A STUDY ON

"NEUTROPHIL-TO-LYMPHOCYTE RATIO AS A SURROGATE MARKER OF ALBUMINURIA IN TYPE 2 DIABETES MELLITUS"

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THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY

CHENNAI, TAMIL NADU

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GOVERNMENT STANLEY MEDICAL COLLEGE CHENNAI

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

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CERTIFICATE-I

This is to certify that this dissertation entitled "**NEUTROPHIL-TO-LYMPHOCYTE RATIO AS A SURROGATE MARKER OF ALBUMINURIA IN TYPE 2 DIABETES MELLITUS**" submitted by **Dr. P.K.LAVANYA** to the faculty of General Medicine, The Tamilnadu Dr. M.G.R Medical University, Chennai, Tamilnadu, in partial fulfillment of the requirement for the award of M.D DEGREE BRANCH-I (GENERAL MEDICINE) is a bonafide research work carried out by her under my direct supervision and guidance.

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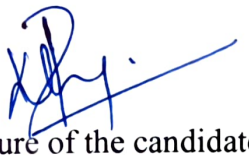
DECLARATION

I, **Dr. P.K.LAVANYA**, solemnly declare that the dissertation titled **"NEUTROPHIL-TO-LYMPHOCYTE RATIO AS A SURROGATE MARKER OF ALBUMINURIA IN TYPE 2 DIABETES MELLITUS "** is a bonafide work done by me at Government Stanley Hospital, Chennai during July 2021 to July2022 under the guidance and supervision of **Prof.Dr.R.THILAKAVATHI,M.D.**, Professor of Medicine, Government Stanley Hospital, Chennai. I also declare that this bonafide work or a part of this work was not submitted by me or any other forward degree or diploma to any other University, board either in India or abroad. This dissertation is submitted to the Tamilnadu Dr. M.G.R Medical University, towards the partial fulfillment of requirement for the award of M.D. Degree (Branch– I) in General Medicine.



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CERTIFICATE II

This is to certify that this dissertation work titled "**NEUTROPHIL-TO-LYMPHOCYTE RATIO AS A SURROGATE MARKER OF ALBUMINURIA IN TYPE 2 DIABETES MELLITUS**" of the candidate **Dr. P.K.LAVANYA** with Registration Number **200120101016** for the award of M.D., DEGREE in the branch of BRANCH-I (GENERAL MEDICINE). I personally verified the ouriginal.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows 1 (one)

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PROF. DR. P. BALAJI MS, FRCS, PhD, FCLS

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ABSTRACT:

Background:Diabetes mellitus is a systemic disease resulting in serious microvascular and macrovascular complications. Diabetic Nephropathy is one of the microvascular complication of diabetes.Diabetic Nephropathy is clinically manifested as an increase in urine albumin excretion starting from microalbuminuria to macroalbuminuria and eventually end stage renal disease (ESRD) .Neutrophil-to-lymphocyte ratio is a crude but sensitive indicator of inflammation and studied in many cardiac and noncardiac diseases as an inflammatory marker such as acute myocardial infarction, stroke, and heart failure.In this study, the association of Neutrophil-to-lymphocyte ratio (NLR) with albuminuria is studied.

Methods:We did an hospital based cross sectional study in patients attending general medicine outpatient department with type 2 diabetes mellitus during periodof July 2021 to July 2022. Patients aged ≥ 40 years and on oral hypoglycaemic agents ≥ 4 years were included in the study.Patients with type 1 diabetes mellitus, patients with recent diagnosis of acute infection,uncontrolled hypertension, chronic kidney disease, hepatic failure,cardiac failure, acute coronary syndrome, arrythmia, patients whose total wbc count > 9000 ,leucopenia, severe anemia,chronic infection, chronic systemic inflammatory disease,patients on anti-inflammatory drugs,steroids,ACEI or ARB,alcohol and p[atients with nephritic syndrome,UTI,renal artery stenosis and dehydration states are excluded from the study.FBS,PPBS,HbA1C ,urine ACR were calculated.The aim of our study is to prove that there is a positive correlation between neutrophil-to-lymphocyte ratio and albuminuria in type 2 diabetes patients.

Results: Out of 120 participants, 79 were male and 41 were female.In the present study about 43.5% were above 60 years of age. About 37.5% were in the range of 51 to 60 years. Only 19% were in the age of 41 to 50 years.In the present study about 72.5% were overweight ,18.5% were obese and 9% were normal. Number of study population with NLR≥2 & microalbuminuria is more in number (N=70) compared to those who have low NLR. The association is statistically significant($P<0.05$).The results of our study have shown that there is a significant correlation between NLR and albuminuria in type 2 diabetes mellitus patients.

Conclusion: In many cardiac and noncardiac disorders, the neutrophil-lymphocyte ratio in a complete blood count is investigated as an inflammatory marker. This ratio is used to predict the prognosis of diseases such as acute myocardial infarction, stroke, and heart failure. Against this background,our study has been conducted to find that whether NLR can be used as an alternate marker instead of albumin-to- creatinine ratio in diabetic nephropathy.The results of our study has shown positive correlation between NLR and albuminuria.In a setting with limited resources,NLR is an simple,cost effective investigation which can be an alternative for urine albumin-to-creatinine ratio.

Key words: NLR, SPOT Urine ACR, Type 2 Diabetes mellitus,Albuminuria.

TITLE

NEUTROPHIL-TO-LYMPHOCYTE RATIO AS A SURROGATE MARKER OF ALBUMINURIA IN TYPE 2 DIABETES MELLITUS

INTRODUCTION :

Chronic inflammation has an important role in the development and progression of type 2 diabetes through immunologic inflammatory mechanisms. The neutrophilto-lymphocyte ratio, also known as the NLR, is a predictor of prognosis in cardiovascular diseases, malignancies, and metabolic syndrome. It is a new, simple, and inexpensive marker of subclinical inflammation. It has been used recently as a systemic inflammatory marker in chronic diseases. In addition, the NLR has been classified as a marker of systemic inflammation in different phases of chronic kidney disease and diabetic nephropathy, in addition to having the value of predicting unfavourable outcomes in medical and surgical diseases.[1,2] The value of NLR in predicting diabetic nephropathy, on the other hand, has not been clarified as of yet.

Activation of leukocytes is something that happens during an inflammatory reaction. Atherogenesis and thrombus development are both processes that involve leukocytes.[3-5] It has been found that the development of cardiovascular disease is linked to the presence of elevated amounts of inflammatory mediators in the circulation. In addition, the NLR should be utilised as a marker of diabetic control level in addition to the HbA1c in patients with type 2 diabetes.[6] Other investigations indicated that a high NLR in otherwise healthy subjects may be indicative of underlying impaired glucose metabolism.

In a retrospective study conducted in Turkey, the researchers demonstrated a positive correlation between high levels of NLR, HbA1c, serum creatinine, and systolic blood pressure and longer duration of diabetes. The researchers came to the conclusion that NLR is an efficient, cheaper, and readily available marker of inflammation, and that it is known as an important predictor for the existence of microvascular complications in subjects with type 2 diabetes.

Microalbuminuria, which was shown to be a sign of vascular endothelial damage, is typically the first symptom that appears in patients who have nephropathy. Albuminuria is a well-known predictor of poor renal outcomes in individuals who have type 2 diabetes and in essential hypertension. [7]As a result, it is crucial to monitor and diagnose albuminuria in order to treat it at an early stage. One of the microvascular complications of diabetes is called microalbuminuria.

Patients with diabetes who have microalbuminuria almost always develop proteinuria and full-blown diabetic nephropathy if they do not receive medical treatment. This process happens in people who have type 1 diabetes as well as type 2 diabetes. In addition, microalbuminuria is frequently accompanied in patients with type 2 diabetes by an elevated CRP level, which points to the activation of inflammatory pathways in the course of renal and cardiovascular atherosclerotic disease. Patients with diabetes often experience DN, which is a common micro-angiopathic consequence.

Diabetic nephropathy is one of the most prevalent factors that might lead to endstage renal failure. Clinically, DN presents itself as increased albumin urea excretion, beginning with microalbuminuria and progressing to macroalbuminuria and eventually end-stage renal disease (ESRD). However, the degree of albuminuria in individuals with DN associated with either type 1 or type 2 diabetes mellitus is not always linked to the course of the disease. Once overt diabetic nephropathy (DN) has developed as a result of type 1 diabetes, there is persistent proteinuria, and the trend toward end-stage renal disease (ESRD) can only be delayed but not prevented.

Because of this, there is a need for early predictors of DN so that we can predict the disease and stop the advancement of the disease. These predictors would allow us to do both of these things.

Microalbuminuria is characterized by a urine albumin-to-creatinine ratio of greater than 2.5 mg/mmol in men and greater than 3.5 mg/mmol in women, with a 24-hour urine albumin output ranging from 30 to 299 mg[1]. When compared to the population of Caucasians, the Asian Indian population has a significantly higher prevalence of DN. Chronic inflammation encourages the development of micro- and macro-angiopathic complications in diabetic patients, as well as speeds up the progression of these complications, according to the findings of a number of studies that investigated the connection between systemic inflammation and vascular disease.

A simple but sensitive measure of inflammation is the total white blood cell count, which is something that can be done simply and consistently in a laboratory setting. This inquiry is quite efficient with regard to costs. The production of thrombi and ischemic disorders are both associated with an increase in the neutrophil count.

In many cardiac and noncardiac disorders, the neutrophil-lymphocyte ratio in a complete blood count is investigated as an inflammatory marker. This ratio is used to predict the prognosis of diseases such as acute myocardial infarction, stroke, and heart failure. Because of this, we wanted to conduct a study to investigate the possible role of NLR as a fast and cheaper inflammatory marker in predicting microalbuminuria in type 2 diabetic patients, particularly in hospitals and clinics that are unable to perform microalbumin-creatine ratio.

Specifically, we wanted to see if NLR could replace the need for microalbumin-creatinine ratio in these settings. Misinterpretation of the urine collection process, in addition to the additional expense and time required for urine collection analysis, is one more factor that lends support to the usage of these markers.

AIM:

The aim of our study is to prove that there is a positive correlation between Neutrophil-to-lymphocyte ratio and albuminuria in type 2 diabetes.

OBJECTIVE:

1. To calculate neutrophil-to-lymphocyte ratio and spot urine albumin-to-creatinine ratio in patients with type 2 diabetes.
2. To assess whether neutrophil-to-lymphocyte ratio correlates with microalbuminuria in patients with type 2 diabetes.

Review of Literature

DIABETES MELLITUS

Diabetes Mellitus is defined as a "group of metabolic illnesses that is characterised by persistent hyperglycemia accompanied with modification in carbohydrate, protein, and lipid metabolism arising from abnormalities in Insulin Secretion, Insulin action, or both." [2]

The level of blood glucose is the predictor of morbidity and mortality that is most frequently used. The American Diabetes Association uses the following diagnostic criteria to determine whether or not a patient has diabetes:

- a fasting plasma glucose value that is greater than 126 mg/dl;
- a 2 hour plasma glucose level following meals that is greater than 200 mg/l;
- a random plasma glucose value that is greater than 200 mg/ml;
- and either symptoms of diabetes or a haemoglobin A1c level that is

greater than 6.5 percent.[3]

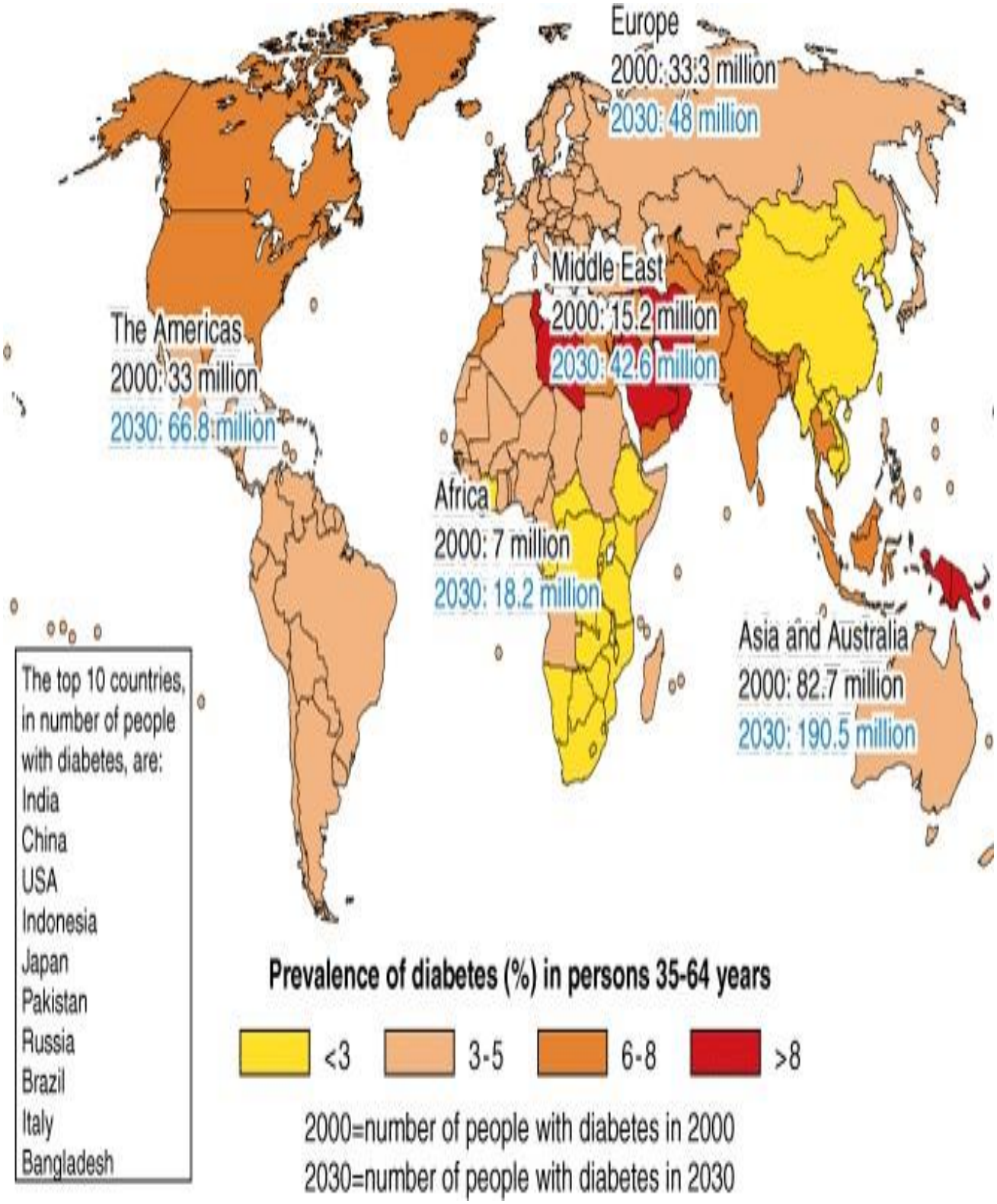
EPIDEMOLOGY[8,11]

The International Diabetes Federation reported that there were 366 million cases of Type II diabetes in adults in the world in 2015, and they anticipated that this figure would rise to 592 million by the year 2035[1].

China's diabetic population ranks top in the world with 98.4 million people in 2013, followed by India's diabetic population with 65.1 million.

Asia is home to five of the world's ten countries with the highest diabetes prevalence.

By the year 2030, it is anticipated that the totals will have increased to 129.7 million and 101.2 million respectively. [4]


Europe
2000: 33.3 million
2030: 48 million
Middle East
2000: 15.2 million
2030: 42.6 million
The Americas
2000: 33 million
2030: 66.8 million
Africa
2000: 7 million
2030: 18.2 million
Asia and Australia
2000: 82.7 million
2030: 190.5 million
The top 10 countries, in number of people with diabetes, are:
India
China
USA
Indonesia
Japan
Pakistan
Russia
Brazil
Italy
Bangladesh
Prevalence of diabetes (%) in persons 35-64 years
<3
3-5
6-8
>8
2000=number of people with diabetes in 2000
2030=number of people with diabetes in 2030

Diabetes

Classification[5]

I. Type 1 Diabetes mellitus (complete cell destruction, leads to absolute insulin loss)

A. Immune-mediated destruction

B. Idiopathic aetiology

II. Type 2 diabetes mellitus (has combination of insulin resistance with Some insulin deficiency to a dominantly insulin synthesis defect with insulin resistance)

III. Other sub- types of diabetes mellitus

A. Genetic alterations in cell function which manifests by mutations in:

1. Hepatocyte nuclear transcription factor (MODY TYPE 1)
2. Glucokinase (MODY TYPE 2)
3. HNF-1 (MODY 3)
4. Insulin promoter factor-1 (MODY 4)
5. HNF-1 (MODY 5)
6. NeuroD1 (MODY 6)
7. Mitochondrial DNA
8. Subunits for ATP-sensitive potassium channel

A. Genetic abnormalities in insulin action

1. Type A insulin resistance

2. Leprechaunism

3. Rabson-Mendenhall syndrome

4. Lipodystrophy syndromes

B. Diseases of the exocrine pancreas – e.g.. Pancreatitis, neoplasia, cystic fibrosis, hemochromatosis, fibro calculous pancreatopathy

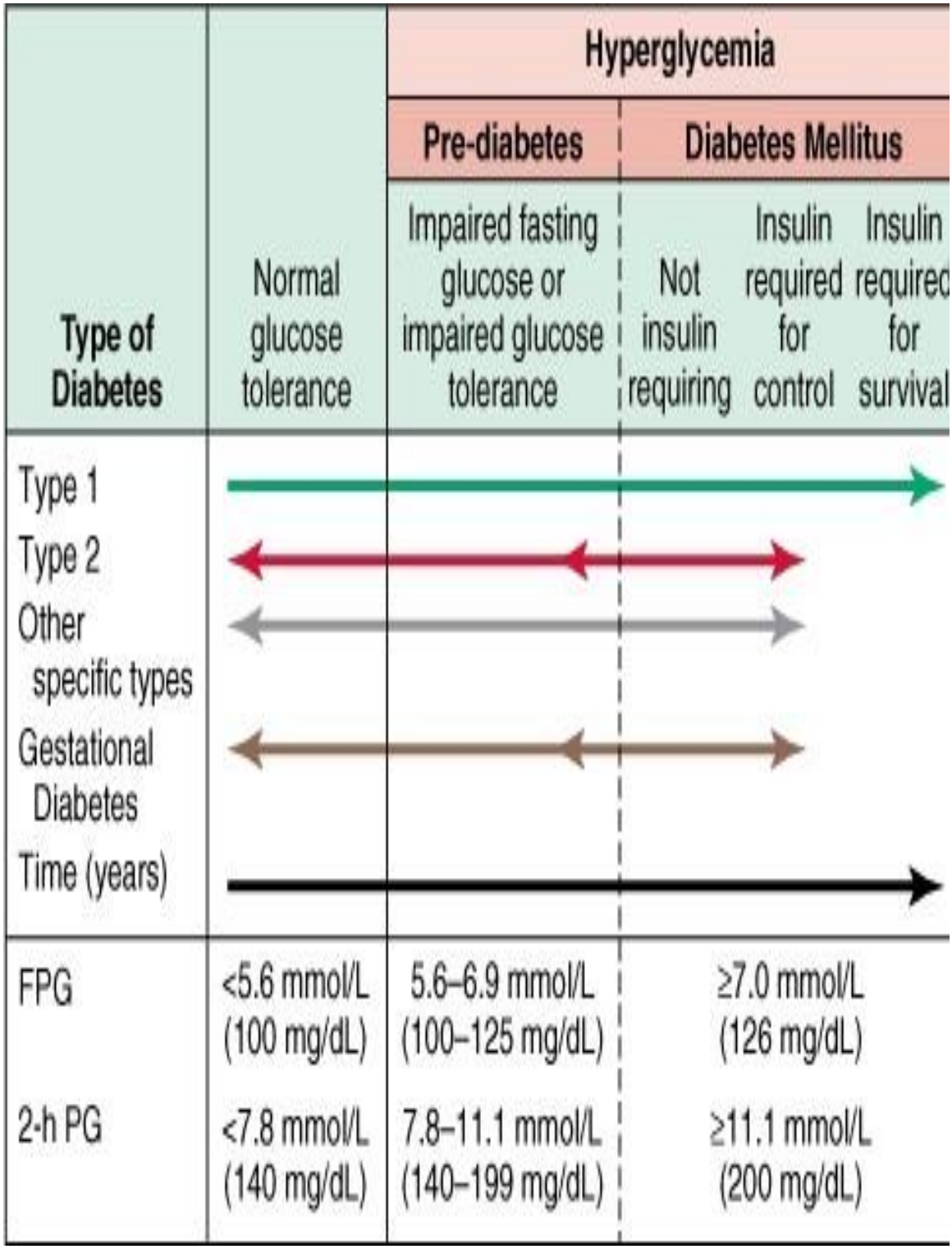
C. Endocrinopathies - includes acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism etc

D. Drugs and chemicals — pentamidine, nicotinic acid, glucocorticoids, thyroid hormone, diazoxide, adrenergic agonists, thiazides, phenytoin, interferon, protease inhibitors, clozapine.

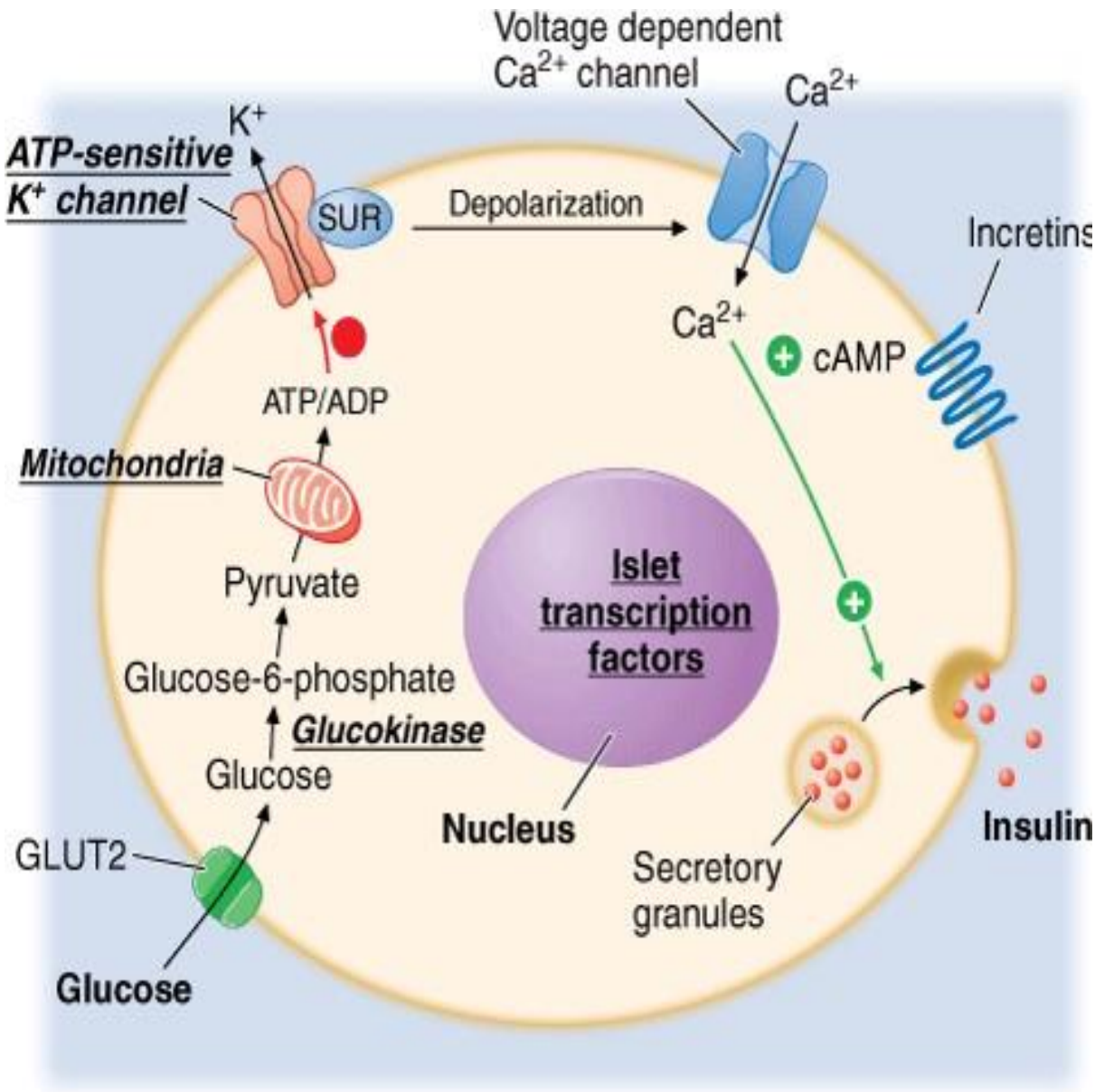
E. Infections—congenital rubella, coxsackie virus,

F. Other genetic syndromes associated with diabetes— Turner's syndrome, Friedreich's ataxia, Huntington's chorea, Laurence-Moon-Biedl syndrome, myotonic dystrophy, Prader-Willi syndrome, Klinefelter's and turner's syndrome.

1V Gestational diabetes


Hyperglycemia
Pre-diabetes
Diabetes Mellitus
Type of Diabetes
Normal glucose tolerance
Impaired fasting glucose or impaired glucose tolerance
Not insulin requiring
Insulin required for control
Insulin required for survival
Type 1
Type 2
Other specific types
Gestational Diabetes
Time (years)
FPG
<5.6 mmol/L (100 mg/dL)
5.6–6.9 mmol/L (100–125 mg/dL)
≥7.0 mmol/L (126 mg/dL)
2-h PG
<7.8 mmol/L (140 mg/dL)
7.8–11.1 mmol/L (140–199 mg/dL)
≥11.1 mmol/L (200 mg/dL)

PHYSIOLOGY OF INSULIN SECRETION :



Risk Factors implicated in Diabetes[6]

- Family history of diabetes mellitus
- People with Impaired fasting or post prandial glucose values
- physical inactivity
- overweight
- Race/ethnicity
- Hypertension
- Low HDL cholesterol and high triglyceride level(greater than 250 mg)
- History of Gestational DM or an overweight new born baby
- Polycystic ovarian disease.

MODIFIABLE RISK FOR TYPE 2 DIABETES

- **OBESITY**

Obesity and weight gain are two of the most important modifiable risk factors for developing diabetes. The body mass index, sometimes known as BMI, is a proxy measure for obesity that is derived by taking a person's weight in kilogrammes and dividing it by their height in metres squared.

People with a body mass index (BMI) of 25-27 kg/m2 have a 2.75-times increased chance of developing diabetes compared to those with a BMI of less than 22 kg/m2.

- **PHYSICAL ACTIVITY**

In most populations, researchers have discovered that the risk of developing diabetes is inversely proportional to the amount of physical exercise they get[3].

Exercising is linked to both an immediate and long-term improvement in insulin sensitivity, as well as a reduction in insulin concentrations, according to a large number of research.

- **SEDENDARY LIFESTYLE**

One study found that the risk of developing diabetes was increased by 66 percent in individuals who engaged in sedentary activities such as watching television or using the internet for more than four hours (2 to 10 hours).

- **DIETARY FACTORS**

A diet high in fat has been linked to increased body fat and obesity. Studies on the effect of various subtypes of fat, such as saturated fat, polysaturated fat, monosaturated fat, and omega-3 fatty acids, on the risk of developing diabetes came to the conclusion that there is a beneficial effect of higher intake of PUFA and long chain omega-3 fatty acids 3, while there is a deleterious effect due to higher intake of saturated fat.

Carbohydrate consumption, in comparison to protein and fat consumption, was hypothesized to pose a greater immediate challenge to beta cells, which led to the association between carbohydrate consumption and the risk of developing diabetes; nevertheless, the findings of the studies were ambiguous. The rise that occurs after eating is determined by how quickly glucose is absorbed.

The pace at which glucose is absorbed is dependent on a number of factors, including the kind of carbohydrates consumed and the total amount of fibre.

RISK FACTORS FOR TYPE 2 DIABETES - NON MODIFIABLE[12,13]

- **INFLAMMATION**

Even while insulin resistance and relative insulin shortage are two of the most prominent characteristics of diabetes, the underlying mechanism of the disease is still a mystery. Recent research has uncovered data suggesting that inflammation plays a crucial role in the pathogenesis of type 2 diabetes and atherosclerosis.

An increased ratio of neutrophils to lymphocytes, which is a measure of subclinical inflammation, was found to be associated with diabetes in a large number of cross-sectional studies.

According to the findings of the study, subclinical inflammation is an essential factor in the development of type 2 diabetes mellitus. It is important to highlight that taking a high dose of aspirin can lower insulin resistance, which in turn improves glucose tolerance in people with type 2 diabetes[3.]

SMOKING

In the study by Facchini and colleagues, the researchers compared chronic smokers with nonsmokers and discovered significantly higher levels of triglycerides and reduced HDL. Following an oral glucose tolerance test with 75 g, there was a rise in cholesterol levels as well as insulin concentration. Oxidative stress, which leads to endothelial dysfunction, is the process that contributes to insulin resistance caused by smoking.

AETIOPATHOGENESIS OF TYPE 2 DIABETES MELLITUS

A significant contribution to the development of type 2 diabetes is made by genetic factors. Research on identical twins has shown that hereditary factors are the primary contributors to the development of type 2 diabetes. This finding has been confirmed by a hundred percent of the studies.

The three anomalies in the development of hyperglycemia that are now thought to be involved in the pathogenesis of type 2 diabetes are as follows:

- **Impaired pancreatic insulin secretion[14]**

Normally During fasting, insulin levels range from 5 to 15 mU/ml. Insulin is normally released in a pulsatile manner known as ultradian oscillations, which secrete every 90 to 120 minutes and are amplified when food is consumed. The insulin secretion that occurs after a load of glucose demonstrates a biphasic response.

The first phase is due to insulin that has been stored in granules, which is then released and suppresses the output of glucose by the liver. This will happen during the next 4 to 5 minutes, and everything will go back to normal within the next 10 minutes.

The second step of the process happens when the glucose level rises, which causes an increase in the peripheral glucose absorption in muscle and adipose tissue[2].

In patients with type 2 diabetes, the pulsatile ultradian oscillations of insulin delivery and first phase insulin release are absent.

- **Impaired peripheral action of insulin:[15,16]**

The relationship between hyperinsulinemia and the development of type 2 diabetes has been the subject of a large number of investigations.

Insulin resistance is seen in a variety of tissue types, including muscular, splanchnic, and others[3]. There is a deficiency in the activity of insulin in the muscle.

1. Activity of the insulin receptor tyrokinase that was inhibited
2. Reduced capacity of the glucose transporters
3. decreased activity of glycogen synthase as well as pyruvate dehydrogenase

- **Increased hepatic glucose output and lipid production**

After a meal containing glucose, insulin will normally be secreted into the portal vein and transported into the liver, where it will work to inhibit hepatic gluconeogenesis.

Because of insulin resistance, the liver is unable to recognize certain signals, which leads to an increase in the amount of glucose that is produced by the liver.

Because of insulin resistance in adipose tissues, lipolysis and the transit of free fatty acids from adipose tissue to the liver will rise, which in turn leads to an increase in the formation of lipids (VLDL and triglycerides) in the liver.

It is possible that the accumulation of lipids could lead to hepatic steatosis and nonalcoholic fatty liver disease, both of which can cause abnormalities in liver function.

INSULIN RESISTANCE AS A PRIMARY DEFECT[21]

According to the findings of prospective research, hyperinsulinemia and insulin resistance come before the development of impaired glucose tolerance.

Impaired glucose tolerance (IGT) is a stage that occurs between normal glucose tolerance and the development of type 2 diabetes.

Studies that use a cross-sectional methodology have demonstrated that insulin resistance is a hereditary problem that triggers the onset of diabetes.

There are three stages involved in the progression from hyperglycemia to insulin resistance.

In the first phase, enhanced insulin secretion ensures that plasma glucose levels stay normal despite the presence of insulin resistance.

Second phase: As insulin resistance progresses, decreased glucose absorption occurs in the muscle; however, adequate insulin is still generated to keep hepatic glucose synthesis at a normal level. Therefore, there is hyperglycemia after a meal, although the blood glucose levels in the morning are normal.

The third phase is when hyperglycemia becomes severe to the point where there is no longer sufficient hyperinsulinemia to keep fasting blood glucose levels normal.

As a consequence of the fasting and postprandial hyperglycemia, more beta cells are stimulated, which leads to hyperinsulinemia, which in turn helps to

downregulate receptors and exacerbate insulin resistance.

NATURAL HISTORY OF TYPE 2 DIABETES MELLITUS[22-30]

The interplay between insulin sensitivity and insulin secretion should be in a state of balance for optimal glucose homeostasis to be maintained.

Fasting glucose

Hepatic glucose production is the primary factor that determines blood glucose levels while the person is fasting. The answer lies in

- Fasting plasma insulin
- Insulin-receptor sensitivity in the liver
- Availability of substrates during fasting

Insulin secretion at rest is reduced, and insulin sensitivity in the liver is lessened, both of which are hallmarks of type 2 diabetes.

Postprandial glucose

It is controlled by the clearance of glucose that has been consumed, the suppression of glucose production in the liver, and the clearance of glucose in the peripheral blood.

Lack of glucagon suppression, delayed and decreased insulin production, and hepatic and peripheral resistance are the hallmarks of type 2 diabetes.

LIPOTOXICITY[31,32]

Adipocytes are found in adipose tissue, which is regarded to be an endocrine organ.

Adipose tissue is the primary site for the storage and secretion of adipokines [13.] Insulin activity can be affected by adipose tissue through the release of free fatty acids and proteins produced from adipose tissue.

Proteins that are produced from adipose tissue are peptides that promote inflammation and have a negative impact on glucose metabolism and insulin action.

Proinflammatory Cytokines

The increased amount of adipose tissue in the body results in an excessive generation of cytokines that promote inflammation. Interleukin-1, interleukin- 18, interleukin-6, CRP-c reactive protein, restin, and tumor necrosis factor (TNF-1) are all examples of proinflammatory cytokines.

The macrophages that are produced from adipose tissue are the principal source of these proinflammatory cytokines, and this is true both in the systemic circulation and locally.

On the other hand, it is unknown to what extent the paracrine and endocrine effects of these cytokines contribute to insulin resistance. [1]

Adiponectin

Adipocytes are responsible for the production of the anti-inflammatory cytokine known as adiponectin. This adiponectin makes insulin more sensitive, and it also slows the inflammatory process in multiple different processes.

Because of adiponectin's ability to block gluconeogenic enzymes, the pace at which the liver produces glucose is slowed down.

The activation of adenosine monophosphate kinase is partially responsible for the effects of adiponectin, which include an increase in the oxidation of fatty acids and an improvement in the transport of glucose in the muscles.

A pathogenic factor that contributes to insulin resistance and type 2 diabetes is a decreased plasma level of the hormone adiponectin..

Diagnosis

According to the American Diabetes Association, a diagnosis of diabetes can be made using any one of the following methods: [5]

- HbA1c or glycosylated haemoglobin test
- FPG - a fasting plasma glucose test
- OGTT - an oral glucose tolerance test

The levels of HbA1c provide information about the average glucose level over the past three months. It provides a reasonable picture of how the treatment is progressing. [18]

Inside the red blood cells is where you will find the haemoglobin. Haemoglobin is responsible for delivering oxygen to the various tissues throughout the body. When red blood cells are subjected to a high amount of blood glucose on a consistent basis, glucose is able to enter the cells and combine with haemoglobin to generate glycosylated haemoglobin. This occurs because glucose enters the cells through the cell membrane.

This HbA1C offers an average reading of how well the patient has controlled their blood glucose levels over the preceding three months. Because of this, it is essential to examine the levels of HbA1C at least twice a year.

The results of the HbA1C test could be given as eAG or as "average glucose," the latter of which has a direct correlation with A1C.

A unit on the CBG machine that is analogous to the self-monitor is called an eAG.

The value of A1C is expressed as a percentage, while eAG is given in mg/dl.

The average glucose level of [16] eAG is not the same as the average of the numbers displayed on the metre.

This is due to the fact that people who have diabetes are more likely to check their blood glucose when it is low (often in the morning and before meals), which results in the average of these readings being significantly lower than eAG.

Fasting Blood Glucose

The values of glucose in the blood are what are measured in the early morning, when an individual has abstained from food and drink for at least eight hours beginning the previous night.

Oral Glucose Tolerance Test (OGTT)

This is a test to detect how efficiently glucose is metabolised by the body. The fasting state is required for the measurement of blood glucose levels here. The patient is given a particular glucose solution to consume, and then the blood glucose levels are measured again after two hours have passed.

Result	Oral Glucose Tolerance Test (OGTT)
Normal	less than 140 mg/dl
Prediabetes	140 mg/dl to 199 mg/dl
Diabetes	200 mg/dl or higher[16]

Random Plasma Glucose Test

This can be done whenever the mood strikes you during the day. It is possible to diagnose diabetes when the random plasma glucose readings are higher than 200 mg/dl.

Prediabetes:

A person is said to have prediabetes when their blood glucose levels are higher than usual but are not yet high enough to be diagnosed with diabetes.

Both impaired glucose at fasting and impaired glucose tolerance are included in the diagnostic category of prediabetes.

Because these individuals have a significant risk of developing overt diabetes as well as cardiovascular problems, it is imperative that they undergo routine monitoring.


DIABETES
≥ 126 mg/dl
< 126 mg/dl
PREDIABETES
≥ 100 mg/dl
< 100 mg/dl
NORMAL
FPG
DIABETES
≥ 6.5%
< 6.5%
PREDIABETES
≥ 5.7%
< 5.7%
NORMAL
A1C
DIABETES
≥ 200 mg/dl
< 200 mg/dl
PREDIABETES
≥ 140 mg/dl
< 140 mg/dl
NORMAL
OGTT

COMPLICATION :

There are two types of problems that can arise from diabetes: acute and chronic.

ACUTE COMPLICATION

- Diabetic keto acidosis
- Hyperglycemia
- hyperosmolar state
- Hypoglycemia

CHRONIC COMPLICATION

Increased blood glucose levels for an extended length of time can lead to development of chronic complications. [20] The length of time a person has diabetes is the primary factor that influences the risk of developing complications.

Diabetes can cause complications that can be broken down into two categories: microvascular and macrovascular. They have an effect on a variety of organ systems, most notably the kidneys, the heart, the eyes, the blood arteries in the brain, and the peripheral vessels in the limbs.

Diabetic nephropathy, myocardial infarction, cerebrovascular accident and gangrene of the limbs are all caused by this condition.

In addition, diabetes puts a person at increased risk for hyperlipidemia and hypertension, both of which contribute to an increased likelihood of complications.

Insulin-dependent diabetes treated with intensive insulin therapy resulted in HbA1c levels that were 2 percentage points lower than those treated with conventional insulin and a lower incidence of complications [12], according to a number of studies, including the Diabetes Control and Complications Trial (DCCT).

According to the findings of the UKPDS, there is a 35% decrease in the risk of microvascular complications for every 1% decrease in HbA1C.

The microangiopathy and atherosclerosis that are associated with diabetes mellitus are the primary causes of the condition's vascular consequences.

Microangiopathy is primarily caused by three factors:

- damage to the endothelial basement membrane,
- proliferation of endothelial cells, and
- malfunction of endothelial cells.

An elevated blood glucose level causes the arterial wall to become more rigid, and when combined with an elevated level of lipids in the blood, this leads to the deposition of lipids in atherosclerotic plaques, which puts the end organ at risk for injury.

There is a great deal of complexity involved in the pathophysiology that leads to the development of microvascular and macrovascular problems in diabetes. There is not one single mechanism that can be identified.

It has been determined that elevated levels of blood glucose for an extended period of time are the single most important factor that contributes to complications caused by diabetes. However, not everyone who has high blood glucose levels will go on to develop problems of diabetes mellitus.

Sometimes, even people whose blood glucose levels are under extremely good control will still end up acquiring complications of diabetes mellitus.

A wide variety of cell types, as well as their extracellular matrix, are impacted when there is an increase in sugar.

The tissues experience both structural and functional shifts as a direct consequence of these modifications.

Phospholipid bilayers are the primary components that contribute to the formation of the cell membrane. Therefore, disruptions in lipid metabolism have an effect on the membranes of the cells, which ultimately leads to damage to the cells.

Individuals who have hyperglycemia experience an increase in oxidative stress in the vessel wall due to the oxidation of low-density lipoprotein.

Because of this, monocytes and macrophages are drawn to the area where the vessel wall has been oxidized. Changes in cell adhesion are a direct consequence of LDL. In addition to this, the production of cytokines and growth factors is stimulated. [20]

Moreover, the proliferation of smooth muscle cells that results from the action of growth factors is responsible for the increased wall thickness of blood vessels. Additionally, there is an increase in the production of atherosclerotic plaques as well as microthrombi in the major blood vessels. Damage to end organs is brought about by shifts in the arterial permeability and malfunction of endothelial cells.

When hyperglycemia is allowed to persist, sugar begins to link up with other molecules, including proteins, lipids, and nucleic acids. There is an increase in the deposition of advanced glycation end products in the micro blood vessels of the retina, glomerulus, and endoneurons, in addition to the walls of the larger blood vessel structures. People whose diabetes is not well controlled have an increased risk of developing advanced glycation end products.

These advanced glycation end products are the culprits behind the structural and functional alterations that occur in the cells of different tissues. The production of AGEs on collagen hinders the healing process of damaged tissues, which in turn disrupts the normal homeostatic process.

The thickening of the vessel walls and the constriction of the lumen that result from the formation of AGE-modified collagen in the walls of the major blood vessels. Because of this, the LDL in circulation becomes immobilized, which contributes to the formation of atherosclerotic plaque.

Because of the production of AGEs, there is a rise in the thickening of the basement membrane in the microvasculature of the retina and around the nerves, as well as an increase in the thickness of the mesangium in the glomerulus. The culmination of all of these changes is a narrowing of the blood arteries, which leads to a reduction in the amount of blood that is supplied to the organs.

The formation of AGE has an effect at the cellular level, which also results in changes in the extracellular matrix and causes abnormalities in the cell-to-matrix and matrix-to-matrix interrelationships. Increased vascular permeability and thrombotic complications, multiplication of smooth muscle in vasculature, and phenotypic changes in monocytes and macrophages are all caused by the binding of AGEs to specific cell receptors that have been identified on the surface of smooth-muscle cells, endothelium, neural cells, monocytes, and macrophages.

These cell receptors have been identified on the surface of these cell types.

Because of this, monocytes and macrophages become more susceptible to stimulation, which ultimately leads to an increase in the production of cytokines that promote inflammation and the growth factors associated with them. These cytokines and growth factors are involved in the formation of atherosclerotic lesions, which are characterised by a chronic inflammatory response. They also alter the events that occur during wound healing. In response to antigens such as germs, increased synthesis of inflammatory mediators leads to increased tissue damage.

Elevated plasma glucose levels are an important aspect of diabetes, which provides a common relation between the various problems that can arise as a result of the disease. These abnormalities in protein and lipid metabolism create these elevated plasma glucose levels. However, people's responses to these metabolic shifts are never the same. AGEs, for instance, can be produced in both diabetic and nondiabetic individuals, but the accumulation of them occurs more frequently in diabetics. Even within the community of diabetics, there are considerable disparities in the creation of AGEs, and it is believed that this may be the factor that explains the variations in the incidence and progression of diabetes

complications[48.]

TREATMENT

ORAL AGENTS

INSULIN SECRETOGOGUES

Sulfonylureas

Because of the higher risk of adverse effects that these medications present, the sulfonylureas of the first generation are no longer utilized in modern medicine. [2]

Chlorpropamide is an example of a sulfonylurea that belongs to the first generation.

The first generation of drugs has been superseded by the second generation medications, which are more effective, have fewer negative drug interactions, and result in less negative side effects.

Sulfonylureas exert their effect on the body by stimulating the beta cells of the pancreas, which results in an increase in the amount of insulin that is secreted. Because of this enhanced insulin production, the insulin resistance that is associated with type 2 diabetes mellitus can be overcome.

As a result, a greater quantity of glucose is carried within the cells, which results in a reduction in the amount of glucose in the blood.

The sulfonylureas are administered either as a single or a double dosage on a daily basis, based on the various action durations of the drugs.

Hypoglycemia is the most significant negative impact that is linked to the use of sulfonylureas. Therefore, patients who take these medications need to be well informed to ensure that they consume a suitable quantity of food after taking the tablets.

Non sulfonylurea secretogogues

Repaglinide enhances pancreatic insulin secretion. On the other hand, the pharmacodynamic characteristics and the mechanism of action are not the same as those of sulfonylureas. The drug repaglinide is rapidly absorbed, and its peak plasma levels are reached within 30 to 60 minutes.

Additionally, the drug is rapidly metabolized. The prescription is taken with meals and minimizes the peaks of PPBS, a condition that is frequent in people who have type 2 diabetes, but to a larger degree than the treatments that contain sulfonylureas.

Because of the speed with which they begin to work and the relatively short amount of time they remain effective for, these medications are frequently used for the management of postprandial hyperglycemia.

Hypoglycemic episodes are another possible side effect of these medicines. The effects of neteglinide are seen more quickly than those of repaglinide, and the drug can be administered to patients with mild to moderate liver dysfunction.

INSULIN SENSITIZERS

Biguanides

Patients who are fat typically benefit most from treatment with biguanides like metformin. These medications bring about a reduction in blood glucose levels by inhibiting glucose production and enhancing glucose utilization. It activate AMP dependent protein kinase . These medications also prevent glucose from being absorbed in the digestive tract. The most serious side effects of these medications are lactic acidosis and megaloblastic anemia, both of which are caused by a lack of vitamin B12. Lactate synthesis in the intestine is stimulated by biguanides through the process of anaerobic glycolysis. Metformin is the only oral drug that has been shown to lessen the severity of macrovascular complications associated with type 2 diabetes.

Thiazolidinedione

PPAR gamma is a nuclear receptor that regulates the transcription of genes involved in glucose and lipid metabolism. The thiazolidinedione group of medicines, which includes troglitazone, rosiglitazone, and pioglitazone, function as agonists of this nuclear receptor. In patients with type 2 diabetes, these medications are taken to reverse insulin resistance. These medications also have a tendency to raise HDL levels. These medications might cause undesirable side effects such as weight gain, swelling, and an increase in plasma volume. Patients suffering from

CHF ought to steer clear of these as a result.

Alpha – glucosidase inhibitors

Alpha glucosidase is the enzyme responsible for converting acarbose-complex carbs into simple carbohydrates, which are then absorbed. Carbohydrate absorption from gut is slowed down by substances that inhibit this enzyme. The fermentation of carbohydrates that aren't absorbed leads to the most significant negative impact, which is flatulence. These medications assist in restoring the activity of beta cells and help prevent new instances of type 2 diabetes in those who already have pre

diabetes.

Dipeptidyl peptidase inhibitors

The administration of DPPT helps to prolong the activity of endogenous GLP-1, which in turn stimulates insulin production. a decrease of 0.5 to 0.8 percentage points in HbA1C. They consist of the medications sitagliptin, saxagliptin, and

vildagliptin.

Sodium glucose co-transporter 2 inhibitors

Inhibitors of the sodium glucose cotransporter 2 enhance the amount of glucose that is excreted in urine, which in turn lowers blood glucose levels. They do not require insulin treatment. Among the adverse effects are infections of the urinary tract. Drugs include canagliflozin ,dapagliflozin , empagliflozin .

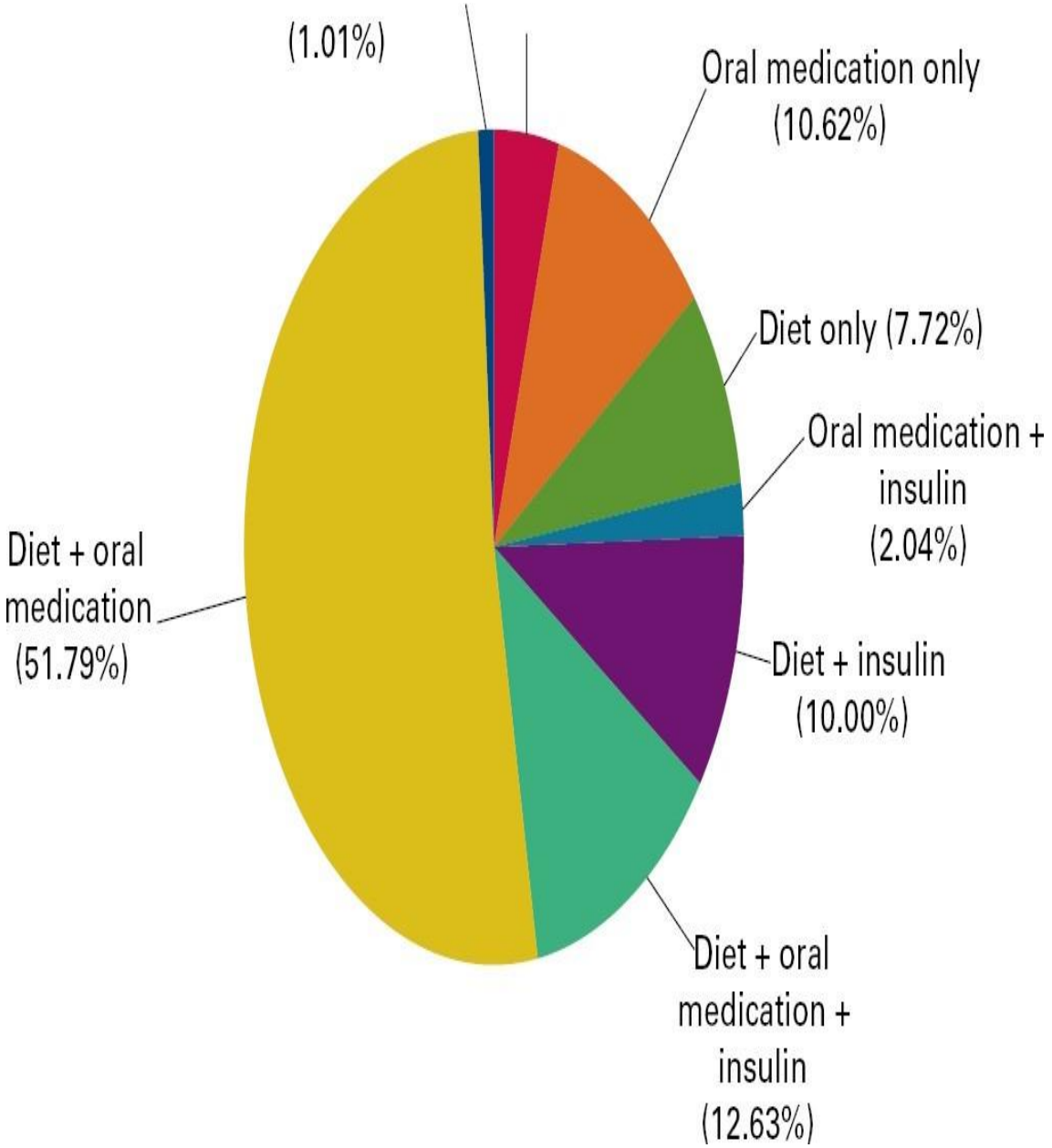
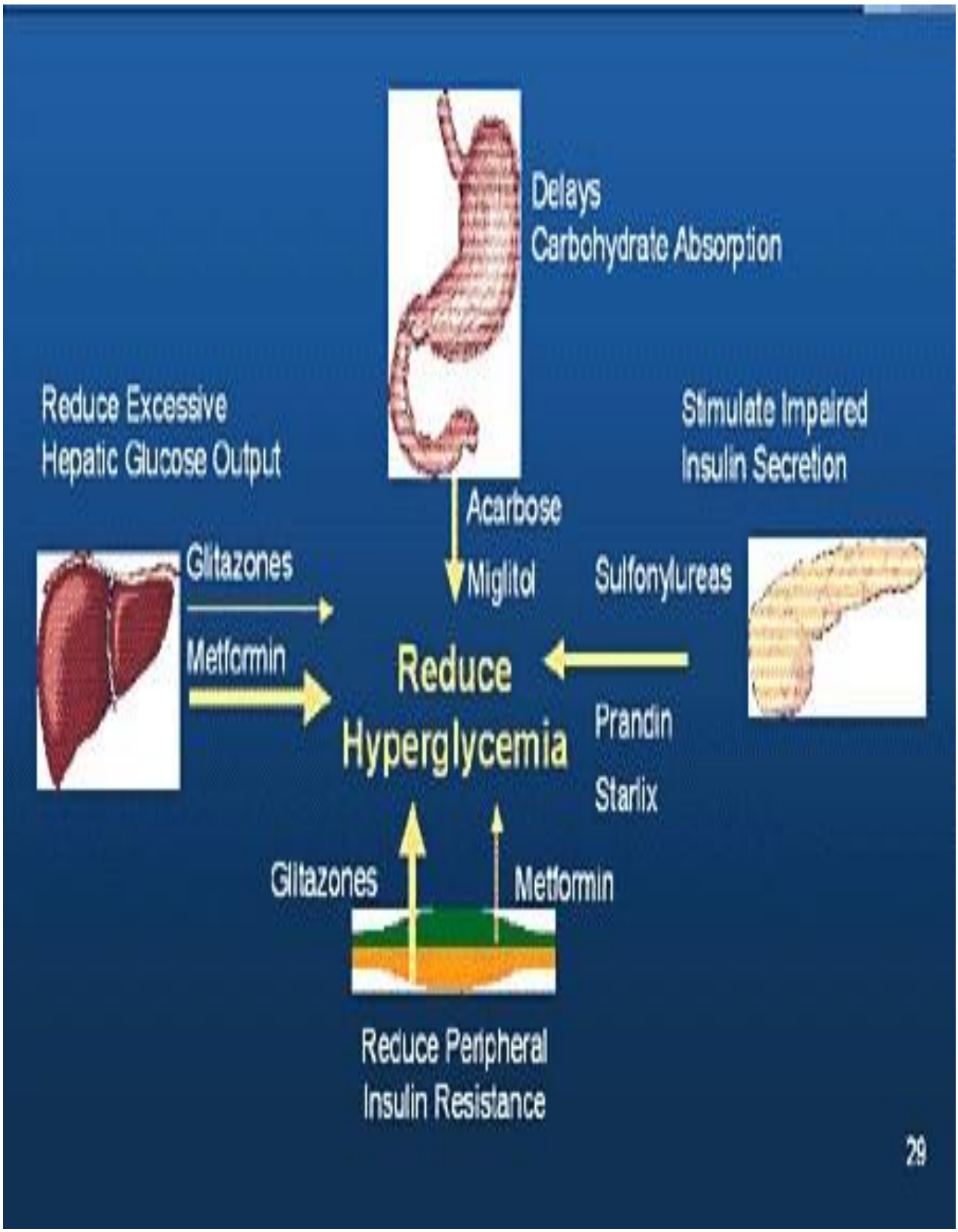


Fig: Chart Showing The Different Treatments

for Diabetes and its Efficacy



. **Fig: Diagram showing site of action of anti-diabetic drugs**

Table 1 – Non-insulin agents available for treatment of diabetes in the United States

Drug class	Route of administration	Advantages	Disadvantages
Biguanides (metformin)	Oral	Effectively lowers HbA_{1c}, low cost, does not cause weight gain	GI complaints, minimal risk lactic acidosis (contraindica in patients older than 80 y those with elevated creatini
Sulfonylureas (tolbutamide, glyburide, glipizide, glimepiride)	Oral	Available as generics (low cost)	Can cause weight gain
Disaccharidase inhibitors (acarbose, meglitol)	Oral	Do not promote weight gain; safe in patients with renal failure; reinforce carbohydrate restriction through averse response	Flatulence, abdominal disco diarrhea; relatively high cos
Thiazolidinediones (rosiglitazone, pioglitazone)	Oral	May preserve beta cells from ongoing destruction	Cause fluid retention (somet leading to heart failure); stir accumulation of adipose tis
Meglitinides (repaglinide, nateglinide)	Oral	Rapid disappearance time results in lower risk of hypoglycemia than with sulfonylureas	Much shorter duration of ac sulfonylureas; thus, these ag be taken before meals; moc high cost
GLP analogs (exenatide)	Parenteral	May result in progressive weight loss in some patients	Nausea (often severe); must injected twice daily; high co
Amylin analogs (pramlintide)	Parenteral	Weight loss can occur	Nausea; unpredictable hyp high cost
DPP-IV inhibitors (sitagliptin)	Oral	No prominent side effects, low risk of hypoglycemia	Does not lead to weight los

HbA_{1c}, glycosylated hemoglobin; GLP, glucagonlike peptide; DPP-IV, dipeptidyl peptidase IV

Insulin

In 1921, Banting and Best made the discovery that led to the production of insulin. The release of insulin from beta cells in the pancreas is primarily stimulated by glucose. Beta cells are located in the pancreas. Glucose has the ability to stimulate GLUT-2 while at the same time inhibiting ATPsensitive k+ channels. Insulin's effects include enhancing glycolysis and glycogenesis, inhibiting glycogenolysis and gluconeogenesis, and stimulating the entrance of glucose into muscle and fat. Insulin also prevents glycogenolysis from occurring. Insulin, through all of the mechanisms described above, brings the levels of glucose in the blood down. Additionally, it impedes the process of lipolysis and promotes the deposition of triglycerides. Because of the enhanced protein synthesis that it caused, it has an anabolic effect on the body as a whole.

Recombinant DNA technology is used to produce human insulin, which has a rapid absorption rate but a shorter duration of action. In recent years, there has also been progress made in the development of preparations with ultra-short and ultra-long acting types. Except for glargine, which is delivered at a pH of 4, all insulin formulations are provided at a pH that is neutral, ranging from 7.2 to 7.4 . Because of this, it is extremely vital that glargine cannot be used with any other type of insulin preparation.

Only the subcutaneous method should be used for administering any insulin preparation. Through the intravenous method, the only type of insulin that can be administered is normal insulin. Insulin absorption is influenced by a number of factors, including the type of injection, where it is given, how deeply it is given, and how much blood is flowing

subcutaneously.

Hypoglycemia is the most prevalent type of problem that can arise with insulin therapy. Glucose administered intravenously is an effective treatment for this condition. Some people have trouble recognizing the symptoms of hypoglycemia. In most cases, when the levels of glucose in the blood drops to less than 60 milligrams per deciliter, one may begin to experience the symptoms of hypoglycemia. Patients who suffer from hypoglycemic unawareness, on the other hand, do not experience any symptoms until their blood glucose levels drop to 40 mg/dl. The patient loses consciousness, which is frequently a sign of a condition that is lifethreatening. After then, it has the potential to develop lipodystrophy at the injection site. It has been discovered that allergic reactions as well as salt and water retention can develop.

All instances of insulin-dependent diabetes mellitus are considered to be appropriate candidates for insulin therapy. Insulin therapy is recommended

for patients with type 2 diabetes who are not insulin dependent when their glucose levels cannot be managed with oral hypoglycemic agents, when they are pregnant, and when they develop complications such as diabetic ketoacidosis and hyperosmolar coma in response to stressful conditions such as surgery or infections.

Using exogenous insulin results in a profile that is comparable to that of a person who does not have diabetes. This profile is characterised by a constant availability of insulin, which is increased by an increase in availability after each meal[6] . There is currently no single insulin formulation on the market that is capable of accomplishing this goal with only one or two injections per day. There are combinations of insulin preparations that can be taken three or more times a day, or a subcutaneous infusion pump can be used to get a better approximation of the ideal conditions. Despite these options, however, blood glucose levels can still be unpredictable even when following conditional regimens.

The insulin with the longest duration of action is ultralente, which is also known as "peakless" insulin.

It has a very sluggish action start, it peaks very minimally, and it has an activity that lasts for a longer period of time. Its operation is comparable to that of insulin[6] for the basal metabolic rate. Several hours after injection, the

insulins with an intermediate duration of action (lente and neutral protamine Hagedorn [NPH]) reach their maximum level of activity.

The time period between 4 and 10 hours following an injection is when activity is at its peak. If a patient takes intermediate-acting insulin in the morning, their plasma insulin levels will reach their peak around lunchtime. This is because intermediate-acting insulin takes longer than rapid-acting insulin to work.

Regular insulin has a shorter duration of action, with its beginning occurring between 30 minutes and 1 hour after injection and its peak occurring between 2 and 3 hours after injection. Lispro insulin is a quick acting insulin that, as a result of its rapid absorption, becomes active approximately fifteen minutes after injection and reaches its peak activity between one and one and a half hours later.

Insulin with a rapid or short acting time is typically administered soon before or while the patient is eating. If you take your usual insulin before breakfast, the highest effect will occur in the middle of the morning. If you take it before lunch, the peak effect will occur in the middle of the afternoon.

Insulin preparation	Onset of action	Peak	Duration of action
Lispro (Humalog)	<15 minutes	1-2 hours	3-6 hours
Aspart (Novolog)	<15 minutes	1-2 hours	3-6 hours
Glulisine (Apidra)	<15 minutes	1-2 hours	3-6 hours
Regular (Novolin R, Humulin R)	30-60 minutes	2-4 hours	6-10 hours
Humulin R Regular U-500	30-60 minu tes	2-4 hours	Up to 24 hours
NPH (Novolin N, Humulin N, ReliOn)	2-4 hours	4-8 hours	10-18 hours
Glargine (Lantus)	1-2 hours	Usually no peak	Up to 24 hours
Detemir (Levemir)	1-2 hours	Usually no peak**	Up to 24 hours**

Premixed Insulins***	Onset of action	Peak	Duration of action
Novolin70/30, Humulin 70/30	30-60 minutes	2-10 hours	10-18 hours
Humalog 75/25, Novolog 70/30, Humalog 50/50	10-30 minutes	1-6 hours	10-24 hours

Prevention

Studies have shown that by making changes to one's lifestyle, one can significantly lower their risk of having type two diabetes mellitus as well as their risk of developing cardiovascular illnesses. Approximately 3234 obese participants with impaired glucose tolerance or impaired fasting glucose were divided into three groups as part of the diabetes prevention programme. One group was given information about how to exercise and modify their diet, while another group was given metformin and also received information about how to exercise and change their diet. A third group was given a placebo and also received information about how to exercise and change their diet. Following patients for a period of three years, it was discovered that a significantly lower percentage of those in the intense lifestyle group got diabetes.

The prevention of diabetes and its complications can be greatly aided by maintaining a healthy weight, engaging in daily routine activity, and maintaining healthy eating habits. Patients with type 2 diabetes who take these can also expect a reduction in their risk of developing heart disease and high blood pressure.

NEUTROPHIL- LYMPHOCYTE RATIO[34-36]

In a typical human blood sample, there are between 4,000 and 11,000 WBCs per microliter. Granulocytes make up the majority of these white blood cells. Granulocytes in their early stages feature nuclei in the shape of a horseshoe, but as they age, these nuclei transform into multilobed structures. Neutrophilic granules can be seen in the majority of them.

NEUTROPHILS

Biologically active chemicals that are involved in inflammatory reactions can be found in the cytoplasmic granules that are found in neutrophils. In the circulation, a neutrophil has a half-life of approximately six hours on average. They roll along the surface of the endothelium, which selectins cause them to be drawn to in the first place.

Neutrophil adhesion molecules belonging to the integrin family assist in the process of neutrophils becoming attached to selectins. They do this through a process called diapedesis, which involves pushing themselves through the walls of the capillaries.

A significant portion of those that exit the circulation reach the gastrointestinal system, where they are subsequently eliminated from the body.

In addition to numerous proteases, neutrophil granules also include enzymes including NADPH oxidase, catalase, and myeloperoxidases in their composition. The term "respiratory burst" refers to the rapid increase in oxygen consumption and metabolism that occurs in neutrophils as a result of NADPH oxidase. This reaction is responsible for the production of a great deal of free O-radicals.

Myeloperoxidase is the enzyme that catalyzes the transformation of halides and cyanides into the acid forms that correspond to them. These acids, in turn, are powerful oxidants when present on their own.

Neutrophil granules include not just myeloperoxidase and NADPH oxidase, but also an elastase and two metalloproteinases in addition to these two enzymes.

The total number of neutrophils in the body can be broken down into two distinct pools: the circulating pool (CGP), and the marginating granulocyte pool (MGP). The cells in these two pools are the same size, and they maintain a state of equilibrium throughout the experiment. Venipunctured blood does not contain MGP, which are neutrophils that are engaged in adhesion and rolling along the endothelial cells in post capillary venules. Venipunctured blood does not contain MGP. Therefore, the neutrophil content accounts for approximately half of the total number of neutrophils that are present in the vascular compartment.

LYMPHOCYTES

Lymphocytes are mobile cells that do not phagocytose their surroundings. There are various subpopulations of lymphocytes, all of which interact with one another as well as with the monocytes and macrophages that make up the immune system. They contribute to the upkeep of both the humoral and cellmediated immune systems. Lymphocytes that are dividing have higher concentrations of the enzyme n-terminal deoxyribonucleic acid transferase than those that are not dividing. It is only found in immature lymphoid cells in the bone marrow and thymocytes, not in adult lymphocytes. Thymocytes are the cells that produce thymocytes. T lymphocytes contain a significant amount of adenosine de aminase, which is an enzyme that is essential to the functioning of T lymphocytes in the immune system.

INFLAMMATION

Inflammation is a natural defense mechanism that is triggered in response to the invasion of pathogens or poisons. There are two primary aspects that make up the inflammatory response; these are the vascular reaction and the cellular reaction. Both reactions are mediated by chemical components that are obtained from plasma proteins or cells produced as a result of an inflammatory response. These plasma proteins and cells are products of the inflammatory response.

Chronic inflammation is inflammation that has been present for a long period of time and is characterised by concurrent active inflammation, tissue destruction, and tissue healing. Both atherosclerosis and vascular disease are examples of chronic inflammatory processes that affect the arterial wall. These processes are in part triggered by endogenously harmful components of plasma lipids.

Morphological features of chronic inflammation[37-42]

- Mononuclear cell infiltration
- Tissue destruction
- Healing by connective tissue replacement
- New blood vessel formation by elaboration of vascular endothelial growth factor and other angiogenic factors.
- Fibrosis
- The majority of these components of persistent inflammation are present in the etiology of problems associated with diabetes.

NLR IN SUBCLINICAL INFLAMMATION

There are many different disease states that affect the vascular system, and one indication of subclinical inflammation is a high neutrophil-to-lymphocyte ratio. NLR is a reflection of the systemic inflammatory response that is accompanied by chronic disease. However, systemic infections, atherosclerosis, hypertension, chronic renal disease, and diabetes may all have an affect on NLR.

Subclinical vascular inflammation, as evaluated by derived NLR, has been shown to have a correlation with established risk factors of chronic diseases, such as smoking, obesity, hypertension, and increased levels of triglycerides.

MECHANISMS[43-46]

The first stages of inflammation are signaled by endothelial dysfunction, which is caused by the biological reaction of blood components. Endothelial dysfunction causes a reduction in the amount of nitric oxide and prostacylins that are produced. Because of this, the vascular endothelium loses some of its anti-atherogenic, antithrombotic, and vasodilator characteristics.

The normal d-NLR is < 2.0 in control population.

DIABETES AND INFLAMMATION[47,48]

Diabetes type 2 is a condition that is pro-inflammatory, proatherosclerotic, and pro-clotting, and it has a strong connection with the morbidity of cardiovascular disease.

Diabetes mellitus has been linked to having an association with acute phase reactions. In patients with type 2 diabetes, there is a rise in levels of sialic acid, alpha-1 acid glycoprotein, c-reactive protein, amyloid, and interleukin-63. In addition, at the same time, the number of leukocytes is much higher than that of other markers, which indicates continued

subclinical vascular inflammation.

Population-based projections for the future The EPIC-Postsdam project investigated type 2 diabetes and the function of central inflammatory cytokines in the disease (interleukin IL -6 , IL-1beta and tumour necrosis factor). According to the findings of this study, the pathophysiology of diabetes involves some form of subclinical immunological activation.

DIABETES AND NEUTROPHIL LYMPHOCYTE RATIO[42]

NLR is new marker in determining inflammation . It consists of two markers that are active yet nonspecific, which are the mediators neutrophil

and lymphocyte, both of which are productive components of inflammation.[6]

It has been established that poor expression of interleukin-2 receptors is responsible for the reduced lymphocyte proliferation that occurs in type 2

diabetes.

According to the findings of the recent investigations, uncontrolled diabetes is associated with a higher neutrophil count and a lower lymphocyte count.

On the basis of these research, it was proven that uncontrolled diabetes leads to an elevated NLR, which is related to problems of type 2 diabetes.

NEUTROPHIL LYMPHOCYTE RATIO AND MALIGNANCY

Numerous studies demonstrated the importance of a high NLR in determining the prognosis of solid tumors [43.] The following are some of the mechanisms that contribute to a high NLR in malignancy:

1. Inflammation

2. Cytokine production

METHODOLOGY :

Study design- Hospital based cross sectional study.

Study centre- Government STANLEY Medical College and Hospital.

Study period- JULY 2021 TO JULY 2022

Study population- Patients coming to general medicine outpatient department with type 2 diabetes.

INCLUSION CRITERIA:

1 .Adults ≥ 40 years.

2. Patient on oral hypoglycaemic agents for ≥ 4 years .

EXCLUSION CRITERIA:

1.Patients with type 1 DM

2.Patient with recent diagnosis of acute infection or inflammation 3.Patient with uncontrolled hypertension, and secondary hypertension, any chronic kidney injury, end stage kidney disease, hepatic failure, and/or manifest active heart disease such as cardiac failure, acute coronary syndrome, arrhythmia, and cardiac valve disease.

4.patient who total wbc count > 9000, leukopenia, severe anemia, chronic infection, chronic systemic inflammatory disease

5.Patients on anti-inflammatory drugs, systemic or topical steroids, ACE inhibitors, angiotensin II receptor blockers, alcohol.

6.Patients having diseases affecting urinary protein excretion as nephritic syndrome, urolithiasis, renal insufficiency, renal artery stenosis, dehydration state, and UTI.

SAMPLE SIZE :

Based on the reference study done by Sagar Ashokrao Khandare, Sachin Chittawar, Nitin Nahar, T. N. Dubey, Zahraan Qureshi

Sample size calculation for comparison of two proportion

$N=\{2[Z1-\alpha/2+Z1-\beta]2*[p1q1]+[p2q2]\}/d2$

N=120 total sample size

Z =1.96

Z1-α/2= 95% level of confidence

Z1-β= power of test i.e., 80%

P1= 48 Probability of Albuminuria in Diabetic Patient

P2= 25 Probability of NLR ratio Elevated in Diabetic Patient

Q1Q2= (1-P1), (1-P2) d2= expected difference in error margin i.e, 9%

N=120

STUDY TOOLS :

- Pro forms including history and physical examination.

- Neutrophil-to-lymphocyte ratio.

- Spot urine albumin-to-creatinine ratio.

ETHICAL COMMITTEE:

Permission from Institutional Ethical Committee(IEC) is awaited.

CONFLICT OF INTEREST:

There are no conflicts of interest for this study.

DATA COLLECTION : After getting permission from the Institutional Ethical Committee(IEC), information regarding the study were explained to the patients. Written and informed consent was obtained from them. Patient coming to general medicine outpatient department with type 2 diabetes who are above 40 years of age and on oral hypoglycaemic agents for more than 4 years are selected and samples from blood and urine are collected and finally assessed whether NLR ratio is useful in predicting albuminuria or not.

ANALYSIS :

After collection, the data were compiled and entered in Microsoft Excel sheet. SPSS statistical software (SPSS for Windows, version 20.0; SPSS, Inc., Chicago, IL, USA) was used for statistical calculation Continuous data were expressed as mean (±standard deviation) or Median (with interquartile range) according to distribution. Categorical variables were presented as frequency and percentages.P value of <0.05 Confidence Interval(CI).

RESULTS:

Table 1: Age wise distribution of study participants

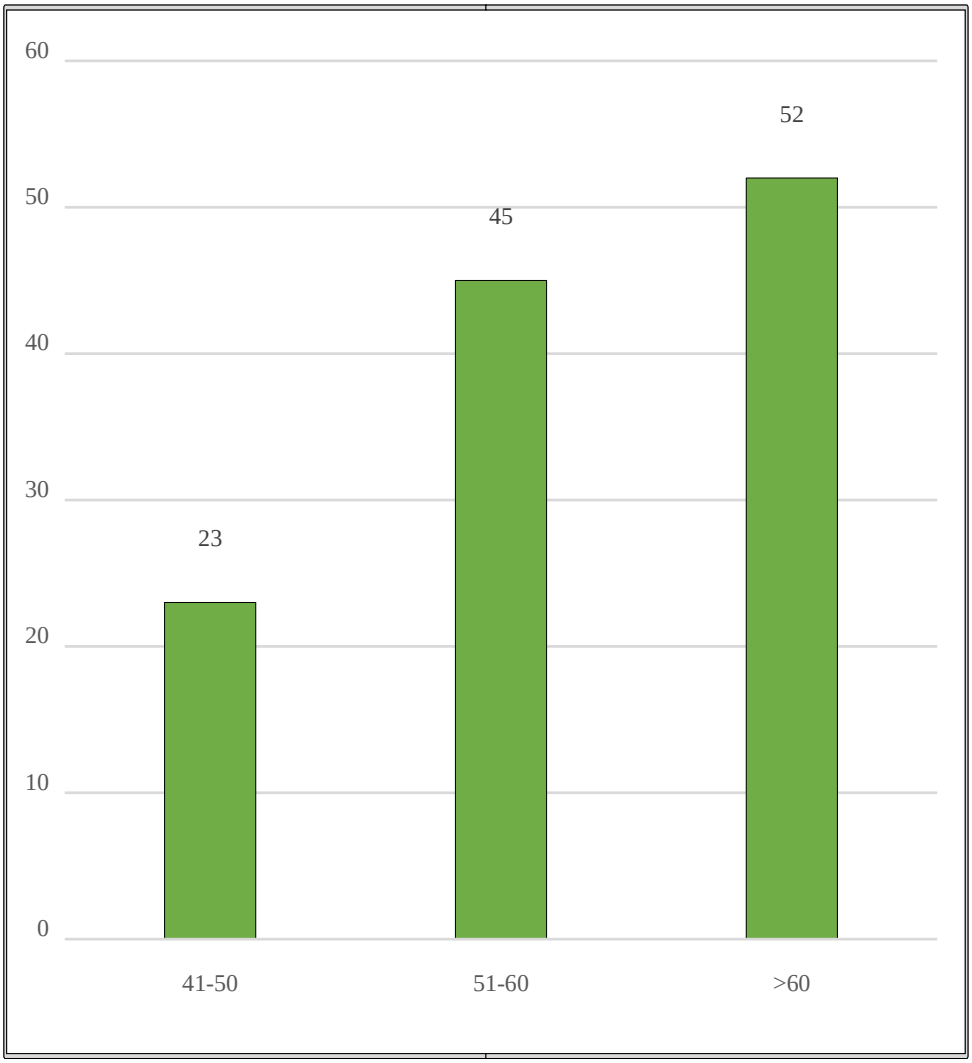
Age in years	Frequency	Percentage	Mean±S.D
41-50	23	19	
51-60	45	37.5	59.67±12.97
>60	52	43.5	
TOTAL	120	100	

In the present study about 43.5% were above 60 years of age. About 37.5% were in the range of 51 to 60 years.

Only 19% were in the age of 41 to 50 years. Mean age is

59.67 and standard deviation is 12.97.

Figure 1: Age wise distribution of study participants



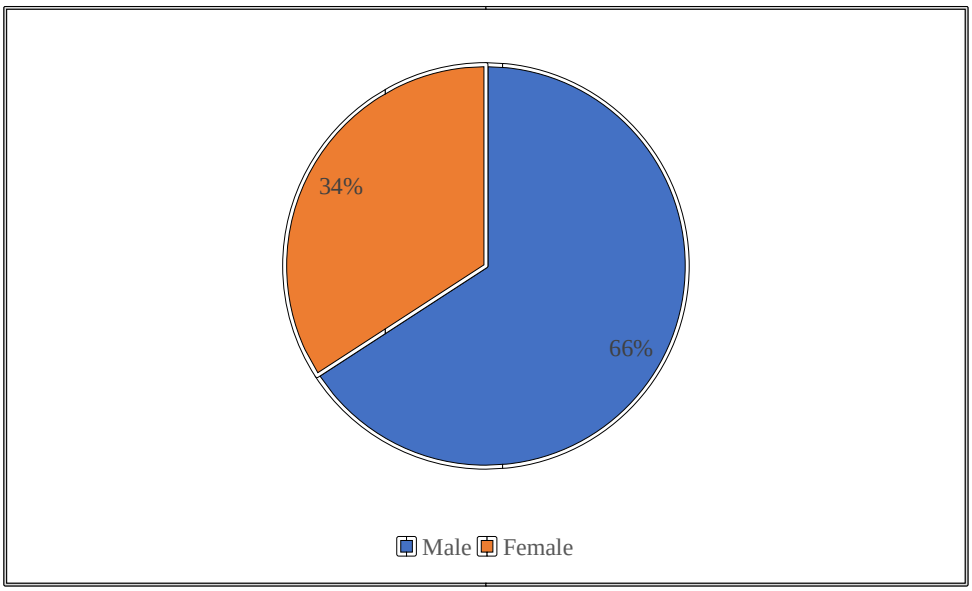
Table

2:Sexwise distribution of study participants

Sex	Frequency	Percentage
Male	79	65.83
Female	41	34.17
Total	120	100

In the present study about 66% were males and 34% were females

Figure 2:Sexwise distribution of study participants



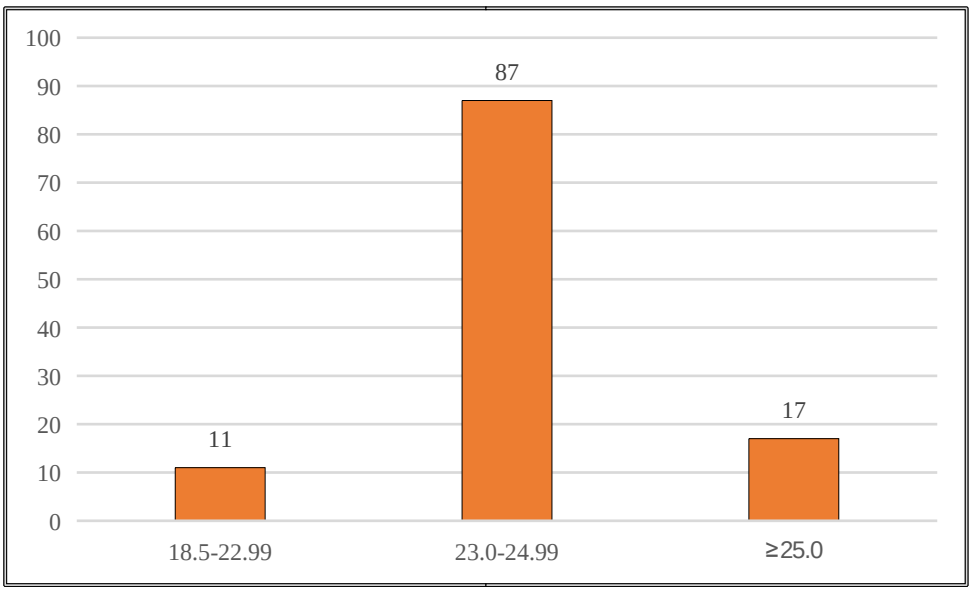
Table

3:Body mass index among study participants

BMI	Frequency	Percentage	Mean ±S.D
18.5-22.99	11	9	
23.0-24.99	87	72.5	24.38±5.48
≥25.0	17	18.5	
Total	120	100	

In the present study about 72.5% were overweight ,18.5% were obese and 9% were normal .Mean body mass index is 24.38 and standard deviation is 5.48

Figure 3:Body mass index among study participants



Table

4: Distribution of duration of diabetes mellitus among study participants

Duration of DM in years	Frequency	Percentage
4 to 10 years	48	40
>10 years	62	60
Total	120	100

About 40% had diabetes for 4 to 10 years. About 60% had diabetes for more than 10 years.

Figure 4: Distribution of duration of diabetes mellitus among study participants

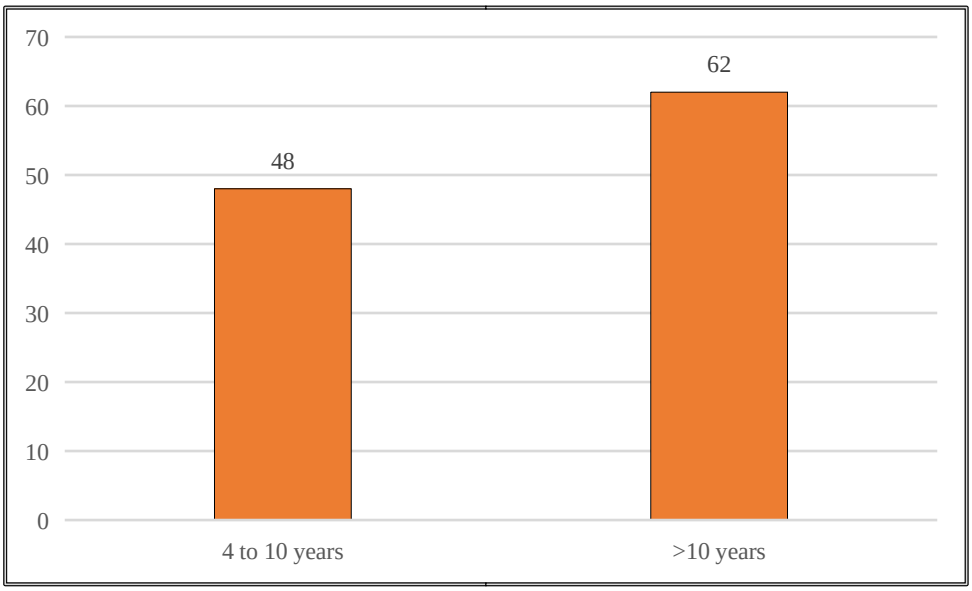


Table
5:Descriptive statistic of biochemical variables

Variables	Mean	Std. Deviation
Hb	13.02	1.74
Platelet	2.67	.67
HbA1C	7.86	2.39
FBS	122.64	26.60
PPBS	202.68	40.69
Total Cholesterol	168.53	41.20
HDL	43.85	7.91
LDL	114.53	28.56

Table

TGL	141.97	68.16
Serum urea	28.26	4.12
Serum creatinine	1.12	0.16
Spot urine ACR	1.76	0.28
GFR(ml/min)	921	2.86
SGOT	130.21	113.2
SGPT	123.1	14.6
Total bilirubin	0.75	0.01

Table

6:Association between NLR and albuminuria

NLR	Albuminuria present (Spot urine ACR > 0.35)	Albuminuria absent (<0.35)	P value
≥ 2.00	66	12	0.01
<2.00	4	38	
Total	70	50	

Number of study population with NLR ≥ 2& microalbuminuria is more in number compared to those who have low NLR. The association is statistically significant (P<0.05).

Table

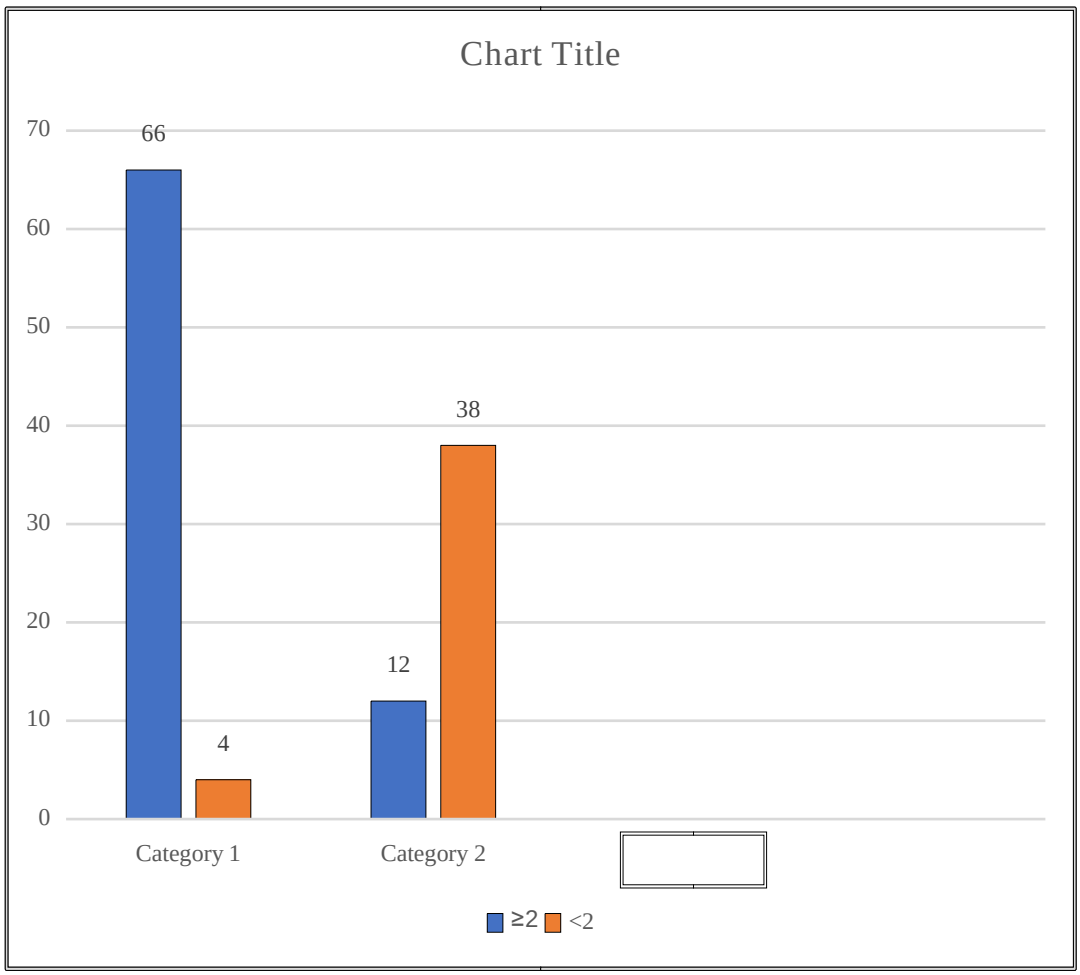


Figure 5: Association between NLR and microalbuminuria

Discussion

It is a new, simple, and inexpensive marker of subclinical inflammation. It has been used recently as a systemic inflammatory marker in chronic diseases.

In addition, the NLR has been classified as a marker of systemic inflammation in different phases of chronic kidney disease and diabetic nephropathy, in addition to having the value of predicting unfavourable outcomes in medical and surgical diseases.[1,2]

The value of NLR in predicting diabetic nephropathy, on the other hand, has not been clarified as of yet.

It has been found that the development of cardiovascular disease is linked to the presence of elevated amounts of inflammatory mediators in the circulation.

In addition, the NLR should be utilized as a marker of diabetic control level in addition to the HbA1c in patients with type 2 diabetes.[6]

Other investigations indicated that a high NLR in otherwise healthy subjects may be indicative of underlying impaired glucose metabolism.

Specifically, we wanted to see if NLR could replace the need for microalbumincreatinine ratio in these settings.

Misinterpretation of the urine collection process, in addition to the additional expense and time required for urine collection analysis, is one more factor that lends support to the usage of these markers.

In the present study about 43.5% were above 60 years of age. About 37.5% were in the range of 51 to 60 years. Only 19% were in the age of 41 to 50 years.

Mean age is 59.67 and standard deviation is 12.97 .In the present study about 66% were males and 34% were females.

In the present study about 72.5% were overweight ,18.5% were obese and 9% were normal .Mean body mass index is 24.38 and standard deviation is 5.48 .About 40% had diabetes for 4 to 10 years. About 60% had diabetes for more than 10 years.

Number of study population with NLR ≥ 2& microalbuminuria is more in number , compared to those who have low NLR.

So,The association is statistically significant ($P<0.05$).

In a retrospective study conducted in Turkey, the researchers demonstrated a positive correlation between high levels of NLR, HbA1c, serum creatinine, and systolic blood pressure and longer duration of diabetes.

The researchers came to the conclusion that NLR is an efficient, cheaper, and readily available marker of inflammation, and that it is known as an important predictor for the existence of microvascular complications in subjects with type 2 diabetes.

Microalbuminuria, which was shown to be a sign of vascular endothelial damage, is typically the first symptom that appears in patients who have nephropathy. Albuminuria is a wellknown predictor of poor renal outcomes in individuals who have type 2 diabetes and in essential hypertension. [7]

As a result, it is crucial to monitor and diagnose albuminuria in order to treat it at an early stage. One of the microvascular complications of diabetes is called microalbuminuria.

Patients with diabetes who have microalbuminuria almost always develop proteinuria and full-blown diabetic nephropathy if they do not receive medical treatment. This process happens in people who have type 1 diabetes as well as type 2 diabetes. In addition, microalbuminuria is frequently accompanied in patients with type 2 diabetes by an elevated CRP level, which points to the activation of inflammatory pathways in the course of renal and cardiovascular atherosclerotic disease. Patients with diabetes often experience DN, which is a common micro-angiopathic consequence.

Diabetic nephropathy is one of the most prevalent factors that might lead to endstage renal failure. Clinically, DN presents itself as increased albumin urea excretion, beginning with microalbuminuria and progressing to macroalbuminuria and eventually end-stage renal disease (ESRD). However, the degree of albuminuria in individuals with DN associated with either type 1 or type 2 diabetes mellitus is not always linked to the course of the disease.

Once overt diabetic nephropathy (DN) has developed as a result of type 1 diabetes, there is persistent proteinuria, and the trend toward end-stage renal disease (ESRD) can only be delayed but not prevented.

Because of this, there is a need for early predictors of DN so that we can predict the disease and stop the advancement of the disease. These predictors would allow us to do both of these things.

Microalbuminuria is characterized by a urine albumin-to-creatinine ratio of greater than 2.5 mg/mmol in men and greater than 3.5 mg/mmol in women, with a 24-hour urine albumin output ranging from 30 to 299 mg[1].

When compared to the population of Caucasians, the Asian Indian population has a significantly higher prevalence of DN. Chronic inflammation encourages the development of micro- and macro-angiopathic complications in diabetic patients, as well as speeds up the progression of these complications, according to the findings of a number of studies that investigated the connection between systemic inflammation and vascular disease. A simple but sensitive measure of inflammation is the total white blood cell count, which is something that can be done simply and consistently in a laboratory setting.

Conclusion

In many cardiac and noncardiac disorders, the neutrophil-lymphocyte ratio in a complete blood count is investigated as an inflammatory marker. This ratio is used to predict the prognosis of diseases such as acute myocardial infarction, stroke, and heart failure. Against this background,our study has been conducted to find that whether NLR can be used as an alternate marker instead of albumin-to- creatinine ratio in diabetic nephropathy.The results of our study has shown positive correlation between NLR and albuminuria.In a setting with limited resources,NLR is an simple,cost effective investigation which can be an alternative for urine albumin-to-creatinine ratio.

LIMITATIONS OF THE STUDY

- Our study is a single center study with only 120 participants. Larger populations needed to be studied to conclude the effect of many variables used in the study on the outcomes of the study.
- Our study is a cross sectional study and the sample size was relatively small.
- Further research with a prospective design and multiple NLR measurements is needed to shed more light on NLR as a marker of inflammation and a probable risk factor for diabetic nephropathy.
- Our study did not include patients of different ethnic groups and races, hence it cannot be generalized to the population.

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PLAGIARISM CERTIFICATE

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ETHICAL COMMITTEE CERTIFICATE

GOVERNMENT STANLEY MEDICAL COLLEGE & HOSPITAL,CHENNAI_-01
INSTITUTIONAL ETHICS COMMITTEE
EC Registration No.ECR/131/Inst/TN/2013/RR-22
DHR Registration Number : EC/NEW/INST/2020/461

TITLE OF THE WORK	:	" NEUTROPHIL TO LYMPHOCYTE RATIO AS A SURROGATE MARKER OF ALBUMINURIA IN TYPE 2 DIABETES MELLITUS "
PRINCIPAL INVESTIGATOR	:	DR. LAVANYA. P.K
DESIGNATION	:	PG IN GENERAL MEDICINE
DEPARTMENT	:	DEPARTMENT OF GENERAL MEDICINE

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 29.06.2021 at the Council Hall, Stanley Medical College, Chennai-1 at 10.30 am.

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

MEMBER SECRETARY,
IEC, SMC, CHENNAI

INFORMED CONSENT

NAME :

AGE : SEX :

ADDRESS :

CONTACT :

PRINCIPAL INVESTIGATOR :

GUIDE :

The details of the study have been provided to me in writing in my own language. I confirm that I have understood the above study and had the opportunity to ask questions. I am willing for blood investigations , clinical examination during the course of the study. I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). I fully consent to participate in the above study.

SIGNATURE OF PARTICIPANT SIGNATURE OF INVESTIGATOR

PLACE:

DATE:

ஆராய்ச்சி ஒப்புதல் படிவம்

பெயர்:

வயது: **பாலினம்:ஆண் / பெண்**

பங்குபெறுபவர் அடையாள எண்:

இந்த ஆராய்ச்சியின் விவரங்களும் அதன்நோக்கமும் முழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டது.

இந்த சோதனையில் நான் கலந்து கொண்டு ரத்த பரிசோதனைக்ககு சம்மதிக்கிறேன்.

எனக்கு விளக்கப்பட்ட விஷயங்களை புரிந்துகொண்டு நான் எனது சம்மதத்தை தெரிவிக்கிறேன்.

நான் என்னுடைய சுயநினைவுடன் மற்றும் முழு சம்மதத்துடன் இந்த ஆராய்ச்சிக்கு என்னை பரிசோதிக்க சம்மதிக்கிறேன்.

பங்கேற்ப்பாளர் கையொப்பம் ஆராய்ச்சியாளர் கையொப்பம்

இடம் :

நாள் :

ஆராய்ச்சி தகவல் தாள்

இதனால் தங்களது ஆய்வறிக்கையோ, அன்றாட செயல்பாடுகளோ பாதிக்கப்படாது என்று தெரிவித்துக்கொள்கிறோம்.

ஆராய்ச்சியின் முடிவுகளை அல்லது கருத்துக்களை வெளியிடும்போதோ தங்கள் பெயரையோ அல்லது அடையாளங்களையோ வெளியிடமாட்டோம் என்பதையும் தெரிவித்துகொள்கிறோம்.

இந்த சிறப்பு பரிசோதனைகளின் முடிவுகளை ஆராய்ச்சியின்போது அல்லது அதன்முடிவில் அறிவிக்கப்படும் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில்தான் இருக்கிறது. மேலும் நீங்கள் எந்த நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

பங்கேற்ப்பாளர் கையொப்பம் ஆராய்ச்சியாளர் கையொப்பம்

இடம் :

நாள் :

NEUTROPHIL-TO-LYMPHOCYTE RATIO AS A SURROGATE MARKER OF ALBUMINURIA IN TYPE 2 DIABETES MELLITUS

PROFORMA

Name Age

Gender

OP No

Presenting Complaints :

Fever/Breathlessness/Palpitation/Abdominal pain:

Others:

Past history :DM/SHTN /CAD/ CKD/Others

Personal history: Smoker/Alcoholic

Clinical examination

BP	
HR	
SPO2	
RR	

Sensorium (GCS)

Temperature

CVS

P/A

RS

CNS

INVESTIGATIONS:

Neutrophil-to-lymphocyte ratio

Spot urine albumin-to-creatinine ratio

USG abdomen

PRINCIPAL INVESTIGATOR

MASTER CHART

	Age	Sex	BMI	DURATIOfHb	Platelet	Tot Chol	HDL	LDL	TGL	HR	Hba1c	FBS	PPBS	Neut	Lymph	NLR	urea	creatinine	urine ACR	eGFR	SGOT	SGPT	T.BIL	IRUBIN
1	61	M	20.76125	5	14.4	1.95	220	44	146	198	89	6.8	120	190	69	25	2.76	17	2	3.21	65	21	26	0.32
2	54	M	25.78125	5	15	2.95	183	50	112	127	61	7.2	225	245	79	13	6.076923	20	1.9	3.61	66	360	250	0.76
3	63	M	29.75779	5	14.2	3.88	203	43	125	180	89	8.8	245	320	56	24	2.33	12	2	1.9	67	23	34	0.29
4	72	F	21.10727	4	11	1.87	197	40	118	136	75	6.9	125	197	77	15	5.133333	33	1.4	3.42	65.6	34	27	1
5	67	M	30.85938	3	12.3	2.32	223	54	180	210	87	10.4	289	342	52	33	1.57	44	1.8	1.89	65.4	35	44	0.73
6	55	F	28.34467	4	10.1	3.6	165	51	109	112	100	8	188	224	72	23	3.130435	18	2.3	3.21	65	44	28	0.54
7	60	M	21.54509	5	11.6	2.89	194	56	121	149	68	6.9	123	180	57	22	2.59	21	1.8	1.61	66	360	250	0.73
8	75	M	27.25089	5	12.7	2.47	156	22	126	141	112	7.9	140	200	79.2	13.8	5.73913	20	1.9	3.43	67	23	34	0.36
9	84	M	21.79931	4	10.9	2.74	167	42	114	175	100	8.8	156	112	200	62.5	25	30	1.9	3.42	65.6	34	27	0.8
10	60	M	27.23922	3	12	2.67	131	34	85	120	120	9.7	267	143	73.7	15.8	4.664557	20	1.8	3.36	65.4	35	44	0.74
11	54	M	20.82094	4	11.9	3.5	107	27	66	42	98	14.4	299	455	75	12	6.25	37	1.8	3.21	65	44	28	1
12	37	F	28.54828	7	13.8	1.5	120	56	103	134	74	13.4	270	302	51.7	23	2.247	33	1.8	1.67	66	56	45	0.38
13	40	M	20.47827	7	12.4	2.3	136	49	109	148	82	6.9	134	198	64	25	2.56	41	1.8	3.43	67	83	97	0.72
14	79	M	24.00549	8	11	1.7	230	45	131	149	65	11.5	180	217	71	24	2.958333	15	1.9	3.42	65.6	45	34	0.46
15	43	F	22.49135	40	7.5	2.88	176	30	128	257	104	12.4	188	206	59.4	22	2.7	19	1.8	1.35	65.4	34	46	0.23
16	25	F	26.986	30	11	2.2	123	57	118	136	82	8.2	222	230	73	15	4.866667	15	1.8	3.21	65	40	33	0.45
17	67	M	26.03749	10	8.2	3.26	234	46	150	280	100	7.5	145	276	79	10	7.9	27	1.3	3.61	66	45	28	0.49
18	70	F	27.20961	30	14.2	2.58	91	32	54	69	92	12.7	234	356	54.7	38	1.4394	44	1.3	0.97	67	56	34	0.48
19	41	M	21.875	6	16	2.63	131	31	94	70	73	17.5	345	778	79	15	5.266667	21	0.5	3.42	65.6	55	45	0.56
20	57	M	25.72103	45	13.6	3.03	200	43	139	273	82	12.9	223	342	61	36	1.6944	29	0.8	0.67	65.4	44	36	0.61
21	70	M	25.20809	7	12.1	3.44	174	34	125	243	84	10.2	210	280	62.7	22	2.85	24	1.1	1.24	65	45	48	0.41
22	57	M	32.89474	8	13.1	2.1	162	39	108	108	64	11.8	190	205	70.6	22.3	3.165919	22	0.8	3.61	66	23	34	1.08
23	42	M	20.54569	4	13.8	2.18	173	41	122	61	89	9.2	182	130	52.3	33.4	1.565868	25	0.7	0.98	67	34	49	1.1
24	58	M	23.30668	2	14.1	2.51	135	37	92	57	84	12.3	232	111	55	31	1.774194	69	1.5	1.42	65.6	45	65	0.92
25	60	M	22.52151	35	14.6	3.51	206	36	153	144	90	11.1	234	287	77	18	4.277778	29	1	3.36	65.4	40	45	0.47
26	79	M	25.45236	3	15.7	2.44	240	38	173	320	67	9	179	128	75.4	17.4	4.333333	37	1.2	3.21	65	45	34	0.82
27	38	M	33.12458	4	16	2.4	212	38	168	121	114	6.9	189	342	50.8	22	2.309	56	1.1	1.61	66	34	45	0.81
28	61	M	22.82688	15	14	1.7	166	44	118	62	82	12.2	198	145	62.4	33.2	1.8795	19	0.8	1.43	67	45	23	0.24
29	58	M	27.7671	5	7	1.5	216	41	149	111	84	11.9	243	180	76.4	18	4.244444	21	0.5	3.42	65.6	33	24	1.67
30	38	M	40.42806	3	14.5	2.89	222	53	160	280	82	7.4	127	200	62	31.2	1.987179	26	1.5	0.78	65.4	34	45	0.18
31	42	M	28.44444	4	14	1	158	54	117	100	78	10.1	165	112	70	23	3.043478	28	1	3.21	65	55	34	0.78
32	82	M	36.75698	7	13.2	2.25	140	46	89	98	87	8.2	143	143	73.2	16.8	4.357143	16	0.7	3.61	66	55	34	0.72
33	60	M	34.62604	5	12.2	2.52	140	40	99	88	83	10.9	217	455	62	25.8	1.797	35	1.2	1.43	67	41	43	1.22
34	49	M	25.63117	7	14.2	3.16	184	32	133	124	80	15.3	367	302	62.3	26.5	2.350943	61	1.7	3.42	65.6	35	45	0.49
35	60	M	26.03749	8	14.4	2.11	230	36	168	124	53	10.5	221	132	57	28.7	1.986063	56	1.4	1.36	65	45	56	1.68
36	69	M	28.125	10	14.8	2.75	157	39	110	142	57	9.7	145	217	64.9	28	2.317857	28	1.1	3.21	66	34	41	1.05
37	65	M	21.00767	14	13.3	2.32	170	40	123	98	76	7	132	206	58.4	36.9	1.582	11	0.5	1.54	67	214	148	0.39
38	48	M	26.67276	7	13.7	3.19	134	48	96	109	75	11.1	189	230	70.1	23.5	2.982979	49	1.9	3.43	65.6	35	51	1.09
39	50	M	30.44983	8	15.6	3.5	164	28	124	120	80	8.3	143	180	57.3	23	2.491	50	1.2	1.06	65.4	188	110	1.1
40	46	M	21.10727	15	12	2.73	205	37	139	165	84	11	157	209	70	21.7	3.225806	17	0.8	3.36	65	34	45	0.34
41	37	M	29.00059	14	14.8	2.55	242	47	166	186	105	12.8	269	778	61.6	31.7	1.943218	45	1.2	1.21	66	22	45	0.82
42	71	M	26.10656	7	14.8	2.84	182	40	123	91	82	8	156	342	79.5	15.9	5	20	0.5	3.61	67	45	35	1.18
43	82	M	30.04326	6	12.4	3.3	206	40	156	128	80	6.9	125	280	72	20	3.6	51	1.3	3.43	65.6	34	46	1.2
44	67	M	24.16716	35	11.3	1.89	252	43	186	129	78	7.5	124	205	55	21	2.61	60	1.5	0.45	65.4	35	45	0.76
45	59	M	33.20313	14	14.1	1.78	117	51	57	52	86	9.2	198	130	74	16	4.625	48	1.3	3.36	65	45	34	1.07
46	62	M	26.03749	4	13	2.75	178	43	87	119	84	8.7	157	111	71	19	3.736842	57	1.4	3.21	66	55	23	0.8
47	66	M	27.09925	4	11.4	2.97	111	39	75	68	74	8.6	134	287	56.9	24	2.37	42	1.4	1.61	67	55	23	1.2
48	65	M	26.7094	3	13.3	2.32	170	40	123	98	76	13.5	256	128	58.4	22	2.654	45	1.3	1.78	65.6	34	46	0.41
49	88	M	27.34375	4	10.6	3.54	144	59	74	99	80	10.1	164	342	49.8	26.4	1.886364	26	0.6	1.17	65.4	35	45	0.82
50	75	M	24.80159	5	13.8	2.82	112	25	77	91	80	12.3	267	145	63.7	20.4	3.122549	61	1.5	3.36	65	45	34	0.82
51	70	M	29.7442	6	11.7	4.15	202	42	144	127	78	7.2	156	180	63.3	31.5	2.009524	21	0.8	3.21	66	55	23	0.9
52	52	M	25.35154	7	12.5	2.14	192	57	120	146	84	6.9	129	200	59	36	1.638	17	0.9	1.78	67	55	23	1.3
53	55	M	26.76978	5	17	1.71	215	54	152	73	89	9	133	112	78	14	5.571429	38	1.1	3.21	65.6	21	26	0.91
54	58	M	21.45357	5	16.5	2.27	180	29	117	524	82	9.1	154	143	52.6	38.8	1.35567	18	0.7	1.61	65.4	360	250	0.77
55	50	M	28.66889	5	13.7	2.49	139	36	106	147	80	8.4	135	455	73.8	20.7	3.565217	14	2	3.43	65	23	34	0.58
56	48	M	22.14533	5	16.2	1.93	144	51	86	90	78	10.8	176	302	57.2	29.7	1.925	45	1.9	1.42	66	34	27	0.49
57	52	M	26.57313	5	15.1	3.37	256	49	177	186	82	7.8	146	132	77.7	17.4	4.465517	19	2	3.36	67	35	44	1.13
58	39	M	26.89232	4	15.6	2.74	187	25	135	182	80	7.3	154	217	57.9	35.3	1.640227	42	1.4	1.21	65.6	44	28	0.74
59	56	M	25.72103	3	17	1.72	170	45	87	98	88	11.5	242	206	60.9	31.9	1.909091	39	1.8	1.61	65.4	360	250	0.27
60	59	M	26.986	4	17	2.53	143	51	100	112	80	7	145	230	63.3	29.4	2.153061	44	2.3	3.43	65	23	34	0.48

61	60M	20.76125	5	12.2	2.52	150	43	105	120	78	9.8	267	339	53.3	15.1	3.529801	42	1.8	3.42	66	34	27	1.29
62	54M	25.78125	5	15.5	2.98	198	34	87	104	72	12.4	193	209	59	34	1.7352	19	1.9	0.79	67	35	44	0.37
63	76M	29.75779	4	15	2.2	110	48	96	125	74	6.9	165	203	67	25	2.68	21	1.9	3.21	65.6	44	28	1.2
64	31M	21.10727	3	15.2	3.76	196	41	130	55	50	9.5	176	342	59	36	1.638	37	1.8	0.98	65.4	56	45	1.6
65	78F	30.85938	4	13.1	2.91	166	36	121	77	88	9.9	165	280	80	11	7.272727	22	1.8	3.21	65	83	97	0.35
66	64F	28.34467	7	12	2.57	127	38	76	98	72	7.6	127	205	57.5	32	1.796	20	1.8	0.87	66	45	34	0.57
67	59M	21.54509	7	14.8	2.64	254	57	149	208	64	7.5	136	216	67.6	27.7	2.440433	30	1.8	3.43	67	34	46	0.98
68	62M	27.25089	8	11.4	2.24	140	53	88	134	92	7.5	137	230	72	18	4	25	1.9	3.42	65.6	40	33	1.3
69	61M	21.79931	40	14	1.7	166	44	118	62	82	7.9	158	295	62.4	35	1.7825	38	1.8	0.67	66	45	28	0.56
70	79M	27.23922	30	13	2.1	128	48	108	79	65	6.9	199	298	70	24	2.916667	33	1.8	3.21	67	56	34	0.63
71	65M	20.82094	10	12.4	1.91	118	56	78	120	84	10.1	302	453	65	27	2.407407	16	1.3	3.61	65	55	45	0.78
72	62M	28.54828	30	13.3	3.18	119	37	79	121	90	9.7	198	287	78	12	6.5	20	1.3	3.43	66	44	36	0.44
73	57M	20.47827	6	15	2.36	109	48	59	41	80	10.6	201	387	60	34	1.7647	41	0.5	0.76	67	55	23	0.41
74	75M	24.00549	45	13.8	2.11	186	37	140	142	79	12.9	323	487	60.9	24.5	2.485714	85	0.8	3.36	65.6	55	23	0.51
75	56F	22.49135	7	9.3	3.53	140	45	116	98	98	14.7	311	564	76.9	16.4	4.689024	36	1.1	3.21	65.4	21	26	0.49
76	52M	26.986	8	12.9	2.75	136	41	78	108	87	15.5	365	467	65.5	24	2.729167	18	0.8	3.61	65	360	250	0.79
77	67F	26.03749	4	11.9	2.93	124	46	110	138	76	8.9	165	200	54	31.5	1.7142	56	0.7	0.61	66	23	34	0.6
78	43M	27.20961	2	14	1.98	132	56	118	130	64	10.2	243	321	70	21	3.333333	23	1.5	3.43	67	34	27	0.88
79	72M	21.875	35	11	1.85	110	43	67	98	72	6.9	124	160	67	20	3.35	21	1	3.42	65.6	35	44	0.7
80	65F	25.72103	3	12.7	2.65	230	42	126	178	76	7.2	135	206	52	39	1.333	48	1.2	0.98	65.4	44	28	0.76
81	59M	25.20809	4	13.8	3.7	187	54	118	128	85	11	265	387	69	18	3.833333	44	1.1	3.61	65	360	250	0.75
82	68M	32.89474	15	12.1	2.2	165	41	64	134	68	7.7	187	201	57	37	1.54	42	0.8	0.8	66	23	34	0.61
83	72M	20.54569	5	13	3.67	109	48	78	102	74	7.8	156	209	63.9	24	2.6625	31	0.5	4.51	67	34	27	0.44
84	58F	23.30668	3	12.3	1.9	130	40	117	120	87	11.3	208	778	72	18	4	70	1.5	7.41	65.6	35	44	0.32
85	49M	22.52151	4	15	3.57	180	56	102	98	88	10.4	288	342	55	34	1.617	32	1	0.89	65.4	44	28	1.3
86	63M	25.45236	7	14	2.98	109	58	78	120	62	15.6	325	583	56	35	1.6	75	0.7	6.86	65	56	45	0.3
87	78M	33.12458	5	11	1.78	140	43	80	110	88	13.8	293	487	72	16	4.5	35	1.2	12.34	66	83	97	1.04
88	52F	22.82688	7	12.4	2.82	200	48	107	138	78	6.9	139	200	58	34	1.705	23	1.7	1.89	67	45	34	1.44
89	67M	27.7671	8	13.7	2.67	230	45	123	156	100	8.2	190	256	72	26	2.769231	17	1.4	4.51	65.6	34	46	0.77
90	61M	40.42806	10	15	3.86	202	51	136	160	76	7.4	135	198	74	18	4.111111	20	1.1	7.41	65.4	40	33	0.48
91	48M	28.44444	14	12.4	3.38	120	56	118	128	80	11.5	238	278	58.9	34	1.7323	37	0.5	1.56	65	45	28	0.73
92	74M	36.75698	7	13.1	1.45	135	44	57	78	66	9.7	148	204	61.9	34	1.82	38	1.9	0.89	66	56	34	0.7
93	66M	34.62604	8	14	2.9	210	48	148	190	89	7.1	153	187	71.5	22	3.25	11	1.2	12.34	67	55	45	0.71
94	58F	25.63117	15	12.6	3.45	230	40	124	136	78	7.8	187	207	56	36	1.555	32	0.8	1.56	65.6	44	36	1
95	62M	26.03749	14	12.6	2.23	156	56	112	180	98	8	214	274	54	34.8	3.043478	16	1.2	4.51	65.4	55	23	0.35
96	55M	28.125	7	13.6	2.35	180	45	108	125	65	11.9	250	380	61	34	1.79411	30	0.5	7.41	65	55	23	0.62
97	60F	21.00767	6	11.8	2.76	220	43	130	198	78	7.2	136	192	56	34	1.647	17	1.3	0.89	66	21	26	1
98	70F	26.67276	35	10.8	3.67	180	38	98	126	68	7.5	129	176	78	15	5.2	14	1.5	6.86	67	360	250	0.95
99	65M	30.44983	14	11.6	3.24	230	46	198	320	78	10.1	162	290	66	21	3.142857	18	1.3	12.34	65.6	23	34	1.22
100	60F	21.10727	4	11.2	2.89	160	47	112	126	89	6.9	127	190	60	38	1.57	42	1.4	1.86	66	34	27	0.6
101	58M	28.44444	4	12.6	3.21	180	45	127	150	78	6.9	132	160	80	14.6	5.479452	60	1.4	6.86	65	35	44	1.8
102	61M	36.75698	3	13.2	3.45	160	38	116	150	98	8.9	228	310	56	33.5	1.671	17	1.3	0.98	66	44	28	0.4
103	78M	34.62604	4	12.3	1.86	189	43	108	190	68	9.3	137	280	77.6	22	3.527273	32	0.6	4.42	67	360	250	0.46
104	50F	25.63117	5	11.6	3.24	140	38	98	146	112	11.5	238	278	54	35	1.542	37	1.5	0.98	65.6	23	34	0.76
105	55M	26.03749	6	12.3	2.59	110	32	78	89	82	9.7	148	204	74	12.6	5.873016	38	0.8	7.41	65.4	34	27	0.29
106	40F	28.125	7	11.9	1.67	108	48	80	98	84	7.1	153	187	57	34	1.6764	11	0.9	14.26	65	35	44	1
107	46M	21.00767	5	13.2	3.2	140	50	104	160	80	7.8	187	207	56	31	1.8	32	1.1	1.05	66	44	28	0.73
108	69M	26.67276	5	12.5	1.98	236	42	142	320	70	8	214	274	72	26.4	2.727273	16	0.7	12.34	67	56	45	0.54
109	45F	30.44983	14	10.7	3.89	134	44	110	126	98	11.9	250	380	61	34	1.7941	30	1.3	0.78	65.6	83	97	0.73
110	46F	21.10727	7	12.8	2.46	118	52	109	140	78	7.2	136	192	73	14.6	5	17	1.5	4.51	65.4	45	34	0.36
111	62M	28.44444	6	9.6	1.56	220	44	148	320	69	7.5	129	176	72	10	7.2	14	1.3	7.41	65	34	46	0.8
112	68F	36.75698	35	12.3	2.56	100	38	67	110	89	10.1	162	290	75.3	20.2	3.727723	18	1.4	14.26	66	40	33	0.74
113	52M	34.62604	14	15.8	3.48	126	44	108	98	110	6.9	127	190	58.5	34	1.7205	42	1.4	0.87	67	45	28	1
114	40M	25.63117	4	11.8	1.85	180	56	112	180	88	6.9	132	160	64	31.2	2.051282	60	1.3	12.34	65.6	56	34	0.38
115	43F	26.03749	4	13.6	1.87	140	48	102	100	80	8.9	228	310	51	36	1.41	17	0.6	1.51	65.4	55	45	0.72
116	70M	28.125	3	14.6	2.59	136	44	86	104	78	9.3	137	280	74.2	15.6	4.75641	32	1.5	4.51	65	44	36	0.46
117	50M	21.00767	4	13.3	2.56	150	50	109	98	88	6.9	127	190	77	13.2	5.833333	37	0.8	7.41	66	40	33	0.23
118	50M	26.67276	5	13.8	3.45	178	42	129	130	79	6.9	132	160	64	36	1.777	38	0.9	1.26	67	45	28	0.45
119	62F	30.44983	6	12.5	3.12	220	32	148	280	65	8.9	228	310	57	34	1.6764	11	1.1	0.78	65.6	56	34	0.49
120	59M	21.10727	7	11.9	4.1	148	40	126	150	60	9.3	137	280	77.6	14.6	5.315068	32	0.7	12.34	65.4	55	45	0.48