from acute blood loss, hemolytic anemia) will falsely lower HbA1c test results regardless of the assay method used.[96] HbA1c results from patients with HbSS, HbCC, and HbSC must be interpreted with caution given the pathological processes, including anemia, increased red cell turnover, and transfusion requirements, that adversely impact

HbA1c as a marker of long-term glycemic control. Alternative forms of testing such as glycated serum protein or glycated albumin should be considered for these patients.

Iron deficiency anemia, is associated with higher HbA1c and higher fructosamine.[97] Consistent with these observations, iron replacement therapy lowers both HbA1c and fructosamine concentrations in diabetic and non-diabetic individuals.[97] HbA1c , but not glycated albumin, is increased in late pregnancy in nondiabetic individuals owing to iron deficiency.[98] Insight into the mechanism was recently obtained by the observation that malondialdehyde, which is increased in patients with iron deficiency anemia,[97] enhances the glycation of hemoglobin.[99] Alternative measures of glycemic assessment (e.g., glucose monitoring) must be used in the presence of significant iron deficiency anemia, at least until the iron deficiency has been successfully treated.

Chronic renal failure develops in many diabetic patients. The role of glycemic control and the value of HbA1c in diabetic subjects with renal disease are controversial. While interference from carbamylatedHb can be evaluated, the role of renal anemia, erythropoietin intake, and other factors in chronic renal failure is more difficult to evaluate. Recent reports suggest HbA1c underestimates glycemic control in diabetic patients on dialysis and that glycated albumin is a more robust indicator of glycemic control.[100]Further studies are needed to clarify the role of HbA1c in diabetic patients with chronic renal failure.

Table: Effects of frequently encountered Hb variants and derivatives on HbA1c measurement

Some interferences for some methods are highlighted in gray indicating that they have been tested using a new stricter criterion of >7% difference at 6 and 9% HbA1c to

define clinical significance.[101]The other methods were tested using either criteria of >10% at 6 and 9% HbA1c or some other criteria.

Method (listed in alphabetical order by manufacturer)	Interference (Yes/No)					
	Hb C trait	Hb S trait	Hb E trait	Hb D trait	Elevated HbF	Carb Hb
Abbott Architect (Seradyn Reagents)	Yes 12	Yes 12	@	@	$	-
Arkray ADAMS A1c HA-8180 (Menarini)	No 13,46	No 13,46	HbA1c not quantified 13, 46	HbA1c not quantified 46/ Yes 13	No 46	-
Axis-Shield Nycocard	No 14	No 14	@	@	$	-
Axis-Shield Afinion	No 15	No 15	No 16	No 16	$	-
Bayer A1cNow	Yes 17	Yes 17	No 16	No 16	$	-
Beckman AU System	Yes 12,18, 15	Yes 12,18, 15	No 16	No 16	Yes >10% 18	-
Beckman Synchron	No 14	No 14	No 16	No 16	$	-
Bio-Rad D-10 (short Program)	Yes 17 /No 15	No 15,17	No 16	No 16	Yes >10% 20	No 47
Bio-Rad D-10 (extended program)	No 15	No 15	No 16	No 16	-	No 47
Bio-Rad in2it	Yes 13,21	No 13,21	Yes 13,21	No 13,21	$	-
Bio-Rad Variant II A1c (NU)	-	-	No 16	No 16	Yes >10% 20	No 47
Bio-Rad Variant II Turbo (270-2415/2417)	No 15	No 15	Yes 16	Yes 16	Yes >5% 20	No 47
Bio-Rad Variant II Turbo 2.0	No 13,21	No 13,21	No 13,21, Yes 45	No 13,21	Yes >25% 20	No 47-
Diazyme Direct Enzymatic HbA1c	No 15,23	No 15,23	No 16,23	No 16	-	No 47
Drew Scientific DS5	No 17	Yes 17	-	-	-	-
Helena Glyco-Tek	Yes 14,24	No 14,24	@	@	$	-

JEOL BM Test HbA1c on JCA-BM 6010/C	**No 51**	**No 51**	**No 51**	**No 51**	**-**	**-**
Menarini HA-8140	**No 14**	**Yes 14**	**Yes 1, 25**	**Yes 26**	**No 1, 25**	**Yes 19, 27, 28**
Menarini HA-8160 (Diabetes Mode)	**No 17**	**No 17**	**Yes 16**	**Yes 16, 52**	**-**	**No 47**
Menarini HA-8160 (Thalassemia Mode)	**-**	**-**	**No 16**	**HbA1c not quantifed 16**	**-**	**-**
Ortho-Clinical Vitros	**No 15,29**	**No 15,29**	**No 16**	**No 16**	**$**	**-**
Pointe Scientific Hemoglobin A1c	**No 15,29**	**No 15,29**	**No 16**	**No 16**	**$**	**-**
RandoxHaemoglobin A1c	**Yes 30**	**Yes 30**	**@**	**@**	**Yes >10% 30**	**-**
Roche Cobas Integra Gen2	**No 15,31,32**	**No 15,31,32**	**No 16**	**No 16**	**$**	**No 47**
Roche Tina-quant II on Hitachi	**No 1, 33,35**	**No 1, 33,35**	**No 1, 6,35**	**No 16**	**$**	**No 1, 27, 28**
SebiaCapillarys 2 Flex Piercing	**No 13**	**No 13**	**No 13**	**No 13**	**No ≤15% 48**	**No 48,49, 50**
Siemens Advia HbA1c (original version)	**Yes 34**	**Yes 34**	**@**	**@**	**$**	**-**
Siemens Advia A1c (new version)	**No 22,36**	**No 22,36**	**@**	**@**	**$**	**-**
Siemens DCA 2000/DCA Vantage	**No 1, 24,33,37 /yes 38**	**No 1, 24**	**No 1, 16,39,40**	**No 16**	**Yes (>10%) 41,43**	**No 27, 42, 47**
Siemens Dimension	**No 17**	**No 17**	**No 16**	**No 16**	**$**	**-**
Tosoh G7	**Yes 13,21 /No 15,17**	**No 13, 15, 17,21**	**Yes 13,16, 21**	**No 13,16, 21**	**No ≤30% 20, 41, 43**	**No 47**
Tosoh G8	**No 13,21, 22**	**No 13,21, 22**	**Yes 13,16, 21**	**No 13,16, 21**	**No ≤30% 20**	**No 47**
Trinity (Primus) Boronate Affinity HPLC	**No 1, 15, 17,33**	**No 1, 15, 17,33**	**No 1, 16, 39**	**No 16**	**Yes >15% 20,41, 43**	**No 1, 27, 42,44**

In the absence of specific method data, it can generally be assumed that immunoassay methods do not have clinically significant interference from HbE and HbD because the E and D substitution are distant from the N-terminus of the hemoglobin beta chain.[102]

In the absence of specific method data, it can generally be assumed that both immunoassay and boronate affinity methods show interference from HbF levels above ~10-15%.103

Yes/No indicates that there is conflicting data in the literature. The indicator in bold is the opinion of the NGSP based on review of the literature cited.

- Not yet evaluated

NOTE:

- Many other publications have been reviewed. Only those with conclusions that are reasonably supported by data are included.
- For ion-exchange HPLC methods, interference from Hb variants and adducts may be dependent on the lot of reagents used.104

Role of CRP in diabetes mellitus

Low-grade systemic inflammation is associated with type 2 diabetes as indicated by elevated high-sensitivity C-reactive protein levels in a North Indian population.

C-reactive protein, an acute-phase reactant produced by liver, is an extremely sensitive marker of systemic inflammation. It is perceived that chronic low-grade inflammation as evidenced by elevated high-sensitivity C-reactive protein (hsCRP) might potentially be a cause underlying the etiology and manifestation of type 2 diabetes (T2D), although the exact mechanisms are still not well

understood.[105]Additionally, hsCRP has also emerged as a powerful predictor of cardiovascular disease (CVD).[106] However, hsCRP levels are known to vary among populations, influenced by gender, age, and obesity.[107]

India has the distinction of having the highest number of T2D individuals worldwide, with a prevalence of 11.6% in urban populations.[108] Furthermore, Asian Indians are known to be at a high risk for T2D, CVD, and metabolic syndrome.[109] Although elevated levels of hsCRP have been observed in expatriate adult Indians[110] and adolescents residing in India,[111] data on adult individuals residing in India are scanty. A solitary study done in South Indians considering 150 subjects has attempted to investigate the role of hsCRP in T2D.[112]

C-Reactive Protein (CRP):

C-reactive protein (CRP) is one of the common test parameters used in clinical practice, to assess, diagnose, and prognose inflammation. However, the role of CRP in physiological processes is not clearly elucidated. CRP, belonging to pentraxin family of proteins shows a 1000-fold or more increase in concentration during the occurrence of an injury, inflammation or tissue death.[113] The plasma half-life of CRP is around 19 hours and is constant under all conditions of health and disease.[114] In addition to CRP, the levels of few other proteins termed as acute phase proteins (APR) are also increased during inflammation. CRP, the first acute-phase protein to be described, is a sensitive systemic marker of inflammation and tissue damage.[114]

Production of CRP

CRP is produced in many sites within the human body. It is produced in the liver in response to IL-6. Products of activated monocytes in Hep 3B cells activate the

production of human serum amyloid A (SAA) protein and CRP, but not by IL-1β, TNF-α, or some hepatocyte-stimulating factor preparations. It is also produced in very limited concentration by non-hepatic cells like neurons, atherosclerotic plaques, monocytes, Kupffer cells and lymphocytes.[113,115] Studies have shown that epithelial cells of both respiratory tract and renal epithelium can also produce CRP under certain circumstances.[116,117] Recent studies have demonstrated that human coronary artery smooth muscle cells could also synthesize CRP upon stimulation by inflammatory cytokines.[118] Cogent data have indicated that the protein is also produced by the atherosclerotic lesions (especially by smooth muscle cells and macrophages), kidneys, neurons, and alveolar macrophages.[119]Additionally, there is evidence to suggest that lipid peroxidation and infection, such as cytomegalovirus may trigger a pro-inflammatory cytokine cascade resulting in CRP release.[120]CRP may be secreted from active human peripheral blood monocytes, while generation from peripheral blood mononuclear cells (PBMC) is poorly established.[116,118] Expression of CRP by human respiratory epithelial cells and alveolar macrophages suggests contribution to bacterial clearance and direct involvement in pulmonary host defense and immune response.[121]Biosynthetic labeling with S-met and immuno-precipitation with anti-CRP antibodies and Staphylococcus aureus indicate that cell surface CRP is produced by lymphocytes.[121,122]

Structure of CRP

CRP is a pattern recognition molecule binding to specific molecular configurations that are typically exposed during cell death or found on the surfaces of pathogens. It is a calcium-dependent ligand-binding plasma protein, which is phylogenetically highly conserved with homologues in vertebrates and many invertebrates.[113]

Human CRP is a non-glycosylated polypeptide with five identical subunits or protomers.[123]Each subunit is constituted by 206 amino acid residues and bound to each other by non-covalent bonds.[114] Structure of CRP based on the amino acid composition, as derived from the sequence data and a minimal molecular weight of 20,946, has been calculated for human CRP.[113] X-ray crystallography has demonstrated the structure of the protomer as two antiparallel β-sheets with a flattened jelly-roll topology similar to that of lectins, especially concanavalin.[113,124] Each subunit has a recognition face with a phosphocholine binding site consisting of two coordinated calcium ions adjacent to a hydrophobic pocket. Phe-66 and Glu-81 are the two key residues mediating the binding of phosphocholine to CRP. Phe-66 provides hydrophobic interactions with the methyl groups and Glu-81 is found on the opposite end of the pocket where it interacts with the positively charged nitrogen of phosphocholine.[113]The opposite face of the pentamer is the effector face, where complement C1q binds and serves as Fcγ receptors. CRP binding to C1q activates the classical complement pathway up to the level of the C3 convertase.

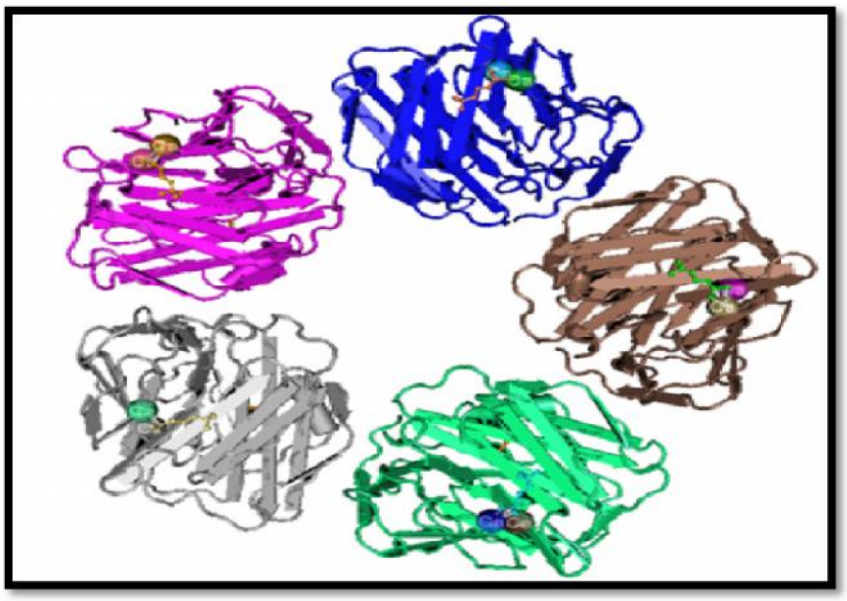


Figure 2: Pentameric structure of CRP. Phosphocholine along with the tow calcium ions are located at the binding sites of each promoter.

Functions of CRP

CRP, an inducible protein secreted secondary to inflammatory stimulus, binds to pathogens and activates the complement to enhance opsonisation and clearance, even before the production of specific IgM or IgG. Involvement of CRP in various immunological processes is mapped in figure.[126] CRP is bound to a multivalent ligand initiates the assembly of a C3 convertase through classical pathway, which leads to the presentation of ligand with opsonic complement fragments.[127]However, the protein does not favor the formation of a C5 convertase and hence, CRP-initiated complement activation does not mediate acute inflammatory reactions and membrane damage.[127]The protein has been shown to induce the synthesis of IL-1α, IL-1β, TNF-α, and IL-6 in human peripheral blood mononuclear cells and alveolar macrophages.[123] Furthermore, soluble and immobilized CRPs have been demonstrated to mediate the uptake of native low density lipoprotein (LDL) into macrophages. CRP may also function as a substrate for membrane-associated neutrophil serine protease that cannot be up-regulated. On the contrary, the degradation of CRP yields small soluble bioactive peptides that inhibit many of the pro-inflammatory and tissue-destructive potential of neutrophils. These peptides are possibly involved in signal transduction pathways leading to neutrophil activation.[126] CRP shares major amino acid sequences with SAA fragments. Heat-aggregated CRP has been demonstrated to activate platelet aggregation, secretion, and generation of thromboxane A2, similar to heat-aggregated IgG. Human SAA seems to selectively modulate platelet reactivity and down-regulate at least one aspect of the biologic capacity of its acute-phase homologue, CRP.[128]

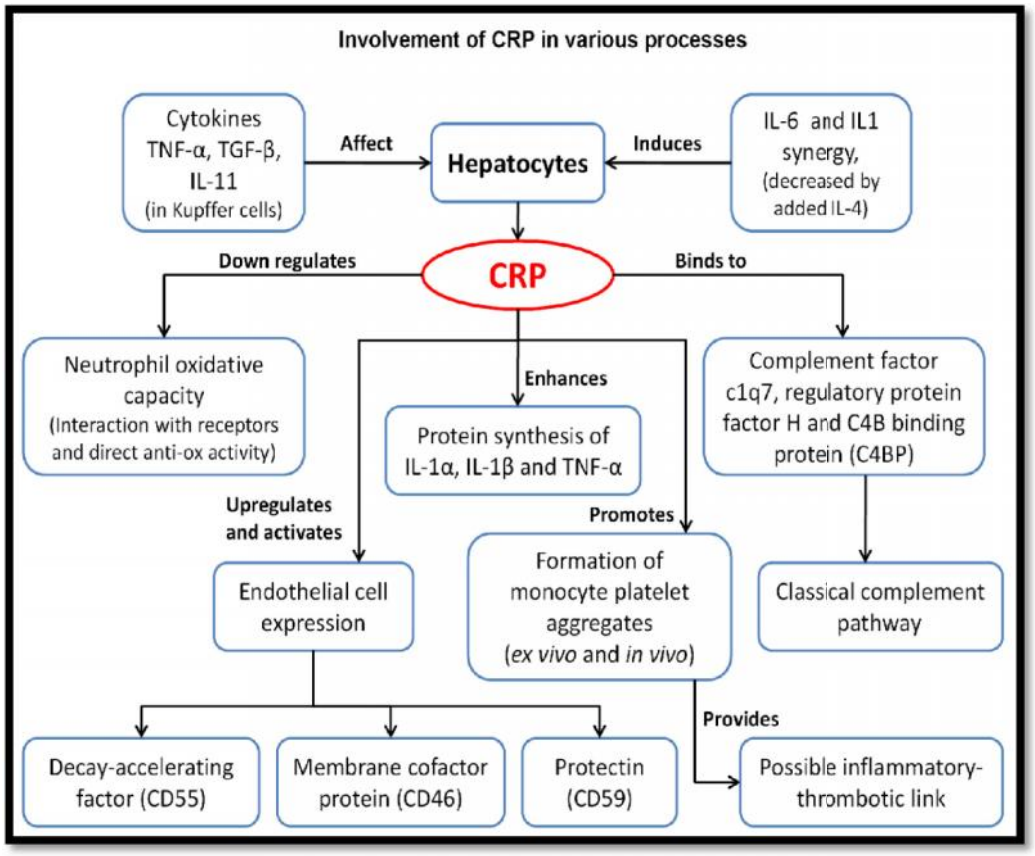


Figure 3: Involvement of CRP in various processes.

Use of CRP as markers in different disease

In the absence of inflammation, CRP is not expressed and its level is undetectable. Baseline concentrations of CRP are influenced by many factors, including chronic microbial infections, smoking, BMI, coffee consumption, oral contraceptive use, and genetics.[129] Lifestyle factors, such as smoking and BMI, have a greater influence on baseline CRP levels than single nucleotide polymorphisms (SNPs), making the identification of a genetic association of CRP SNPs with cardiovascular diseases difficult.[130] The level of CRP is altered in variety of conditions; although the rise in CRP is non-specific, the quantum and the pattern of rise will help deduce the diagnosis. A number of clinical situations are discussed in the following sections.

CRP during normal pregnancy

CRP does not cross the placental barrier and therefore, will be useful in diagnosing infections in newborns.[131]Recently, it has been shown that CRP is present in amniotic fluid and fetal urine, and the elevated levels are associated with adverse pregnancy outcome.[132]These results demonstrate that the human placenta produces and releases CRP, like other placental proteins, mainly into the maternal circulation.

CRP and cardiovascular risk

The association between CRP and cardiovascular risk is driven predominantly by systemic inflammation. CRP is unlikely to contribute directly to cardiovascular disease as a pathogenic factor. Similar conclusions were drawn from recent Mendelian randomization studies. Using widely available high-sensitivity assays, CRP levels of 1, 1 to 3, and 3 mg/L have been classified as low, moderate, and high-risk groups for future cardiovascular events. Individuals with LDL cholesterol below 130 mg/dL and CRP levels of 3 mg/dL represent a high-risk group. The conversion of plasma CRP (pCRP) to monomeric CRP (mCRP) has been described as being mediated by activated platelets, which are associated with cardiovascular risks.[133]

CRP and cancer

CRP levels has been used to predict the risk of cancer, detect cancer recurrence, and in prognosis. CRP is a biomarker of inflammation and indicator of the immune response to tumors.[134]Its role as a predictor of survival has been shown in multiple myeloma, melanoma, lymphoma, ovarian, renal, pancreatic, and gastrointestinal tumors.[134]Recent evidence has also associated CRP elevation with the progression of

melanoma, ovarian, colorectal and lung cancers, and recurrence of cancer after surgery in certain situations.[135]

CRP and infection

CRP is an important factor in determining the etiology of infection. The level of CRP can be significantly higher in bacterial infections. A value higher than 100mg/L strongly suggests bacterial infections, whereas that below 10 mg/L indicates viral infection. In tuberculosis, it is often found to be between 10 to 100 mg/L.[136]Additional determination of pro-calcitonin can add specificity in the case of bacterial infections.[137]The above information is also helpful to distinguish infection from an autoimmune flare. Similarly, the rate of change in CRP levels can differentiate tuberculosis from bacterial pneumonia.[138]

CRP and inflammatory diseases

In the case of inflammatory diseases, CRP level represents the disease activity. Studies have suggested direct correlations of CRP with RA and inflammatory bowel diseases like Crohn's disease.[139] In contrast, in conditions like SLE, CRP is not significantly elevated.

CRP and obesity

CRP levels are elevated, predominantly in obese individuals who are insulin resistant, and are in line with the weight loss-associated improvements in insulin resistance. The relation between CRP concentrations and insulin resistance is independent of obesity.[140]

Association between hs- CRP level and Diabetes Mellitus

AmanullahS et al[141](2010) did a study of the association of hs-CRP with diabetic and non-diabetic individuals and they reported that the type II diabetes Mellitus encompasses -90 % of the diabetic subjects, and it is characterized by insulin resistance often accompanied by obesity and dyslipidemia. hs-CRP, the golden marker of inflammation was analyzed in diabetic and non- diabetic subjects. Anthropometric parameters were found to be high in diabetic subjects compared with non-diabetic subjects. The high hs-CRP levels in diabetic subjects were observed. The hs-CRP levels were seen in diabetes with insulin resistance. Serum hs-CRP levels were positively related to anthropometric parameters. The relationship of hs-CRP with glycaemic control was studied with HbA1c, and it was positively correlated with hs-CRP. The results concluded that hs-CRP has strong association with diabetic individuals. The significance of hs-CRP in diabetic and non-diabetic individuals was discussed.

Mahajan A et al[142] (2011) did a study of the high-sensitivity C - reactive protein levels and type 2 diabetes in Urban North Indians and observed that the median hsCRP levels were significantly higher in both diabetic men and women as compared to their nondiabetic counterparts. Elevated hsCRP was positively associated with T2D (odds ratio, 1.66; 95% confidence interval, 1.21–2.28; P = 0.002) even after adjusting for markers of obesity. After adjustments for age, sex, and BMI, HbA1c was the major correlate of hsCRP in nondiabetic subjects (β = 0.28; P = 0.03). They also observed that T2D patients were at higher risk for cardiovascular disease compared to nondiabetic subjects when classified into low-, intermediate-, and high-risk groups based on hs-CRP levels. Authors concluded that the association of low-grade systemic

inflammation, as indicated by elevated hs-CRP levels, with T2D in North Indian population. This association was independent of obesity. Obesity and poor glycemic control were the major correlates of hsCRP levels.

Sarinnapakorn V and Wanicagool W[143] (2013) did a study of the association between hs-CRP and Hba1c in overweight type 2 diabetic female patients and observed that the 35 patients had hs-CRP levels less than 1 mg/L, and the remaining 40 patients had hs-CRP levels of 1 mg/ L or more, representing 46.67% and 53.33% respectively, and it was found that hs-CRP values correlated with HbA1c levels. The group with hs-CRP of less than 1 milligram per liter had a mean HbA1c of 7.36 +/- 1.23%, while the group with hs-CRP of 1 mg/L or more had a mean HbA1c of 8.77 +/- 1.78%, with statistical significance. Authors concluded that the hs-CRP levels correlated with HbA1c levels. Mean HbA1c levels were significantly higher in patients who had hs-CRP levels of 1 mg/L or more. Other factors such as age, blood pressure, BMI, LDL-C, serum creatinine were not correlated with hs-CRP level.

Bandyopadhyay R et al[144] (2013) did a cross sectional study of the C reactive protein in type 2 diabetes and its relation with various complications from Eastern India and they reported that the presence of any 1 diabetic complication was associated with significantly higher CRP levels (1.8± 1.32 mg/dl vs. 0.49± 0.22; $p < 0.05$ by t test). CRP levels showed significant positive correlation with serum triglyceride and HbA1C. CRP was associated with various diabetic complications. It was also related with the severity of glycemic status, as evidenced by HbA1C. Although their study was cross sectional, still, it showed correlation of CRP with many complications of diabetes and thus this can be an effective marker of clinical status in diabetes.

Abdul hussien MK Al-jebory and Hanan A. M. Al-zubeidi[145] (2014) did a study of the relationship between hs-C- reactive protein and some biochemical variables in Cardiovascular and Type -2- Diabetic Mellitis patients and they reported that there were lowering in Fasting serum adiponectin hormone concentration for (three study groups) Type -2- Diabetic, Type - 2- Diabetic with Cardiovascular, and Cardiovascular diseases groups with respect to than normal subjects. When use hs-CRP measurement as a marker to limitation the kind of pathogenic case and from L.S.D statistical system were observed there were highly significant different between (DMII with CVD and CVD) groups compared to control group and medium significant different with DMII group .There weren't significant different between (DMII with CVD and CVD) groups ,while there were significant different between DMII group and control group less than two previous groups (DMII with CVD and CVD). Therefore measurement of hs-CRP were considered as a predictor to incident by Cardiovascular diseases more than Type -2- Diabetes.

Tutuncu Y et al[146] (2016) did a comparative study of the hs-CRP levels in new diabetes groups diagnosed based on FPG, 2-hPG, or HbA1c criteria and they reported that the mean serum concentration of hs-CRP in women was higher than in men. The people with new-onset diabetes mellitus based on HbA1c had higher mean hs-CRP level than FPG based and 2-hPG based DM cases. In HbA1c, 2-hPG, and FPG based new-onset DM people, cut-off levels of hs-CRP in women were 2.9, 2.1, and 2.5 mg/L [27.5, 19.7, and 23.5 nmol/L] and corresponding values in men were 2.0, 1.8, and 1.8 mg/L (19.0, 16.9, and 16.9 nmol/L), respectively (sensitivity 60–65% and specificity 54–64%). Their results revealed that hs-CRP may not further strengthen the diagnosis of new-onset DM. Nevertheless, the highest hs-CRP level observed in new-onset DM people diagnosed with HbA1c criterion supports the general

assumption that this method might recognize people in more advanced diabetic stage compared with other diagnostic methods.

Deepika G et al[147] (2016) did a study of the serum alkaline phosphatase and high sensitivity C-reactive protein in type II diabetes mellitus as a risk of cardio vascular disease in South Indian population and observed that the mean serum ALP(145.17±23.91) and hsCRP (2.53±0.76) concentration in group II patients when compared to group I serum ALP(142.17±16.48) and Hscrp (1.51±0.15) shows a significance of ALP ($p<0.05$) and Hscrp ($p<0.001$). Study II Mean serum ALP(145.17±23.91) and hsCRP (2.53±0.76) concentration in group II patients when compared to group III serum ALP (147.79±28.95) and Hscrp (3.848±0.47) group shows a significance of ALP ($p<0.001$) and Hscrp ($p<0.05$). Study III Mean serum ALP (147.79±28.95) and hsCRP (3.848± 0.47) concentration in group III patients when compared to group I serum ALP (142.17±16.48) and Hscrp (1.51±0.15) shows a high significance of both ALP and hscrp ($p<0.001$). Further significant correlation was observed between ALP and hsCRP concentration as well as with HbA1c, FBS, and PP2BS. Authors concluded that the inflammation along with the poor glycemic control in diabetes play a role in diabetic macrovascular complication like CVD. All these finding are showing a link between CVD, inflammation and glycemic control in patient with type 2 diabetes mellitus.

Studies on correlation between HbA1c and hsCRP in Diabetic Patients:

Fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c) has been used to diagnose new-onset diabetes mellitus (DM) in order to simplify the diagnostic tests compared with the 2-hour oral glucose tolerance test (OGTT; 2-hPG). Yildiz Tutuncuet al[148] (2016) did a comparison of hs-crp levels in new diabetes groups

diagnosed based on FPG, 2-hPG, or HbA1c criteria.Their results revealed that hs-CRP may not further strengthen the diagnosis of new-onset DM. However, the highest hs-CRP among people with new DM was found in those identified with the HbA1c criterion. This suggests that high HbA1c may recognize new DM cases at a more advanced stage than FPG or 2-hPG in an OGTT. Clinical relevance of this finding deserve further evaluation. It would be important to find out if people with newly detected DM with high hs-CRP require a more intensive therapy than those with low hs-CRP.

Geetha Bhaktha et al[149] (2014) aimed in finding the correlation of hs-crp with other risk factors like BMI, FBS and HbA1c in diabetic subjects who have still not developed any micro and macrovascular complications. Authors observed the level of Hs-crp was high in diabetic subjects when compared to normal individuals. Further when the diabetic subjects were divided into high risk and low risk groups, the difference between the groups were statistically significant. Hs-crp failed to show any correlation with BMI, FBS and HbA1c. Diabetes is considered as an inflammatory disease hence they concluded an increase in the hs-crp level in diabetes than in the normal. Since the vascular complication was totally absent hs-crp failed to show any correlation with BMI, FBS and HbA1c.

In 2013, Ajay Meshram et al[150]aimed to find the association of hs-CRP and diabetes mellitus in the population of Central Rural India region. The analysis was done with 50 diabetic and 50 non-diabetic individuals. Anthropometric and biochemical parameters were studied to assess the association of hs-CRP with in diabetes mellitus. Authors concluded that serum hs-CRP levels were positively affected to anthropometric parameters. The relationship of hs-CRP with glycaemic control was

studied with HbA1c, and it was positively correlated with hs-CRP. It is also concluded that hs-CRP has strong association with diabetic individuals.

Bandyopadhyay Ramtanuet al[151] (2013) were aimed to find the CRP levels in type 2 diabetes and its relation with other parameters. Subjects only newly diagnosed drug naïve type 2 diabetes patients were selected. According to results patients with cardiac and retinal complications had significantly higher levels of CRP. The presence of any 1 diabetic complication was associated with significantly higher CRP levels (1.8± 1.32 mg/dl vs. 0.49± 0.22; $p < 0.05$ by t test). CRP levels showed significant positive correlation with serum triglyceride and HbA1C. CRP was associated with various diabetic complications. It was also related with the severity of glycemic status, as evidenced by HbA1C. It showed significant correlation of CRP with many complications of diabetes and thus this can be an effective marker of clinical status in diabetes.

In 2012, Roopakala M S et al[152]determined the serum level of high sensitivity C-reactive protein (hsCRP) in DN(diabetic nephropathy) patients and to compare with that of normal subjects and to study the association between serum hsCRP levels and glycated hemoglobin (HbA1c) levels. In their study 50 DM patients in the age group of 50- 60 years with more than ten years of duration of diabetes were recruited and 25 age-and sex-matched healthy subjects were included in this study as controls. There was a statistically significant increase in serum hsCRP levels in DN cases as compared to normal controls. The hsCRP levels showed a positive correlation with HbA1c in DN. These results suggest that estimation of serum hsCRP levels and aiming at good glycemic control help in early intervention and prevention of further complications in diabetic patients.

Safiullah Amanullahaetal[153](2010) studied association of hs-CRP with Diabetic and Non-diabetic individuals. They reported that hs-CRP significantly associated with age and positively related to insulin resistance, BMI, systolic and diastolic pressure. Similarly, low HbA1c strongly related to negative hs-CRP levels. It is also observed that hs-CRP levels are the ensitive marker for inflammation.

In 2009, Anubha Mahajan et al[154] did a study was aimed to assess the association of hs-CRP with T2D and to determine its correlates in North Indians of Indo-European origin. They concluded that the association of low-grade systemic inflammation, as indicated by elevated hs-CRP levels, with T2D in North Indian population. This association was independent of obesity. Obesity and glycemic control were the major correlates of hs-CRP levels. Future studies are required to evaluate the influence of modulators including genetic variations on the elevation of hs-CRP levels in this population.

METHODOLOGY

The present study was conducted in the Department of Medicine, KLE'S Dr.Prabhakar Kore Hospital and Medical Research Centre, Belagavi from January 2016 to December 2016.

Study design and duration

The study design was a hospital based cross sectional study.

Study period

The present study was done for the period of one year from January 2016 to December 2016.

Place

The present study was carried out in the Department of Medicine, KLE'S Dr.Prabhakar Kore Hospital and Medical Research Centre, Belagavi a tertiary care teaching hospital attached to Jawaharlal Nehru Medical College, Belgaum.

Source of Data

Patients presenting with type 2 diabetes mellitus in medicine OPD or admitted at KLE'S Dr.Prabhakar Kore Hospital and MRC, Belagavi

Sample Size Calculation:

$z\alpha^2pq/d^2$

Where $z\alpha=1.96$ (constant)

P=51% (51% of the patient had raised hs-CRP levels) (11)

q-(100-p) =49

d- absolute error =10

Sample size:

$1.96^2*51*49/10^2=100$ patients.

Universal Sample Size

All the patients with type 2 diabetes mellitus at KLE'S Dr.Prabhakar Kore Hospital and MRC, Belagavi were enrolled during the study period

Sampling procedure

All the patients with type 2 diabetes mellitus in medicine OPD or admitted at KLE'S Dr.Prabhakar Kore Hospital and MRC, Belagavi were enrolled during the study period

Hence it was a universal sample size.

Selection criteria

Inclusion Criteria:

1) Age above 18
2) Type 2 diabetes mellitus

Exclusion Criteria:

1) Patients less than 18 years of age.
2) Gestational diabetes
3) Cardiovascular abnormalities (IHD, RHD)
4) On anti-inflammatory drugs
5) No history of hypertension
6) No history of RA
7) No history of smoking
8) No history of acute infections (UTI, URTI)
9) No history of chronic infection like HBV, HCV, TB
10) No history of collagen vascular disease like SLE

Ethical clearance

Prior to the beginning, the study was approved by the Institutional Ethics Committee, Jawaharlal Nehru Medical College, Belagavi.

Informed consent

The patients who fulfilled the selection criteria were informed about the nature of study and a written informed consent was obtained (Annexure–I).

Data Collection

Patients will be enrolled on the basis of type 2 diabetes mellitus and inclusion criteria.

Patients were enrolled from medicineOPD and admitted cases in KLE'S Dr.Prabhakar Kore Hosptial and Medical Research Center Belagavi.

Patients were identified who had come for follow up at the OPD for diabetic management, or by using the question "Has your doctor ever told you that you have diabetes?" or on any diabetic medication?

Respondents with diabetes were not identified using laboratory data because blood was drawn on only one occasion and because people with diabetes may not have had elevated serum glucose at the time the blood was drawn.

People who had used anti-inflammatory drugs or cholesterol-lowering drugs within the previous 30 days were excluded from the analysis, due to the possible effects the drugs might have on hs-CRP levels

Investigations:

Patients were subjected to following investigations.

- Complete blood count
- Peripheral smear
- Erythrocyte Sedimentation Rate
- Fasting blood sugar levels
- Serum urea levels
- Serum creatinine levels
- Liver function test
- Urine Sugars
- Urine Proteins
- Hs-CRP
- HbA1c
- ECG
- Fundoscopy

Statistical methods

The data obtained was coded and entered into Microsoft excel spreadsheet and data was analyzed using SPSS version 23 and MedCalc software. The categorical data was expressed in terms of rates, ratios and percentages and the continuous data was expressed in terms of mean ± standard deviation. The comparison of categorical data was done using Chi-square test. A probability value ('p' value) of less than or equal to 0.05 was considered as statistically significant.

RESULTS

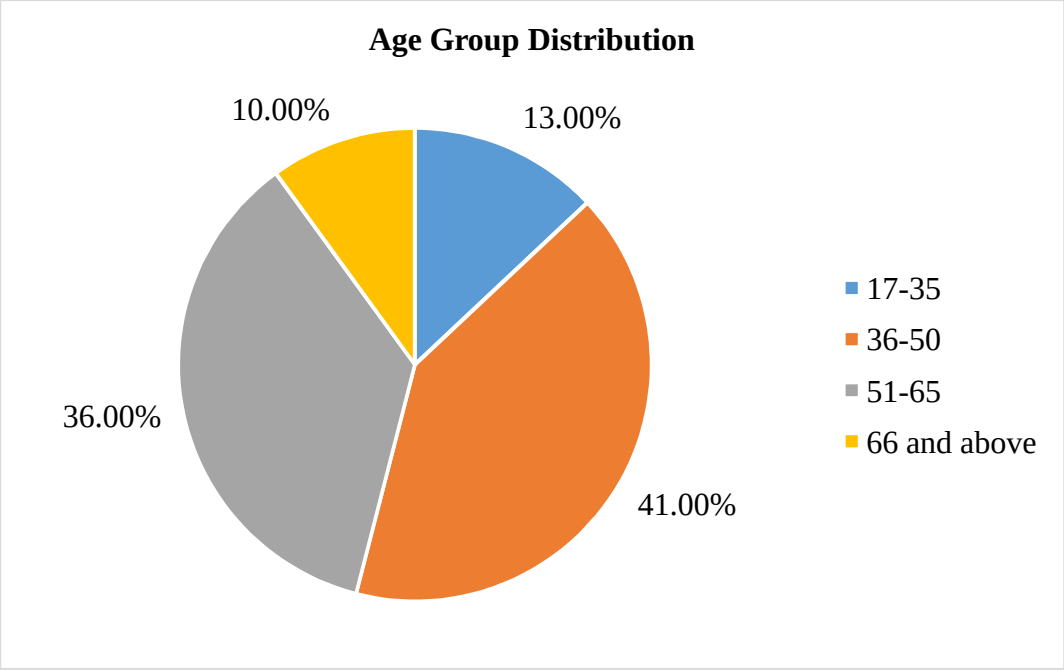
The present one year study titled "A STUDY OF HIGHLY SENSITIVE C-REACTIVE PROTEIN (HS-CRP) IN TYPE 2 DIABETES MELLITUS AND ITS CORRELATION WITH GLYCOSYLATED HEMOGLOBIN (HBA1C) AT TERTIARY CARE CENTRE. A ONE YEAR CROSS SECTIONAL STUDY." was carried out in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. During the study period from January 2016 to December 2016, a total of 100 Type 2 Diabetes mellitus patients were enrolled. The findings/observations and final results are tabulated as below:

AGE

Table 1: Descriptive analysis of Age Group in study population (N=100)

Age Group	Frequency	Percent
17-35	13	13.00%
36-50	41	41.00%
51-65	36	36.00%
66 and above	10	10.00%

Figure 1: Pie chart of Age Group distribution in study population (N=100)



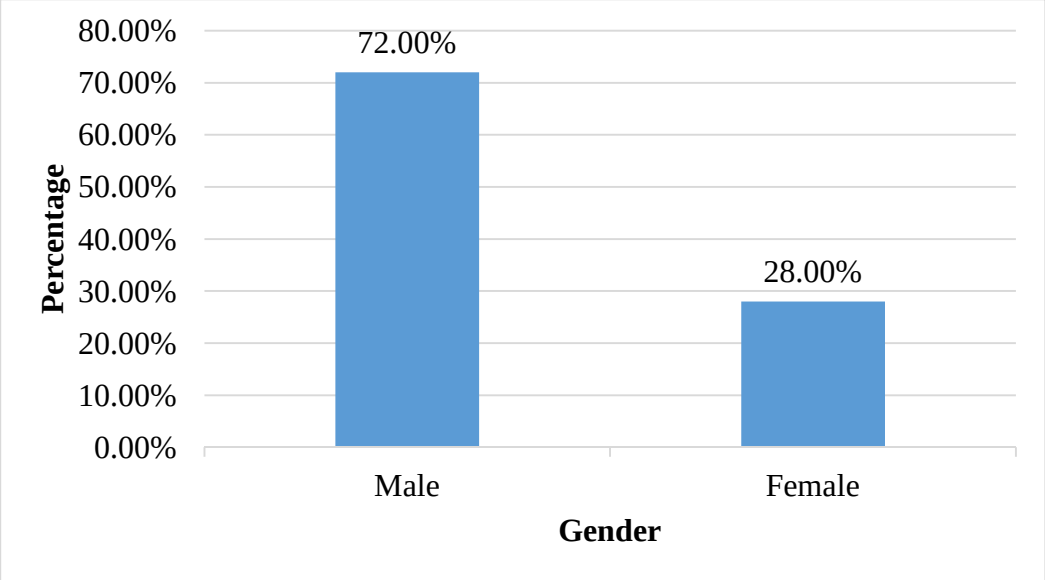
Descriptive analysis of Age Group in study population shows a mean age 50 years with maximum number of samples in the age group of 36-50 years, a maximum age of 89 years and the lowest age of 20 years was observed.

GENDER

Table 2: Descriptive analysis of Gender in study population (N=100)

Gender	Frequency	Percent
Male	72	72.00%
Female	28	28.00%

Figure 2: Bar chart of Gender distribution in study population (N=100)



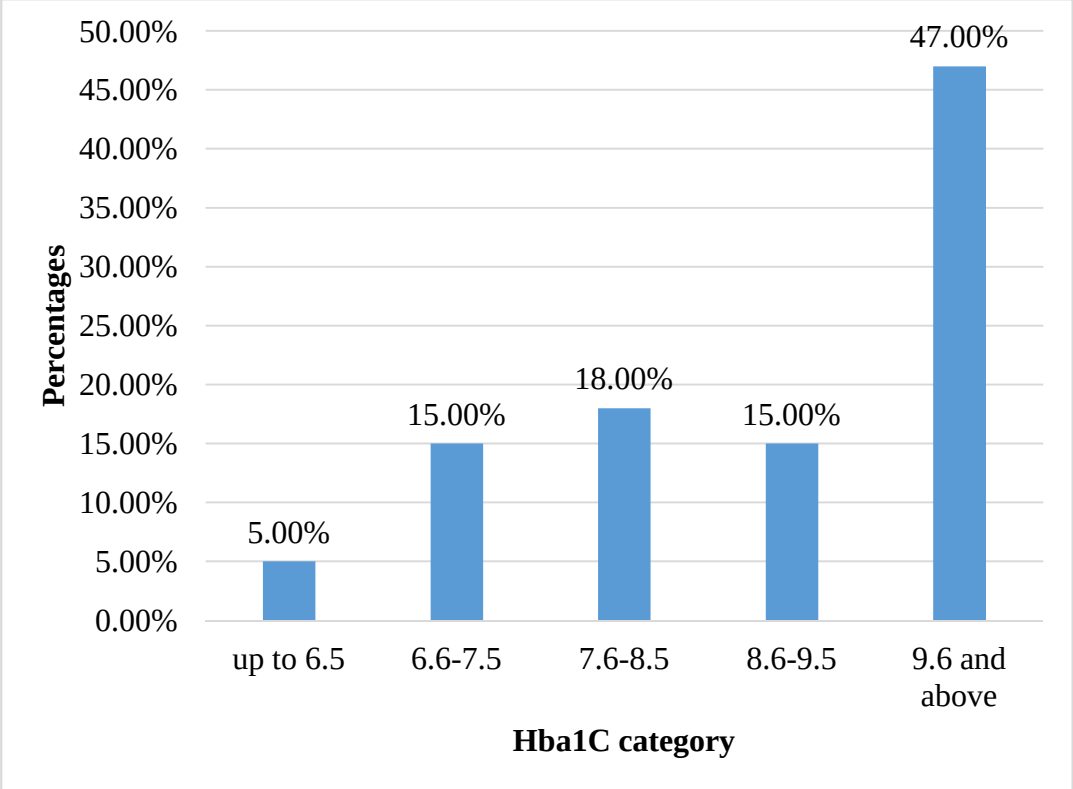
In our study 72% are male and 28% are female that were enrolled. Male to female ratio of 2.57:1.

HbA1c levels

Table 3: Descriptive analysis of HBA1C category in study population (N=100)

HbA1c levels	Frequency	Percentages
up to 6.5	5	5.00%
6.6-7.5	15	15.00%
7.6-8.5	18	18.00%
8.6-9.5	15	15.00%
9.6 and above	47	47.00%

Figure 3: Bar chart of HbA1c levels distribution in study population (N=100)



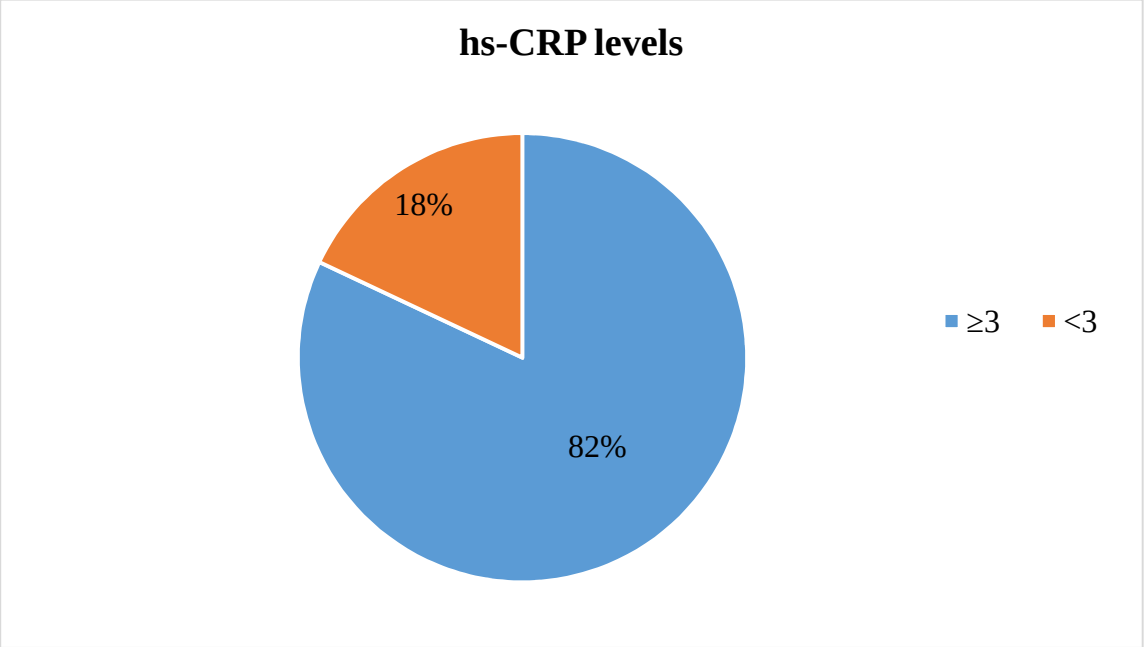
In our study population maximum patients had HbA1c levels more then 9.6; 47%, mean Hba1c levels was 9.86, maximum of 19.90 and a minimum level of 4.90.

hs-CRP

Table 4: Descriptive analysis of HS CRP category in study population (N=100)

hs-CRP levels	Frequency	Percentage
≥3.0	82	82.00%
<3.0	18	18.00%

Figure 4: Pie chart of hs-CRP distribution in study population (N=100)



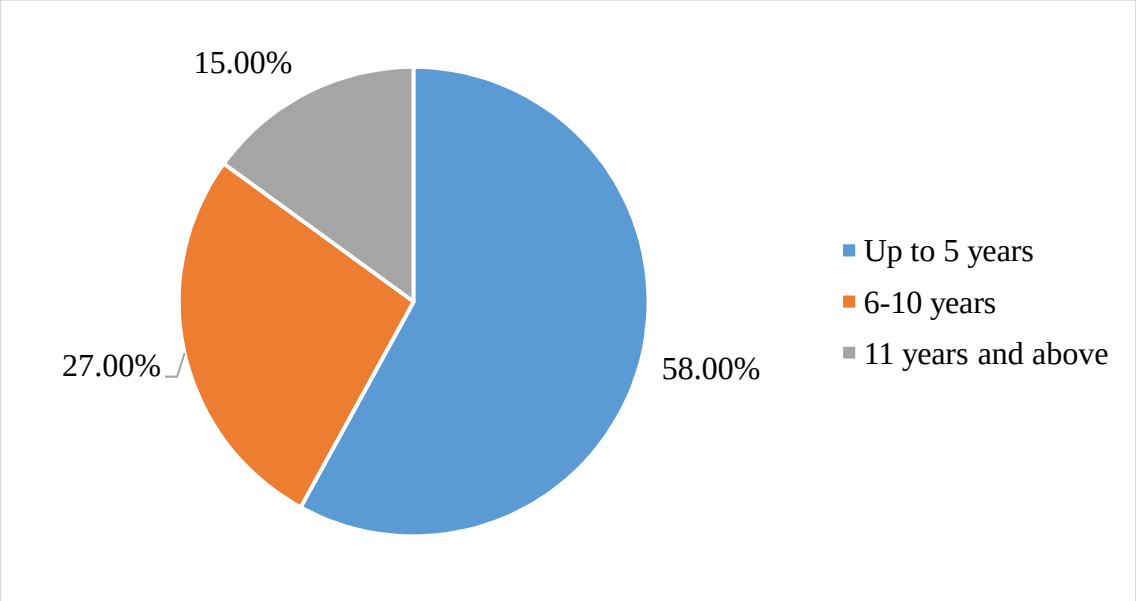
In our study population 82% had hs-CRP levels ≥3.0 and 18% had hs-CRP levels <3.0. Highest level of hs-CRP obtained was 351.1 and the lowest was 0.2.

Duration of Diabetes

Table 5: Descriptive analysis of Duration of Diabetics Mellitus category in study population (N=100)

Duration of Diabetics Mellitus	Frequency	Percentages
Up to 5 years	58	58.00%
6-10 years	27	27.00%
11 years and above	15	15.00%

Figure 5: Pie chart of Duration of Diabetics Mellitus distribution in study population (N=100)



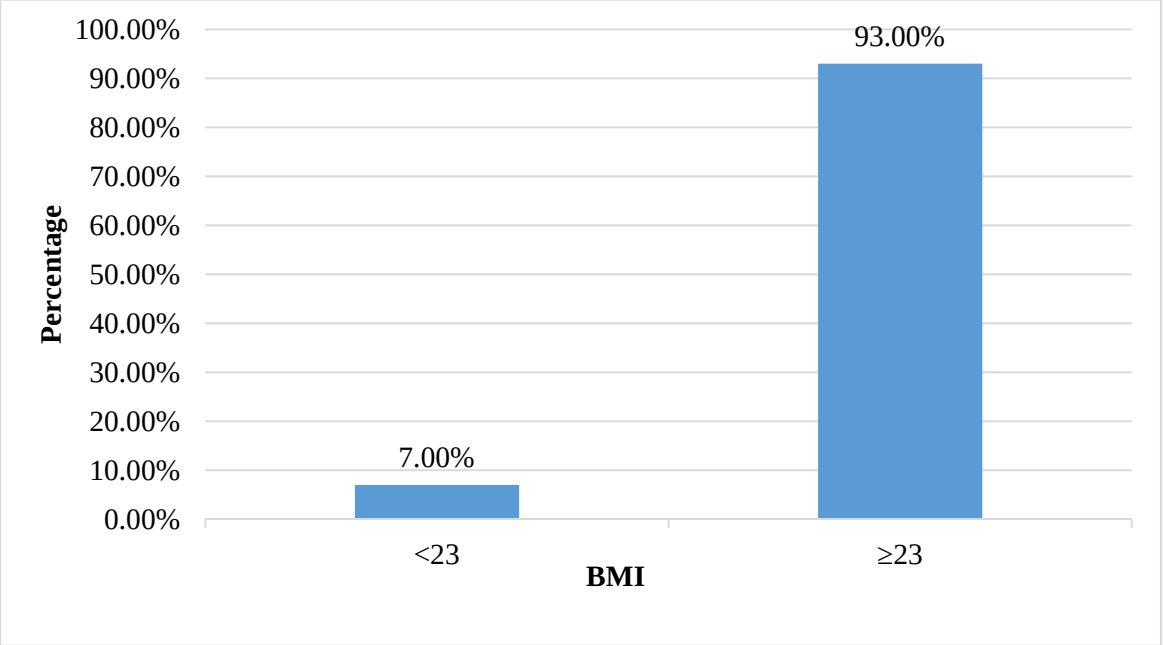
Maximum number of patients had Diabetes less than 5 years 58% followed by 6-10 years 27% and 11 years and above 15%

BMI

Table 6: Descriptive analysis of BMI category in study population (N=100)

BMI (kg/m²)	Frequency	Percentage
<23	7	7.00%
≥23	93	93.00%

Figure 6: Bar chart of BMI category distribution in study population (N=100)



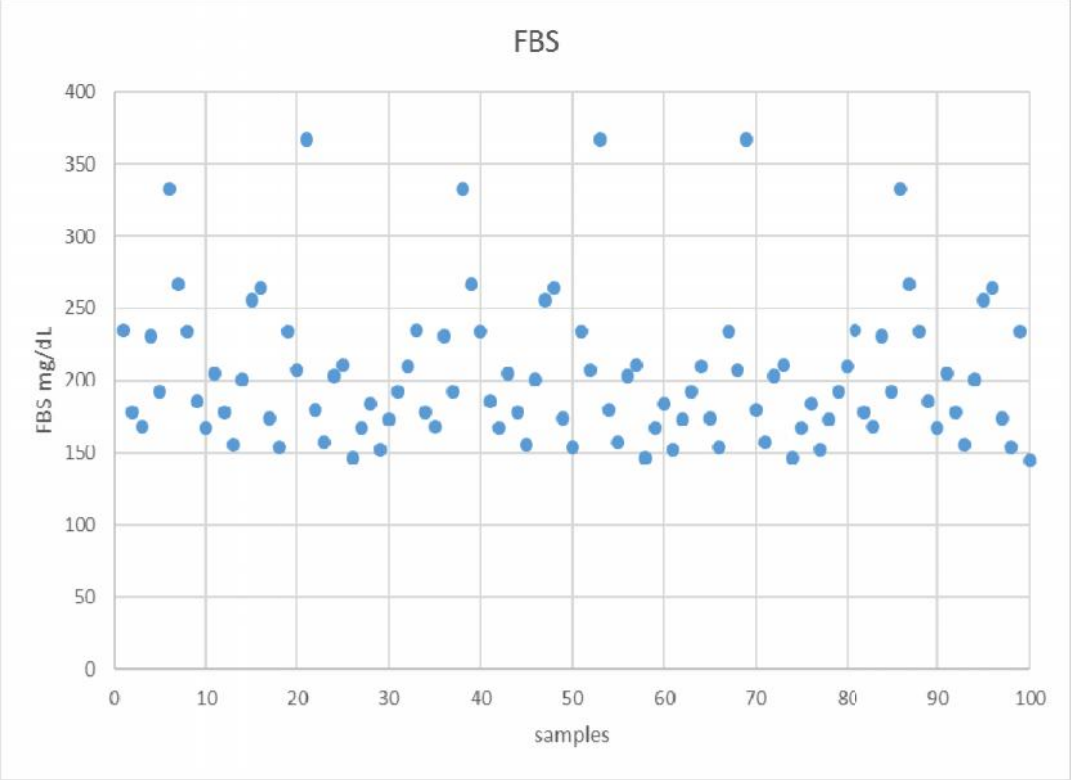
93% of the study population had a BMI ≥ 23 and 7% had a BMI < 23. Mean BMI of the study population is 25.75 with lowest BMI recorded was 22.50 and highest BMI recorded was 29.70

FBS

Table 7: Descriptive analysis for FBS in study population (N=100)

Parameter	Mean ±STD	Median	Min	Max	95% C.I. for EXP(B)	
					Lower	Upper
FBS mg/dL	203.93 ± 49.72	192.00	145.00	367.00	194.06	213.80

Figure 7: showing values of FBS obtained in study population (N=100)



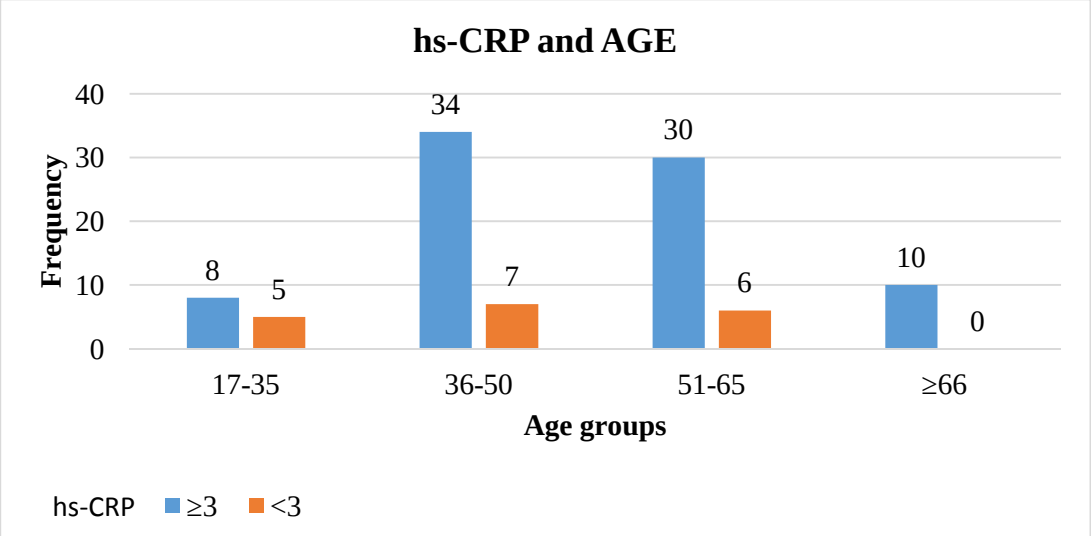
In our study population we achieved a mean FBS 203.93, maximum FBS recorded is 367, and minimum FBS recorded 145.

Inferential analysis: Factors associated with elevated hs-CRP

Table 8: Association of hs-CRP category with Age Group of study population (N=100)

Age Group	hs-CRP (mg/ltr)		Chi square	P-value
	≥3.0(N=82)	<3.0(N=18)		
17-35	8 (9.76%)	5 (27.78%)	5.950a	0.114
36-50	34 (41.46%)	7 (38.89%)		
51-65	30 (36.59%)	6 (33.33%)		
66 and above	10 (12.2%)	0 (0%)		

Figure 8: association with hs-CRP with age group of study population (N=100)

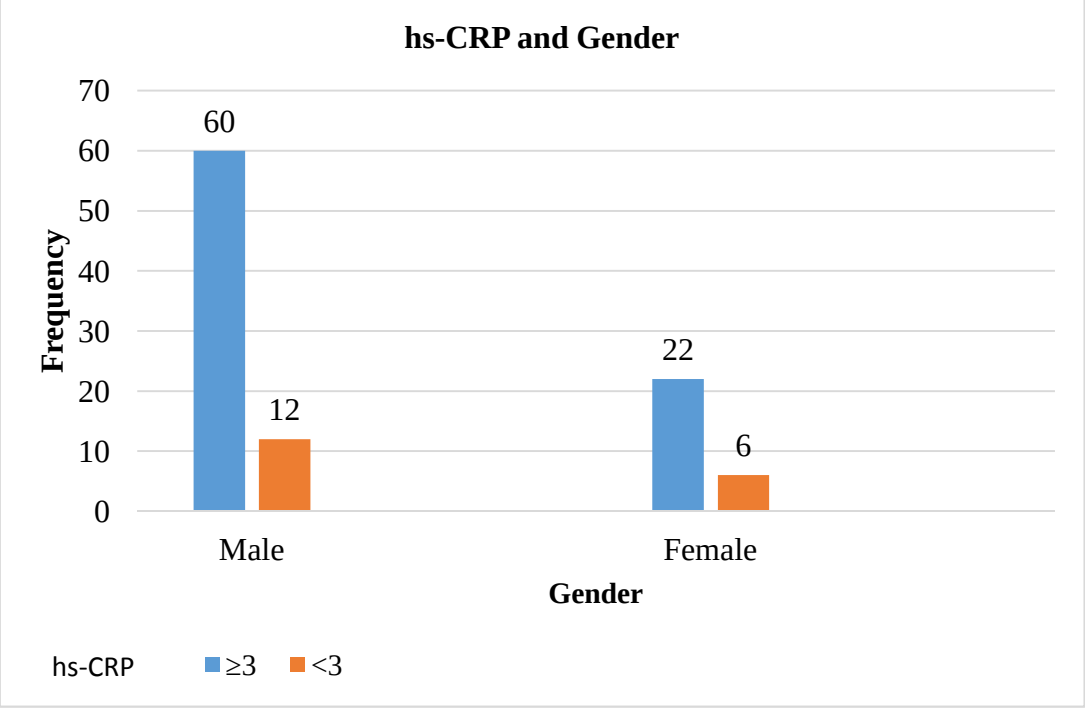


In our study there was no relation between hs-CRP and different Age groups. P value 0.114 (not significant)

Table 9: Association of hs-CRP with Gender of study population (N=100)

Gender	hs-CRP (mg/ltr)		Chi square	P-value
	≥3.0(N=82)	<3.0(N=18)		
Male	60 (83.33%)	12 (16.67%)	.310a	0.578
Female	22 (78.57%)	6 (21.43%)		

Table 9: Association of hs-CRP with Gender of study population (N=100)

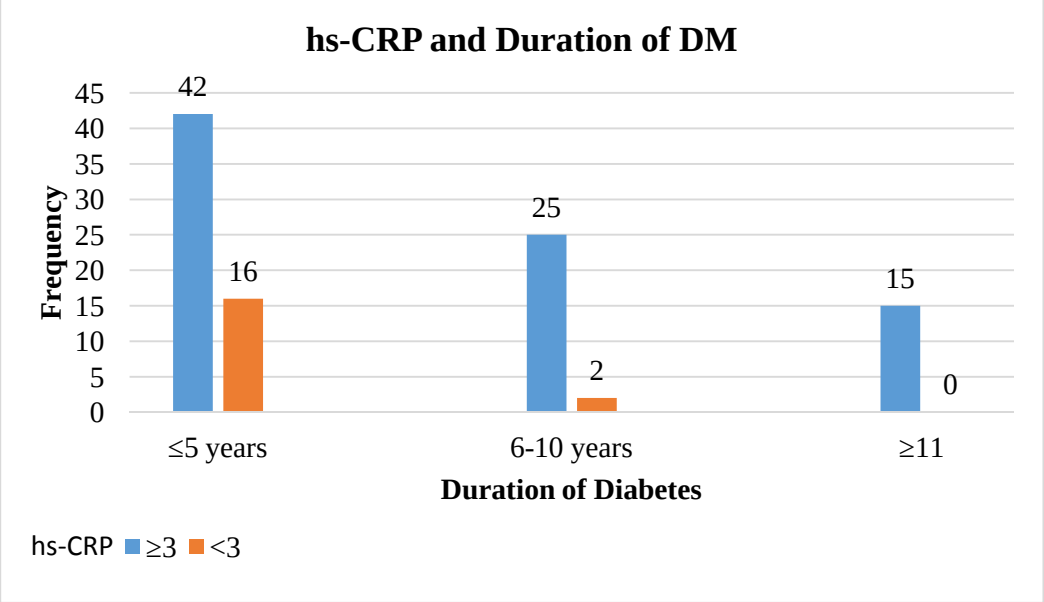


In our study hs-CRP levels were found to be in-dependent of Gender p value 0.578

Table 10: Association of hs-CRP with Duration of Diabetics of study population (N=100)

Duration of Diabetics Mellitus	hs-CRP (mg/ltr)		Chi square	P-value
	≥3.0(N=82)	<3.0(N=18)		
≤5 years	42 (51.22%)	16 (88.89%)	8.956a	0.011
6-10 years	25 (30.49%)	2 (11.11%)		
≥11	15 (18.29%)	0 (0%)		

Figure 10: Association of hs-CRP with Duration of Diabetics of study population (N=100)

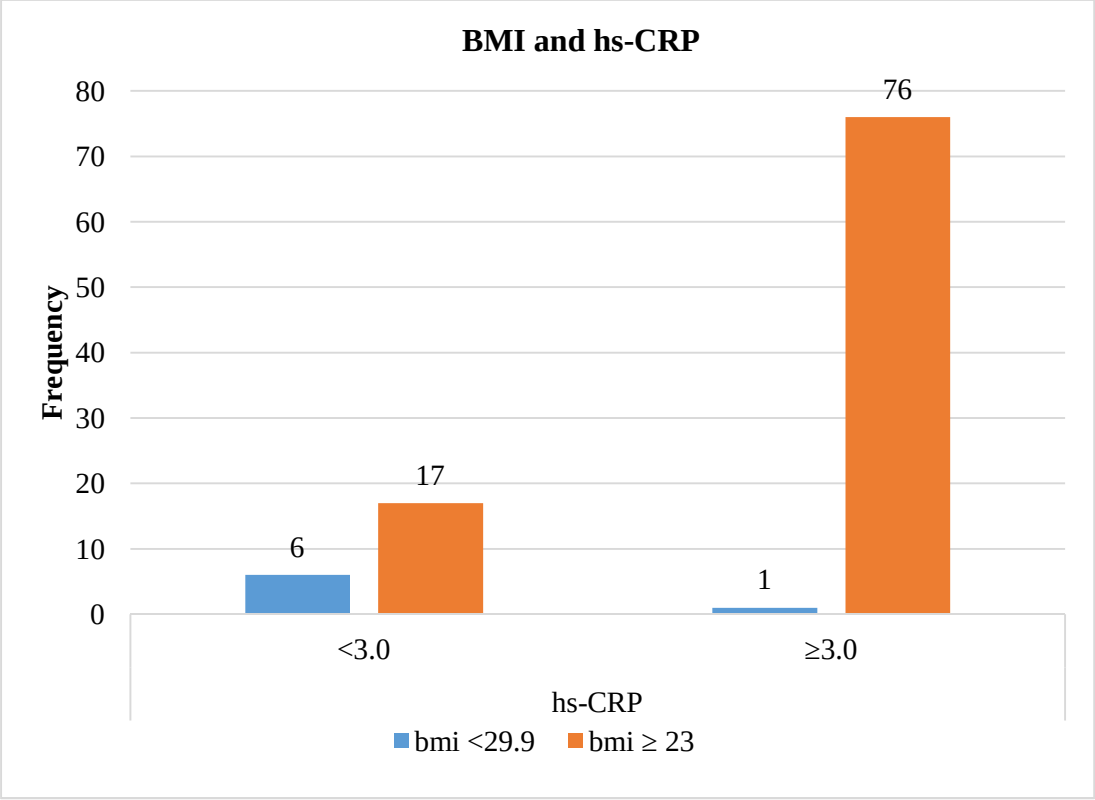


In our study hs-CRP levels were found to be significant with increasing duration of DM p value 0.011

Table 11: association of hs-CRP with BMI of study population (N=100)

BMI(kg/m²)	hs-CRP (mg/ltr)		P-value
	≥3.0(N=77)	<3.0(N=23)	
<23.0	1	6	0.0003
≥23.0	76	17	

Figure 11: bar chart showing the association of hs-CRP and BMI

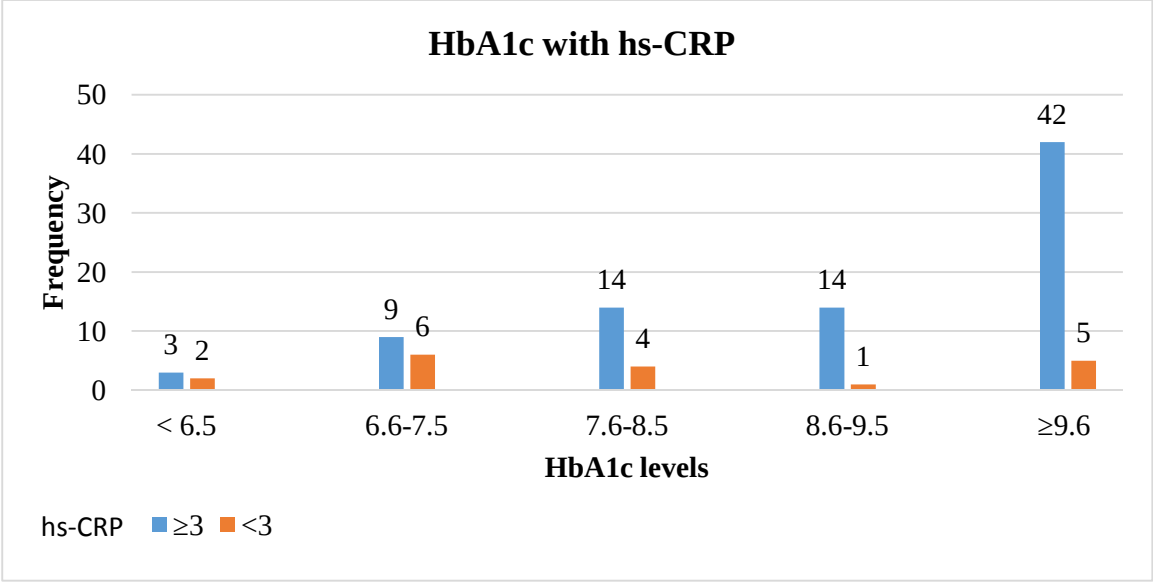


There was a significant association between hs-CRP and increasing levels of BMI. P-value 0.0003 (very significant)

Table 12: Association of hs-CRP with HbA1c levels of study population (N=100)

HbA1c (%)	hs-CRP (mg/ltr)		Chi square	P-value
	≥3.0(N=82)	<3.0(N=18)		
< 6.5	3 (3.66%)	2 (11.11%)	9.807a	0.044
6.6-7.5	9 (10.98%)	6 (33.33%)		
7.6-8.5	14 (17.07%)	4 (22.22%)		
8.6-9.5	14 (17.07%)	1 (5.56%)		
≥9.6	42 (51.22%)	5 (27.78%)		

Figure 12: Association of hs-CRP with HbA1c levels of study population (N=100)



In our study hs-CRP levels were found to significant with increasing levels of HbA1c p value of 0.044

DISCUSSION

In our cross sectional study we enrolled 100 patients who were known diabetics or recently detected and stratified them to demographic, duration of T2DM, BMI, FBS, HbA1c and hs-CRP.

In our study we observed the maximum percentage of patients with DM were in the age group of 36-50 years (41%) followed by 51-65 years (36%). The youngest patient to be enrolled in our study was of 20 years and the maximum age patient was of 89 years, our study had similar statistics to a study done by Mustafa Nafea Al Kubais et al.[155]

In our study we had observed the male population of 72% and female population of 28% with male to female ratio to be 2.57:1 showing a male preponderance, our study was similar to a study conducted by M.Venkateshwarlu et al.[156]

In our study maximum patients had HbA1c greater than 9.6 (47%) with a mean HbA1c level that was observed is 9.86 in our study population, 19.90 was the maximum reading of HbA1c observed and 4.90 was the lowest. Our study had similar figure to a study done by Nitin Sinha et al.[157]

In our study we observed 82% had hs-CRP levels ≥3.0 and 18% had hs-CRP levels <3.0, of this maximum was 351.1 and the lowest was 0.2. Our study was in concordance with a similar study done by Yildiz Tutuncu et al.[158]

We also observed Maximum number of patients had Diabetes less than 5 years 58% followed by 6-10 years 27%, 11 years and above 15% which was similar study done by N. Krishna Mohan et al.[159]

In our study we observed patients who had a BMI ≥ 23 were 93% and patients with a BMI < 23 were 7%, as according to the new Indian standard guidelines BMI ≥ 23 considered overweight, our study was in concordance with a similar study S. Behl et al.[160]

In our study we could not establish a correlation of hs-CRP and different age groups of our study sample, although patients above 66 years none of them had hs-CRP level <3.0 (normal). Our study has shown a similar result to a previous study conducted by Luciana m. Lima et al, which had also concluded hs-CRP and mean age had a non-significant p-value.[161]

Similarly we could not find a correlation between hs-CRP and gender in our study sample, in the male population 83% had hs-CRP levels ≥ 3.0 and 17% males had a hs-CRP < 3.0. Similarly in the female population 78% had hs-CRP ≥ 3.0 and 21% had hs-CRP < 3.0. Our study was in direct contrast by similar studies by Alemzadeh R et al and Nehal N. Mehta et al, [162,163] have concluded that females have a higher hs-CRP levels than males, this significance in their study is due to a bigger sample size N=199 and N=1299 respectively and due to our small samples size of N=100 we could not establish a significant p-value (0.578).

In our study we established a correlation between hs-CRP and duration of Diabetes (p-value 0.011), in our statics we had the maximum percentage of 42% samples in hs-CRP ≥ 3.0 with a duration of ≤ 5 years of diabetes and 16% had hs-CRP < 3.0, and in duration of 6-10 years hs-CRP ≥ 3.0 and hs-CRP < 3.0 is 25%, 2% respectively. With duration ≥ 11 years hs-CRP ≥ 3.0 and hs-CRP < 3.0 is 15%, 0% respectively. In our study hs-CRP levels < 3.0 was 0% in patients who have T2DM for more than 11 years indicating that longer duration of DM will have a positive impact on endothelial

injury. Similar multiple studies have proved a correlation between hs-CRP and duration of Diabetes by Mukesh G. Gohel et al and Minna Soinio et al, (p-value < 0.001), (p-value 0.002) respectively. [164,165]

We also established a very significant correlation (p-value 0.0003) between hs-CRP and BMI, in our study BMI < 23.0 (normal weight) had a hs-CRP ≥ 3.0 (1%) and hs-CRP < 3.0 (6%), on the other hand BMI ≥ 23.0 had a hs-CRP ≥ 3.0 (76%) and hs-CRP <3.0 (17%). Patients who are diabetic and also overweight have higher levels of hs-CRP. Similar studies have shown a significant correlation by Sarinnapakorn V et al.[166]

In our study we established a correlation between hs-CRP and increasing levels of HbA1c (p-value 0.044), highest number of hs-CRP ≥ 3.0 (42%) was in HbA1c levels ≥ 9.6. our study elicited that; poorer the glycemic control in individuals will have a higher level of hs-CRP, similar studies have been done in the past by Dana E. King et al and Pallavi Anand et al having a p-value 0.03, 0.001 respectively[167,168]

CONCLUSION

In our study we enrolled 100 cases who were diabetic,

- We observed majority of cases 41% in the age group of 36-50 years.
- In our study male population was 72% with a male to female ratio of 2.57:1 (male preponderance)
- None of our cases had any other co-morbidity except for T2DM, co-morbidity were ruled out by normal ECG, CBC, RFT, LFT, URINE EXAMINATION and FUNDOSCOPY and even any patients taking medication that could influence the level of hs-CRP.
- Maximum of the patients had poor glycaemic control with 47% of cases had HbA1c levels more than 9.6.
- Most of our DIABETIC patients had ahs-CRP levels ≥ 3.0 (82%) and remaining cases had hs-CRP levels < 3.0 (12%)
- Most number of our cases had duration of T2DM ≤5 years of duration 58%, followed by 27% in the duration of 6-10 years and 15% who had a duration of ≥ 11 years.
- We observed most of our cases had a higher BMI according to Indian standardised BMI ≥ 23kg/m² 93% and BMI < 23 kg/m² 7%.
- hs-CRP was not influenced by age of the patients, but in our study cases above 66 years of age all had hs-CRP ≥ 3.0.
- our study did not show any correlation of hs-CRP and gender
- hs-CRP and duration of Diabetes had a significant correlation in our study (p-value 0.011)

- our study showed a very significant correlation of hs-CRP and BMI, BMI ≥ 23 had 76% with raised hs-CRP ≥ 3.0
- in our study we observed that poor glycaemic control leads to a higher hs-CRP ≥ 3.0 levels
- we concluded that hs-CRP was influenced by duration of diabetes, BMI and poor glycaemic control.

LIMITATIONS

- Due to the cross-sectional design of the study and small sample size, we cannot infer from these results a cause and effect relation, i.e., whether poor glycemic control leads to inflammation or whether inflammation leads to higher glucose levels (or whether a third factor influences both).
- If poor glycemic control leads to inflammation, then better glycemic control should lower inflammation and therefore lower the risk of cardiovascular complications.
- If inflammation leads to poor glycemic control, then treatment of inflammation with NSAIDs or hydroxyl-methyl-glutaryl-CoA reductase inhibitors may help improve glycemic control.
- Prospective studies are needed to evaluate that question.

SUMMARY

The present study of 100 patients with T2DM studied in the Department of Medicine, KLE'S Dr.Prabhakar Kore Hospital and Medical Research Centre, Belgaum were studied between January 2016 and December 2016, to find a correlation between poor glycemic control and the role of inflammatory marker ie. HbA1c and hs-CRP respectively.

In our study we could not elicit statistical significance between hs-CRP with AGE of our patients even though patients above 65 years all had hs-CRP levels ≥ 3.0 and GENDER.

But we concluded hs-CRP levels ≥ 3.0 was very significant with BMI ≥ 23.0 kg/m^2.

hs-CRP levels was also affected by duration of diabetes and poor glycemic control (HbA1c).

The result we concluded that hs-CRP was affected by longer duration of diabetes, poor glycemic control and high BMI.

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ANNEXURE - I - INFORMED CONSENT

Title of Research Study:"A Study of Highly Sensitive C-Reactive Protein (hs-CRP) in Type 2 Diabetes Mellitus and its Correlation with Glycosylated Hemoglobin (HbA1C) at Tertiary Care Centre**." – A ONE YEAR HOSPITAL BASED CROSS SECTIONAL STUDY."**

Principal Investigator:-

Dr.

Post Graduate Student,

Department Of General Medicine,

J.N.Medical College, Belagavi.

Introduction and Purpose:-

- There is a rising prevalence of non –communicable diseases in developing countries like India especially Diabetes Mellitus with more than 50% percent of diabetic patients being unaware of their diabetic status in India.
- The rise in Diabetes in India can be attributed to genetic predisposition, the sedentary lifestyles and changing food habits.
- Type II diabetes is disease in which blood sugar level increases the shear stress contributing to inflammation and dysfunction of endothelium leading to coronary artery disease and strokes.
- The purpose of this study was to identify the relationship between serum hs-CRP and HbA1c in type II diabetic subjects.

Procedure:

If you agree to be part of the research study, you will be asked the relevant history and will be subjected to relevant clinical examination and investigations. You will also have to give blood samples for the necessary investigations.

Risk and Benefits:

The only risk and possible discomfort you might get is while taking blood from arm for the investigations. It may cause slight discomfort at the site from where the blood is drawn from.

Benefits proper controlling of sugars and other risk factors contributing to unstable sugars and to whether to start on anti-inflammatory drugs.

Alternatives:

Taking part in this study is voluntary. You may choose not to take part in this study, or if you decide to take part you can later change my mind and withdraw from the study. Your decision will not change the present or future health care or other services that you receive. The study doctor or sponsor may stop your participation in this study at any time. If you choose not to take part in the study, you will receive the standard treatment for patients with your condition.

Privacy and Confidentiality:

All information collected about you during the course of this study will be kept confidential to the extent permitted by law. The code numbers will identify you in this research record. Information from this study may be published but your identity will be confidential in any publication.

Institution / Sponsor's policy:

Does not apply to this research

Financial incentives for participation:

You will not be paid / offered any gifts /incentives for participating in the study.

Authorization to publish the results:

The results of the study would be forwarded to the KLE University, Belgaum as part of requirement towards the completion of MD degree, review and publishing. In case of the queries during study or in future you may contact following persons,

Study participant kindly contact:

DR. GANGA S PILLI,
Professor of Pathology & Chairman,
JNMC Institutional Ethics Committee
On Human Subjects Research,
J.N. Medical College, Belagavi.
Ph no. 9480275601

Consent Statement

I voluntarily agree to take part in this study by signing below. I may withdraw at any time. I am not giving up any of my legal rights by signing this form. My signature below indicates that I have read, or it has been read to me, this entire consent form, and have had all my questions answered.

Name of the Participant : _____ Signature / Thumb print _____

Name of the Witness _____Signature/ Thumb print _____

Investigator Name: _____Signature :_____

Date:

Place

ANNEXURE - II - PROFORMA

Cross Sectional Study of Highly Sensitive C-Reactive Protein (Hs-Crp) In Type 2 Diabetes Mellitus And Its Correlation With Glycosylated Hb (HbA1C) At Tertiary Care Centre.

Case No:

NAME:

AGE/SEX:

IP/OP No.

ADDRESS:

OCCUPATION:

COMPLAINTS AT PRESENTATION:

RISK FACTORS

DIAGNOSIS:

PHYSICAL EXAMINATION: Patient will undergo complete general physical examination

VITALS:

Temperature: FEBRILE/AFEBRILE

Pulse:

Respiratory rate:

Blood pressure:

GCS:

SYSTEMIC EXAMINATION:

CVS:

RS:

PA:

CNS:

INVESTIGATIONS:

HbA1C

hsCRP

CBC

LIVER FUNCTION TEST

MINI RENAL

URINE ROUTINE/MICROSCOPY

ECG

FUNDOSCOPY

ANNEXURE - III - KEY TO MASTER CHART

f	Female
m	Male
Hb	Hemoglobin
Tlc	Total Leukocyte Count
P.S.	Peripheral Smear
nn	Normocytic normochromic
ESR	Erythrocyte Sedimentation Rate
TB	Total Bilirubin
DB	Direct Bilirubin
SGOT	Serum Glutamic-Oxaloacetic Transaminase (AST)
SGPT	Serum Glutamic Pyruvic Transaminase (ALT)
ALP	Alkaline Phosphatate
N	Normal
T2DM	Type 2 Diabetes Mellitus

serial number	ip/op number	address	occupation	sex	age	name	HbA1c			hs - CRP		duration of DM	duration of drinking	fbs	bmi	IHD	duration of smoking	complete blood count					liver function test							MINI RENAL		URINE		Fundoscopy	diagnosis	ECG
							<5.6	5.7 - 6.4	>6.5	<3.0	>3.0							hb	tlc	platelet	p.s	ESR	TB	DB	SGPT	SGOT	ALP	TOTAL PROTEIN	ALBUMIN	UREA	CREATININE	PROTEINS	SUGARS			
1	3852040	belgaum	housewife	f	65	pushpa			10.6		189.2	12 years	nil	235	27	nil	nil	12.6	4.3	2.3	nn	10	0.9	0.6	33	24	123	6.3	3.7	14	1.1	-	+	N	T2DM	normal
2	729482	belgaum	business	m	50	shoukatbaig			9.1		86.5	10 years	nil	178	23.8	nil	nil	12.3	5.6	2.9	nn	11	0.7	0.6	37	8	122	6.7	4.1	15	1	-	+	N	T2DM	normal
3	728741	belgaum	student	m	21	chetan			13.2		30.5	5 years	1 year	168	24.8	nil	nil	14.1	7.2	3.3	nn	14	0.8	0.7	42	32	48	6.6	3.9	19	0.75	-	-	N	T2DM	normal
4	3638156	belgaum	farmer	m	67	shankar			10.2		3.3	2 years	5 years	231	25.7	nil	nil	13.6	7.4	1.8	nn	15	0.9	0.7	12	38	52	6.8	4.9	15	0.66	-	-	N	T2DM	normal
5	3683864	belgaum	farmer	m	46	irappa			11.6	1.5		recently detected	nil	192	26.1	nil	nil	12.8	6.6	4.1	nn	14	1.1	0.6	26	22	56	6.7	4.1	23	0.95	-	-	N	T2DM	normal
6	3847424	belgaum	housewife	f	50	ningavva			15.1		23.5	6 years	nil	333	22.5	nil	nil	12.3	7.2	2.6	nn	10	1.2	0.9	38	26	77	6.2	4.2	15	1.17	-	-	N	T2DM	normal
7	3847362	belgaum	farmer	m	60	bhimappa			12.9		108.6	4 years	nil	267	26.7	nil	nil	13.2	4.5	2.1	nn	8	0.9	0.8	44	33	88	6.9	4.1	21	1.28	-	-	N	T2DM	normal
8	728678	belgaum	retired	m	70	gurnagouda			9		3.6	2 years	7 years	234	28.4	nil	nil	13.6	9.2	1.7	nn	26	0.9	0.7	18	27	67	7.3	3.3	19	0.89	-	-	N	T2DM	normal
9	3689221	belgaum	business	m	40	santosh			9.1	2.5		recently detetced	3 years	186	26.3	nil	nil	13.8	4.9	2.6	nn	17	0.7	0.4	51	29	76	7.2	3.7	20	0.66	-	-	N	T2DM	normal
10	728358	belgaum	farmer	m	56	annappa		6.3			14.9	5 years	nil	167	27.5	nil	nil	12.5	5.2	3.3	nn	11	0.7	0.4	34	11	54	6.9	3.9	14	0.87	-	++	N	T2DM	normal
11	725714	belgaum	farmer	m	38	ganesh	4.9				47.7	1 year	nil	205	24.7	nil	nil	12.9	6.9	3.45	nn	4	0.8	0.6	32	34	89	6.4	4.2	16	0.88	-	-	N	T2DM	normal
12	3911792	belgaum	housewife	f	45	shivakka			19.9	0.7		4 years	nil	178	27.9	nil	nil	13.2	4.8	1.9	nn	7	0.8	0.7	36	44	69	6.6	4.6	15	0.75	-	-	N	T2DM	normal
13	3928518	belgaum	farmer	m	65	mallesh			8.1		79.9	8 years	occasional	156	25.6	nil	nil	12.5	5.5	1.45	nn	14	0.9	0.8	12	21	121	6.9	5	18	1.14	-	-	N	T2DM	normal
14	3929912	belgaum	farmer	m	70	nagappa	5.6				124	2 years	occasional	201	26.1	nil	nil	12.1	6.2	2.3	nn	17	0.7	0.6	44	38	140	7.2	5.2	19	1.26	-	-	N	T2DM	normal
15	4438796	chikkodi	farmer	m	55	abdul			8.3		10.6	8 years	occasional	256	25.3	nil	nil	12.2	7.3	1.7	nn	10	1.1	0.8	46	23	112	7.4	4.7	23	0.98	-	-	N	T2DM	normal
16	4438816	belgaum	housewife	f	65	ganagavva			6.9		3	6 years	nil	264	26.3	nil	nil	13.6	8.8	3.5	nn	11	1.2	0.8	52	13	116	7.8	4.9	17	0.75	-	-	N	T2DM	normal
17	4436414	belgaum	housewife	f	40	sulochana			10.5		12.6	10 years	nil	174	27.3	nil	nil	13.9	8.4	2.9	nn	14	0.9	0.7	9	33	107	7.7	4.1	19	0.87	-	-	N	T2DM	normal
18	3239355	belgaum	housewife	f	50	ningawwa			11.5		18.3	12 years	nil	154	24.8	nil	nil	12.2	9.2	2.1	nn	20	0.7	0.5	36	33	82	6.4	4.1	17	0.69	-	-	N	T2DM	normal
19	1849489	belgaum	housewife	f	65	krishnabai			10.8		5.7	8 years	nil	234	23.2	nil	nil	13.2	9.1	2	nn	18	1.2	0.9	38	19	86	6.9	4.8	14	0.99	-	-	N	T2DM	normal
20	4438753	belgaum	housewife	f	35	sushila			7.9	2.7		1 year	nil	207	22.9	nil	nil	13.8	4.6	3.55	nn	10	1.1	0.8	42	22	104	6.3	3.9	16	1	-	-	N	T2DM	normal
21	44437946	belgaum	farmer	m	50	shivaji			9.4		4.9	5 years	occasional	367	23.8	nil	nil	12.6	4.8	2.3	nn	17	0.9	0.6	45	11	68	6.2	4	23	1.1	-	-	N	T2DM	normal
22	4434039	belgaum	housewife	f	34	laxmi			7.1	2.7		1 year	nil	180	24.3	nil	nil	12.6	5.1	2.9	nn	20	0.8	0.7	51	8	79	6.3	4.7	14	0.62	-	-	N	T2DM	normal
23	4436404	belgaum	farmer	m	60	hondappa			8.1		3.2	3 years	occasional	157	26.7	nil	nil	12.3	4.3	3.3	nn	17	0.7	0.6	26	15	134	7.7	4.3	15	1	-	-	N	T2DM	normal
24	4438798	belgaum	housewife	f	58	chandibai			13.9	2.2		2 years	nil	203	24.6	nil	nil	14.1	5.7	1.8	nn	11	1.2	1.1	27	35	64	7.1	4.4	14	0.7	-	-	N	T2DM	normal
25	4438792	belgaum	business	m	35	suresh			6.8	1		6 months	nil	211	26.8	nil	nil	13.6	4.2	4.1	nn	4	0.5	0.3	43	25	79	6	3.6	17	0.8	-	++	N	T2DM	normal
26	764349	belgaum	farmer	m	42	nandakumar			11.7		351.1	12 years	occasional	146	26.8	nil	nil	12.8	4.3	2.6	nn	7	1.1	0.9	37	27	88	6.7	4.2	16	0.6	-	-	N	T2DM	normal
27	764451	belgaum	farmer	m	58	shivayya			11.3	1.1		8 years	nil	167	25.8	nil	nil	12.3	5.6	2.1	nn	14	0.7	0.5	18	39	62	8	5.2	19	0.65	-	-	N	T2DM	normal
28	768106	belgaum	driver	m	45	jameel			10.7		146.4	recently detected	nil	184	29.7	nil	nil	13.2	7.2	1.7	nn	17	0.9	0.6	27	36	51	6.3	3.4	20	0.66	-	-	N	T2DM	normal
29	766589	belgaum	farmer	m	65	motichand			7.5		139.4	18 years	occasional	152	24.6	nil	nil	13.6	7.4	2.6	nn	10	0.5	0.4	24	12	92	6.2	3.2	23	0.78	-	-	N	T2DM	normal
30	795642	belgaum	housewife	f	49	sunita			10.1		3.9	6 years	nil	173	27	nil	nil	13.8	6.6	3.3	nn	11	1.2	1.1	33	17	49	6.1	3.3	18	0.77	-	-	N	T2DM	normal
31	801329	belgaum	farmer	m	51	govind			14.7		4	4 years	2 years	192	23.8	nil	nil	12.5	7.2	3.45	nn	14	0.7	0.5	27	40	74	6.5	3.5	14	0.98	-	-	N	T2DM	normal
32	3538492	belgaum	farmer	m	47	basavaraj			6.7		195.5	6 years	nil	210	24.8	nil	nil	12.9	4.5	1.9	nn	20	1.1	1	34	9	89	6.9	3.7	17	0.93	-	-	N	T2DM	normal
33	4436206	belgaum	housewife	f	40	basava			12.9		9.3	12 years	nil	235	25.7	nil	nil	13.2	9.2	1.45	nn	18	0.9	0.8	41	6	69	6.9	4.2	19	0.72	-	-	N	T2DM	normal
34	1849487	chikkodi	business	m	70	appasaheb			14.9		6.6	6 years	12 years	178	26.1	nil	nil	12.5	4.9	2.3	nn	10	0.8	0.7	46	41	93	6.2	5.2	23	0.75	-	-	N	T2DM	normal
35	4436567	belgaum	farmer	m	70	vishnu			12.3		24.5	8 years	nil	168	22.5	nil	nil	12.1	5.2	1.7	nn	17	0.9	0.8	44	10	72	6.6	3.7	14	0.64	-	-	N	T2DM	normal
36	3367512	belgaum	farmer	m	57	basappa			9.2		23.4	12 years	nil	231	26.7	nil	nil	12.2	6.9	3.5	nn	20	0.7	0.6	38	20	81	7.4	3.5	17	0.82	-	-	N	T2DM	normal
37	4421055	belgaum	business	m	47	guruappa			7.6	2.9		2 years	2 years	192	28.4	nil	nil	13.6	4.8	2.9	nn	10	1.2	1.1	39	30	108	7.2	3.9	22	0.94	-	-	N	T2DM	normal
38	4435727	belgaum	business	m	45	nataraj			10.2		3.8	3 years	nil	333	26.3	nil	nil	13.9	5.5	2.1	nn	11	0.8	0.6	12	40	94	7.5	3.2	12	0.94	-	-	N	T2DM	normal
39	4428994	belgaum	driver	m	38	hemant			6.7		3.3	2 years	nil	267	27.5	nil	nil	12.2	6.2	2	nn	14	0.6	0.4	16	32	73	7.7	3.6	16	0.76	-	-	N	T2DM	normal
40	4428964	belgaum	business	m	62	rakesh			8.9		10.6	10 years	nil	234	24.7	nil	nil	13.2	7.3	3.55	nn	15	0.9	0.6	26	21	134	7.4	3.9	17	0.79	-	-	N	T2DM	normal
41	4205333	belgaum	business	m	35	pramod			6.8		3.9	2 years	nil	186	27.9	nil	nil	13.8	8.8	3.5	nn	14	0.9	0.6	33	24	123	6.3	3.7	14	1.1	-	+	N	T2DM	normal
42	3755432	belgaum	farmer	m	56	shivaputra			8.4		12.6	14 years	5 years	167	25.6	nil	nil	12.6	8.4	2.9	nn	10	0.7	0.6	37	8	122	6.7	4.1	15	1	-	+	N	T2DM	normal
43	4428968	belgaum	farmer	m	53	md sharif			11.6	2.6		recently detected	nil	205	26.1	nil	nil	13.6	9.2	2.1	nn	8	0.8	0.7	42	32	48	6.6	3.9	19	0.75	-	-	N	T2DM	normal
44	3870311	belgaum	business	m	48	sarfraz			8.2		6.2	4 years	nil	178	25.3	nil	nil	13.8	9.1	2	nn	17	0.9	0.7	12	38	52	6.8	4.9	15	0.66	-	-	N	T2DM	normal
45	4428423	chikkodi	farmer	m	58	mangal			9.2		3.9	12 years	nil	156	26.3	nil	nil	12.5	4.6	3.55	nn	11	1.1	0.6	26	22	56	6.7	4.1	23	0.95	-	-	N	T2DM	normal
46	2644877	belgaum	business	m	45	satish			9.9		5	8 years	nil	201	27.3	nil	nil	12.9	4.8	2.3	nn	4	1.2	0.9	38	26	77	6.2	4.2	15	1.17	-	-	N	T2DM	normal
47	4435841	belgaum	housewife	f	65	channama	5.2			2.1		1 year	nil	256	24.8	nil	nil	13.2	5.1	2.9	nn	7	0.9	0.8	44	33	88	6.9	4.1	21	1.28	-	-	N	T2DM	normal
48	4437934	belgaum	housewife	f	40	shainaj			12.6		3.9	3 years	nil	264	23.2	nil	nil	12.5	4.3	3.3	nn	14	0.9	0.7	18	27	67	7.3	3.3	19	0.89	-	-	N	T2DM	normal
49	4393703	belgaum	housewife	f	32	chandralata			6.7		3.6	5 years	nil	174	22.9	nil	nil	12.1	5.7	1.8	nn	17	0.7	0.4	51	29	76	7.2	3.7	20	0.66	-	-	N	T2DM	normal
50	4426253	belgaum	farmer	m	59	sharad			8.1		8.6	8 years	3 years	154	23.8	nil	nil	12.2	4.2	4.1	nn	10	0.7	0.4	34	11	54	6.9	3.9	14	0.87	-	++	N	T2DM	normal
51	3843604	belgaum	farmer	m	60	krishna			18.6		26.8	11 years	nil	234	24.3	nil	nil	13.6	6.9	2.6	nn	11	0.8	0.6	32	34	89	6.4	4.2	16	0.88	-	-	N	T2DM	normal
52	4436414	belgaum	housewife	f	46	sulochana			9.7		9	5 years	nil	207	26.7	nil	nil	13.9	4.8	2.1	nn	14	0.8	0.7	36	44	69	6.6	4.6	15	0.75	-	-	N	T2DM	normal
53	4435856	belgaum	housewife	f	47	padmavati			8.6		7.7	3 years	nil	367	24.6	nil	nil	12.2	5.5	1.7	nn	20	0.9	0.8	12	21	121	6.9	5	18	1.14	-	-	N	T2DM	normal
54	4394633	belgaum	farmer	m	83	vasant			10.6		9.3	15 years	occasional	180	26.8	nil	nil	13.2	6.2	2.6	nn	18	0.7	0.6	44	38	140	7.2	5.2	19	1.26	-	-	N	T2DM	normal
55	3436155	belgaum	housewife	f	43	vanishri			8.1		3	2 years	nil	157	26.8	nil	nil	13.8	7.3	3.3	nn	10	1.1	0.8	46	23	112	7.4	4.7	23	0.98	-	-	N	T2DM	normal
56	4437146	belgaum	farmer	m	65	nazera			10.2		5.4	4 years	nil	203	25.8	nil	nil	12.6	8.8	1.45	nn	17	1.2	0.8	52	13	116	7.8	4.9	17	0.75	-	-	N	T2DM	normal
57	4399176	belgaum	farmer	m	55	noushad			11.6		6.4	6 years	nil	211	29.7	nil	nil	12.6	8.4	2.3	nn	20	0.9	0.7	9	33	107	7.7	4.1	19	0.87	-	-	N	T2DM	normal
58	4296031	belgaum	farmer	m	60	anil			9.1		5.1	10 years	11 years	146	24.6	nil	nil	12.3	9.2	1.7	nn	17	0.7	0.5	36	33	82	6.4	4.1	17	0.69	-	-	N	T2DM	normal
59	4436708	belgaum	business	m	62	bhavakanna			18.7		13.3	14 years	nil	167	25.6	nil	nil	14.1	9.1	3.5	nn	11	1.2	0.9	38	19	86	6.9	4.8	14	0.99	-	-	N	T2DM	normal
60	2906377	belgaum	retired	m	89	basawaneppa			14.7		4.8	20 years	nil	184	26.1	nil	nil	13.6	4.6	2.9	nn	4	1.1	0.8	42	22	104	6.3	3.9	16	1	-	-	N	T2DM	normal
61	4428384	belgaum	driver	m	35	tippeswamy			8.3		6.6	2 years	nil	152	25.3	nil	nil	12.8	4.8	2.1	nn	7	0.9	0.6	45	11	68	6.2	4	23	1.1	-	-	N	T2DM	normal
62	4428390	belgaum	farmer	m	40	appasab			7.4		3.1	2 years	occasional	173	26.3	nil	nil	12.3	5.1	2	nn	14	0.8	0.7	51	8	79	6.3	4.7	14	0.62	-	-	N	T2DM	normal
63	4429002	belgaum	farmer	m	60	ayyappa			8.8		5.2	5 years	4 years	192	27.3	nil	nil	13.2	4.3	3.55	nn	17	0.7	0.6	26	15	134	7.7	4.3	15	1	-	-	N	T2DM	normal
64	4428911	chikkodi	business	m	37	sidaray			6.6	2.3		recently detected	nil	210	24.8	nil	nil	13.6	5.7	3.5	nn	10	1.2	1.1	27	35	64	7.1	4.4	14	0.7	-	-	N	T2DM	normal
65	4250772	belgaum	farmer	m	49	riyazahmed			12.6		8.8	4 years	nil	174	23.2	nil	nil	13.8	4.2	2.9	nn	11	0.5	0.3	43	25	79	6	3.6	17	0.8	-	++	N	T2DM	normal
66	1270612	belgaum	business	m	65	mallappa			9.2		4.8	8 years	nil	154	22.9	nil	nil	12.5	4.3	2.1	nn	14	1.1	0.9	37	27	88	6.7	4.2	16	0.6	-	-	N	T2DM	normal
67	4421639	belgaum	housewife	f	37	sapnaanand			14.7		4.9	1 year	nil	234	23.8	nil	nil	12.9	5.6	2	nn	20	0.7	0.5	18	39	62	8	5.2	19	0.65	-	-	N	T2DM	normal

serial number	ip/op number	address	occupation	sex	age	name	HbA1c			hs - CRP		duration of DM	duration of drinking	fbs	bmi	IHD	duration of smoking	complete blood count					liver function test							MINI RENAL		URINE		Fundoscopy	diagnosis	ECG
							<5.6	5.7 - 6.4	>6.5	<3.0	>3.0							hb	tlc	platelet	p.s	ESR	TB	DB	SGPT	SGOT	ALP	TOTAL PROTEIN	ALBUMIN	UREA	CREATININE	PROTEINS	SUGARS			
68	4428456	belgaum	business	m	45	sanjay			8.6		4.1	3 years	nil	207	24.3	nil	nil	13.2	7.2	3.55	nn	18	0.9	0.6	27	36	51	6.3	3.4	20	0.66	-	-	N	T2DM	normal
69	1022003	belgaum	farmer	m	54	sabappa			8.1	2.2		6 years	nil	367	26.7	nil	nil	12.5	7.4	2.3	nn	10	0.5	0.4	24	12	92	6.2	3.2	23	0.78	-	-	N	T2DM	normal
70	4437901	belgaum	business	m	60	ullasa			13.2		56.7	12 years	occasional	180	24.6	nil	nil	12.1	6.6	2.9	nn	17	1.2	1.1	33	17	49	6.1	3.3	18	0.77	-	-	N	T2DM	normal
71	4435720	belgaum	farmer	m	49	bismilla			10.8		13.1	7 years	nil	157	26.8	nil	nil	12.1	7.2	4.1	nn	20	0.7	0.5	27	40	74	6.5	3.5	14	0.98	-	-	N	T2DM	normal
72	4393706	belgaum	farmer	m	33	abhijeet			9.9		5.7	1 year	nil	203	26.8	nil	nil	12.2	4.5	2.6	nn	10	1.1	1	34	9	89	6.9	3.7	17	0.93	-	-	N	T2DM	normal
73	4428329	belgaum	student	m	28	siddarth			8.8		3.3	recently detected	nil	211	25.8	nil	nil	13.6	9.2	2.1	nn	11	0.9	0.8	41	6	69	6.9	4.2	19	0.72	-	-	N	T2DM	normal
74	4296331	belgaum	housewife	f	57	gangawwa			6.8		3.6	6 years	nil	146	29.7	nil	nil	13.9	4.9	1.7	nn	14	0.8	0.7	46	41	93	6.2	5.2	23	0.75	-	-	N	T2DM	normal
75	3430336	belgaum	business	m	49	balchandra			7.8	2		5 months	nil	167	24.6	nil	nil	12.2	5.2	2.6	nn	15	0.9	0.8	44	10	72	6.6	3.7	14	0.64	-	-	N	T2DM	normal
76	3183616	belgaum	housewife	f	80	kashawwa			10.6		10.2	22 years	nil	184	27	nil	nil	13.2	6.9	3.3	nn	14	0.7	0.6	38	20	81	7.4	3.5	17	0.82	-	-	N	T2DM	normal
77	4373563	chikkodi	driver	m	65	shivaputra			7.9		4.8	9 years	nil	152	23.8	nil	nil	13.8	4.8	1.45	nn	10	1.2	1.1	39	30	108	7.2	3.9	22	0.94	-	-	N	T2DM	normal
78	4255759	belgaum	labourer	m	62	marembi			9.6		8.3	5 years	nil	173	24.8	nil	nil	12.6	5.5	2.3	nn	8	0.8	0.6	12	40	94	7.5	3.2	12	0.94	-	-	N	T2DM	normal
79	3644247	belgaum	student	m	20	sagar		5.8		0.2		recently detected	nil	192	25.7	nil	nil	13.6	6.2	1.7	nn	17	0.6	0.4	16	32	73	7.7	3.6	16	0.76	-	-	N	T2DM	normal
80	2385392	belgaum	housewife	f	50	yallama			13.6		4.1	8 years	nil	210	26.1	nil	nil	13.8	7.3	3.5	nn	11	0.9	0.6	26	21	134	7.4	3.9	17	0.79	-	-	N	T2DM	normal
81	4341632	belgaum	housewife	m	67	gangappa			11.2		3.9	3 years	occasional	235	22.5	nil	nil	12.5	8.8	2.9	nn	4	0.9	0.7	9	33	107	7.7	4.1	19	0.87	-	-	N	T2DM	normal
82	2887768	belgaum	farmer	m	48	shankar			10.4		3.9	4 years	nil	178	26.7	nil	nil	12.9	4.6	2.1	nn	7	0.7	0.5	36	33	82	6.4	4.1	17	0.69	-	-	N	T2DM	normal
83	4315546	chikkodi	business	m	56	jija			8.2		7.7	6 years	nil	168	28.4	nil	nil	13.2	4.8	2	nn	14	1.2	0.9	38	19	86	6.9	4.8	14	0.99	-	-	N	T2DM	normal
84	4429005	belgaum	housewife	f	40	anita			6.7		3	1 year	nil	231	26.3	nil	nil	12.5	5.1	3.55	nn	17	1.1	0.8	42	22	104	6.3	3.9	16	1	-	-	N	T2DM	normal
85	4428366	hubbali	housewife	f	50	hanamawwa			16.3		4.5	4 years	nil	192	27.5	nil	nil	12.1	4.3	3.5	nn	10	0.9	0.6	45	11	68	6.2	4	23	1.1	-	-	N	T2DM	normal
86	4418389	belgaum	housewife	f	60	muskan			8.3		3.2	8 years	nil	333	24.7	nil	nil	12.2	5.7	2.9	nn	11	0.8	0.7	51	8	79	6.3	4.7	14	0.62	-	-	N	T2DM	normal
87	4417953	belgaum	housewife	f	55	roopa			9.3		3.8	6 years	nil	267	27.9	nil	nil	13.6	4.2	2.1	nn	14	0.7	0.6	26	15	134	7.7	4.3	15	1	-	-	N	T2DM	normal
88	4429003	belgaum	business	m	70	dundappa			10.5		8	18 years	nil	234	25.6	nil	nil	13.9	6.9	2	nn	20	1.2	1.1	27	35	64	7.1	4.4	14	0.7	-	-	N	T2DM	normal
89	2696355	belgaum	business	m	49	yallappa			9.9		12.6	3 years	nil	186	26.1	nil	nil	12.2	4.8	4.1	nn	18	0.5	0.3	43	25	79	6	3.6	17	0.8	-	++	N	T2DM	normal
90	4429000	belgaum	driver	m	38	raju			11.7		4.1	2 years	nil	167	25.3	nil	nil	13.2	5.5	2.6	nn	10	1.1	0.9	37	27	88	6.7	4.2	16	0.6	-	-	N	T2DM	normal
91	4429006	belgaum	farmer	m	40	bakkarsab			11.3		3.6	4 years	nil	205	26.3	nil	nil	13.8	6.2	2.1	nn	17	0.7	0.5	18	39	62	8	5.2	19	0.65	-	-	N	T2DM	normal
92	3909254	belgaum	farmer	m	58	vasant			7.2	2.1		5 years	nil	178	27.3	nil	nil	12.6	7.3	1.7	nn	20	0.9	0.6	27	36	51	6.3	3.4	20	0.66	-	-	N	T2DM	normal
93	4428279	belgaum	housewife	f	30	shashikala			6.6	1.2		2 years	nil	156	24.8	nil	nil	12.6	8.8	2.6	nn	10	0.5	0.4	24	12	92	6.2	3.2	23	0.78	-	-	N	T2DM	normal
94	2583029	belgaum	farmer	m	43	ramesh			8.2		3.9	2 years	nil	201	23.2	nil	nil	12.3	8.4	3.3	nn	11	1.2	1.1	33	17	49	6.1	3.3	18	0.77	-	-	N	T2DM	normal
95	4427444	hubbali	driver	m	38	sidrai			10.2		6.5	1 year	nil	256	22.9	nil	nil	14.1	9.2	1.45	nn	14	0.7	0.5	27	40	74	6.5	3.5	14	0.98	-	-	N	T2DM	normal
96	3204986	belgaum	farmer	m	60	ramesh			7.9		3.3	8 years	occasional	264	23.8	nil	nil	13.6	5.2	2.3	nn	15	1.1	1	34	9	89	6.9	3.7	17	0.93	-	-	N	T2DM	normal
97	4426687	belgaum	driver	m	37	sangamesh			7.2	1.2		recently detected	nil	174	24.3	nil	nil	12.8	6.9	1.7	nn	14	0.9	0.8	41	6	69	6.9	4.2	19	0.72	-	-	N	T2DM	normal
98	1257557	belgaum	farmer	m	33	basavaraj			9.8		3.2	1 year	nil	154	26.7	nil	nil	12.3	4.8	3.5	nn	10	0.8	0.7	46	41	93	6.2	5.2	23	0.75	-	-	N	T2DM	normal
99	4428185	belgaum	business	m	32	gajendra			8.4		4.5	1 year	nil	234	24.6	nil	nil	12.1	5.5	2.9	nn	8	0.9	0.8	44	10	72	6.6	3.7	14	0.64	-	-	N	T2DM	normal
100	2199622	belgaum	housewife	f	38	meetty			9.2		3.3	1 year	nil	145	26.8	nil	nil	12.9	6.2	2.1	nn	17	0.7	0.6	38	20	81	7.4	3.5	17	0.82	-	-	N	T2DM	normal