A CROSS SECTIONAL STUDY OF LOW HEMOGLOBIN IN DIABETIC PATIENTS AND ITS ASSOCIATION WITH NEPHROPATHY AND RETINOPATHY

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CHENNAI

MAY 2019

BONAFIDE CERTIFICATE

This is to certify that the dissertation entitled **"A CROSS SECTIONAL STUDY OF LOW HEMOGLOBIN IN DIABETIC PATIENTS AND ITS ASSOCIATION WITH NEPHROPATHY AND RETINOPATHY**" is a bonafide work done by **Dr. LAKSHMI PRIYA,** post graduate student in the Department of General Medicine, Government Kilpauk Medical College, Chennai-10,under our guidance and supervision in partial fulfillment of the rules and regulations of **The Tamil Nadu Dr. M.G.R. Medical University** for the award of **M.D. Degree Branch I (General Medicine)** during the Academic period from **2016 to 2019.**

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ACKNOWLEDGEMENT FROM THE GUIDE

This dissertation work done by **Dr. LAKSHMI PRIYA,** titled **"A CROSS SECTIONAL STUDY OF LOW HEMOGLOBIN IN DIABETIC PATIENTS AND ITS ASSOCIATION WITH NEPHROPATHY AND RETINOPATHY"** was under my supervision for the entire duration of the study and I ensure that the candidate followed the rules of the ethical committee.

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DECLARATION

I, solemnly declare that the dissertation entitled **"A CROSS SECTIONAL STUDY OF LOW HEMOGLOBIN IN DIABETIC PATIENTS AND ITS ASSOCIATION WITH NEPHROPATHY AND RETINOPATHY"** is done by me at Government Kilpauk Medical College, Chennai – 10 during the academic year 2016 to 2019 under the guidance and supervision of **Prof. Dr. A.SAMUEL DINESH, M.D.**, to be submitted to **The Tamil Nadu Dr. M.G.R. Medical University** towards the partial fulfillment of requirements for the award of **M.D. DEGREE IN GENERAL MEDICINE BRANCH – I.**

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ABBREVIATIONS

ACE	–	Angiotensin Converting Enzyme
CKD	-	Chronic Kidney Disease
DM	–	Diabetes Mellitus
DN	-	Diabetic Nephropathy
DR	-	Diabetic Retinopathy
EMP	–	Embden Meyerhof Parnas Pathway
EPO	–	Erythropoietin
ESRD	–	End Stage Renal Disease
GBM	–	Glomerular Basement Membrane
Hb	-	Hemoglobin
MODY	-	Maturity Onset Diabetes of Young
NPDR	–	Non Proliferative Diabetic Retinopathy
PCT	-	Proximal Convoluted Tubule
PDR	–	Proliferative Diabetic Retinopathy
RAS	–	Renin Angiotensin System
RPI	–	Reticulocyte Production Index

CONTENTS

INTRODUCTION

INTRODUCTION

A country's development is measured in terms of nutritional status of the population as well as the proportion of independent population. In India, the amount of nutrition obtained by an individual is below average and has a strong impact on his health. Anemia is considered as a public health problem because it affects the majority of its population, especially in the economically productive age group. The physiological characteristics of a female make this population more prone to anemia.

The rapidly emerging technology in developing countries together with westernization of culture in India has made it prone to introduction of sedentary lifestyle as a mandatory ingredient for its population. The sedentary lifestyle along with genetic factors and other determinants has made diabetes mellitus as one of the common problems in India. The diabetic population is predicted to raise to about 70 million by 2025 by the International Diabetes Federation. The longer lifespan as expected by growing medical facilities has made the population face the angry face of a disease with its complications.

Diabetes is peculiar in that it stays silent until it rises up with its ferocious picture affecting the vital organs. The delicacy applied to the treatment of diabetes mellitus begins in the asymptomatic stage itself to prevent the damage that incurs on the vital organs. As diabetes is a metabolic disorder, it affects almost all the organs. Of importance the renal failure due to diabetes mellitus is the leading cause of end stage renal disease.

The vision, the sense that cannot be replaced by anything is very unique that it takes away the individual from the existence in the world though he is present physically. Therefore, with importance paid to the causes of blindness, diabetes mellitus ranks the fourth top cause. The hypoxia being the primary cause of retinal damage in diabetes, the hypoxic environment caused by anemia in prior increases the insult caused by diabetes.

When anemia is accompanied by diabetes mellitus, the development of complications is accelerated and more severe. With one hand having anemia and the other hand diabetes mellitus, the general well being is hampered to a considerable extent. Anemia decreases the amount of oxygen delivery to tissues and creates some amount of background damage to the organs. With the diabetes mellitus and with its increasing duration, the already damaged tissue with the effect of anemia is prone to excessive damage due to diabetes mellitus.

AIMS
&
OBJECTIVES

AIM OF THE STUDY

To verify the association between low hemoglobin in diabetic patients with diabetic nephropathy and diabetic retinopathy.

OBJECTIVES OF THE STUDY

- To estimate the prevalence of low hemoglobin in patients with Type 2 diabetes mellitus
- To establish association between anemia and presence of diabetic retinopathy and diabetic nephropathy

REVIEW OF LITERATURE

REVIEW OF LITERATURE

ANEMIA

Anemia is defined as decreased red cell mass resulting in decreased oxygen carrying capacity to the tissues.

WHO DEFINITION OF ANEMIA

WHO defines anemia as hemoglobin less than 13g/dl in men and less than 12g/dl in women.

HEMATOPOIESIS

Erythron is the organ responsible for red cell production. Eythropoiesis occurs primarily in bone marrow and it also occurs in liver and spleen. In the fetus, it occurs in the mesodermal cells of yolk sac. It is a dynamic organ consisting of marrow erythroid precursor cells, which are a rapidly proliferating pool and a large mass of circulating RBCs. Hematopoietic stem cells differentiate into two series – myeloid and erythroid/megakaryocyte. The erythroid/megakaryocyte series with the help of erythropoietin, the series of cells differentiate into erythroid cells. The erythroid series within 4.5 days differentiate into pronormoblast and then into RBCs.[(1)] Red blood cells are about 8 um in diameter, discoid in shape and anucleate. Everyday about 0.8 – 1 % of RBCs are replaced.

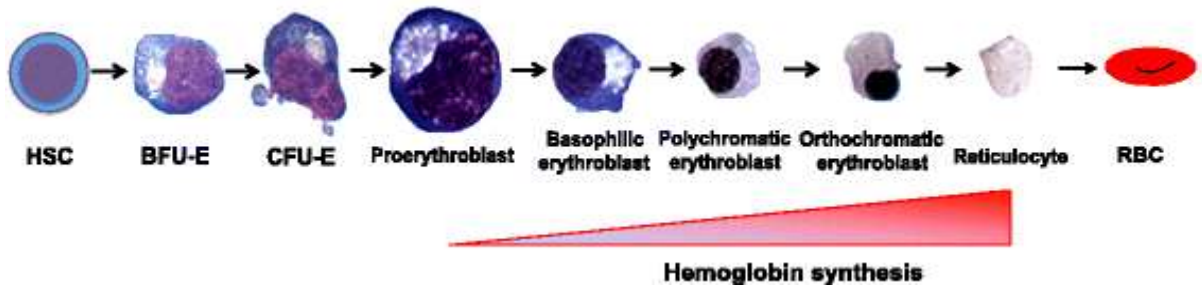


Figure 1. ***Erythropoiesis.*** *In the bone marrow, Hematopoietic stem cell gets committed to myeloid series, which undergoes a developmental pathway of Ribosome synthesis, hemoglobin accumulation and nucleus ejection within 5-7 days to form erythrocyte. (HSC - Hematopoietic stem cell; BFU-E Burst Forming Unit – Erythroid; CFU-E Colony forming Unit – Erythoid; RBC – Red blood cell).*

ERYTHROPOIETIN

Erythropoietin is produced by peritubular capillary lining in kidney; a small amount is also produced in hepatocytes. Erythropoietin production is regulated by EPO gene, which is under the regulation of HIF – 1a (Hypoxia Inducible Factor – 1a). With oxygen, HIF – 1a is hydroxylated with proline and undergoes degradation through proteosome pathway. Normal level of erythropoietin in health is 10 – 25 U/L. It has a half life of 6-9 hours. Erythropoietin stimulation can increase RBC production 4 -5 times in about 2 weeks.[(2)]

HEMOGLOBIN

Hemoglobin is a globular structure made up of four subunits. One heme and a polypeptide chain makes one subunit. Heme is an iron containing porphyrin derivative. All the polypeptides together constitute the globin component. There are two pairs of

polypeptides in each hemoglobin molecule. 2 chains are called α chains, which contain 141 amino acids in each chain. The other 2 chains are called β chains, which contain 146 amino acids in each chain. Therefore, most of the human adult hemoglobin is made up of α2β2. Small amount of hemoglobin in adults is made up of fetal hemoglobin. The terminal valine in each β chain has an importance in that the glucose is attached to it and is termed as HbA1c, which is measured as a marker for the glycemic control in diabetic patients.

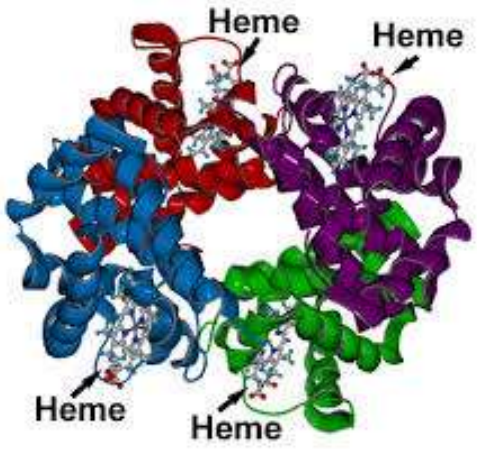


Figure 2. ***Structure of hemoglobin.*** *2 pairs of polypeptide chains (2α and 2β). Each polypeptide has a heme molecule.*

CLASSIFICATION OF ANEMIA

1. Hypoproliferative / marrow production defects
2. Ineffective erythropoiesis
3. Hemolysis / blood loss

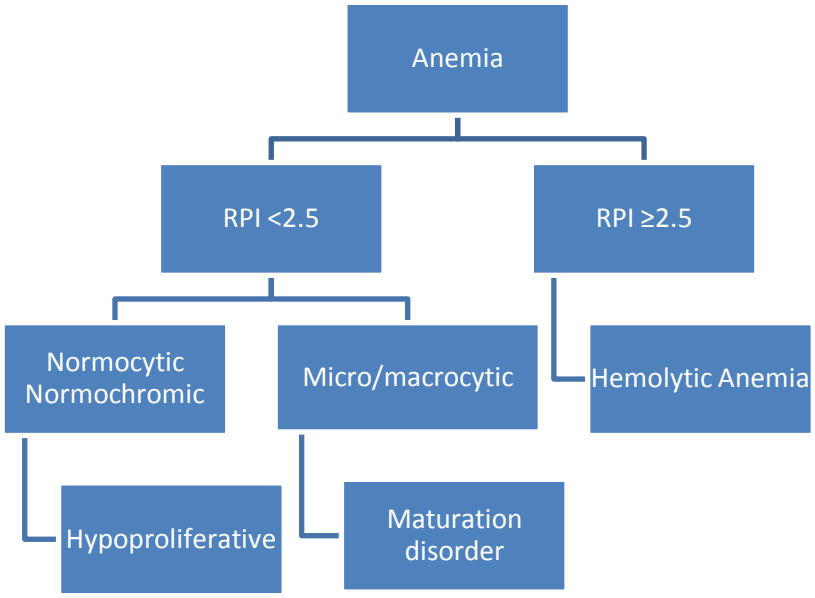


Figure 3. ***Classification of Anemia.*** *Based on morphology on peripheral smear and reticulocyte count. (RPI – Reticulocyte Production Index)*

RETICULOCYTE PRODUCTION INDEX

It is an estimate of marrow production relative to normal. The reticulocytes are prematurely released into the blood circulation from the bone marrow. This is detected by nucleated red cells in peripheral blood (shift cells)

Corrected Reticount = Reticount (%) x (Hematocrit/45)

Reticulocyte Production Index = Corrected Reticulocyte count / Maturation index

Maturation time of reticulocytes:

Hematocrit	Maturation time (days)
45	1
35	1.5
25	2
15	3

The reticulocyte production index provides a refined picture about the status of bone marrow. It defines the bone marrow integrity in responding to the decreased red blood cells in the periphery. Normally, the reticulocyte stay in the bone marrow for about 3 to 4 days before it is matured and released into the peripheral circulation.[3] In severe anemia, to combat the decreased red blood cells, reticulocytes are released in to the circulation in just 1 day of bone marrow life as a compensatory mechanism. These cells are called shift cells and can be detected in the peripheral smear using supravital dye staining.

CAUSES OF HYPOPROLIFERATIVE ANEMIA

The production of red blood cells in the bone marrow is defective due to various factors that affect the structure of the bone marrow or the process of erythropoiesis that occurs in the bone marrow. The process of erythropoiesis can be affected by decreased stimulation of the erythroid precursors or by decreased nutrition for the precursors.

The systemic inflammatory response decreases the stimulation of bone marrow by elaboration of interleukins. Systemic diseases like hypothyroidism decreases the rate of turnover of the bone marrow cells and thus decreased production of red blood cells.

The causes of hypo proliferative anemia are:

- Marrow damage
    - Infiltration
    - Fibrosis
    - Aplasia
- Iron deficiency anemia
- Decreased stimulation
    - Inflammation (Increased IL-1)
    - Metabolic defect (hypothyroidism)
    - Renal disease (decreased erythropoietin)

CAUSES OF MATURATION DEFECTS

The hematopoietic stem cell is committed to form erythroid precursor in the bone marrow, which undergoes a series of changes to form mature red blood cell. The maturation of cytoplasm involves hemoglobin synthesis, where the defect may occur in inadequate production of one more chains of hemoglobin.[4] The nucleus has to undergo maturation and get extruded from the cell. The deficiency of maturation factors causes ineffective erythropoiesis.

Causes of maturation defects are:

- Cytoplasmic maturation defects
    - Severe iron deficiency
        - Ineffective erythropoiesis
    - Heme synthesis defects
        - Sideroblastic anemia
    - Globin synthesis defects
        - Thalessemia
- Nuclear maturation defects
    - Deficiency of Vitamin B12
    - Folate deficiency
    - Alcohol
    - Methotrexate

CAUSES OF HEMOLYTIC ANEMIA

The red blood cells after production in bone marrow enter the blood stream and stays there for about a period of 120 days.[6] When the red blood cells are destroyed earlier than the expected life span, it is termed as hemolytic anemia. Hemolysis may occur as an intravascular process or as a extra vascular process. Intravascular hemolysis occurs within the blood stream, causing hemoglobinuria. Extravascular hemolysis occurs in the extramedullary organs causing hepatomegaly and splenomegaly clinically.

Abnormalities in the structure of hemoglobin may cause its precipitation on the red cell membrane, which is attacked by the macrophages in the spleen and causes hemolysis. The process of immune activation in auto immune hemolytic anemia causes destruction of red blood cells prematurely.

The causes of hemolytic anemia are:

- Blood loss
- Intravascular hemolysis
- Metabolic defect (EMP defect, glutathione reductase pathway defect)
- Hemoglobinopathies (sickle cell disease, thalessemia)
- Membrane abnormality
- Immune destruction (Autoimmune hemolytic anemia)

FUNCTIONAL ANATOMY OF KIDNEY

Nephron is the functional unit of a kidney. Each human kidney has about 1.3 million nephrons.[7] Each nephron is made up of a glomerular apparatus consisting of a bowman's capsule and a tuft of capillaries within it, which is followed by the proximal convoluted tubule, where the reabsorption of solutes occurs. The loop of henle consists of thin descending, thin ascending and thick ascending limb. It is followed be the collecting duct. The nephron situated in the cortex is called cortical nephron and contains short loop of henle.

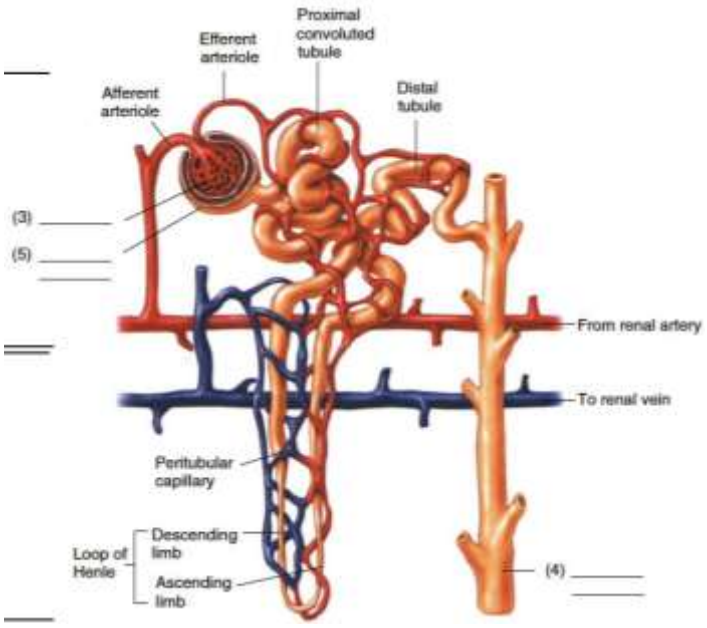


Figure 4. ***Structure of Nephron.*** *(3) tuft of capillaries (5) Bowman's capsule, which together form glomerular apparatus. (4) collecting duct*

GLOMERULAR APPARATUS

Glomerulus is a structure formed by invagination of a tuft of capillaries into dilated, blind end of nephron, which is called Bowman's capsule. Each glomerulus is about 200 μm diameter.[8] Blood flowing into the nephron is separated from bowman's capsule by 2 layers – capillary endothelium and the epithelium of capsule.

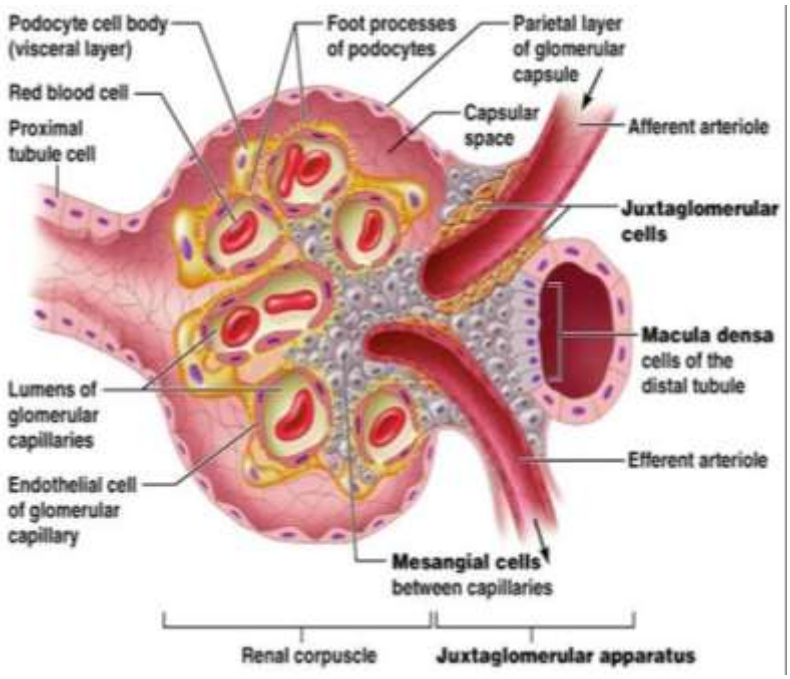
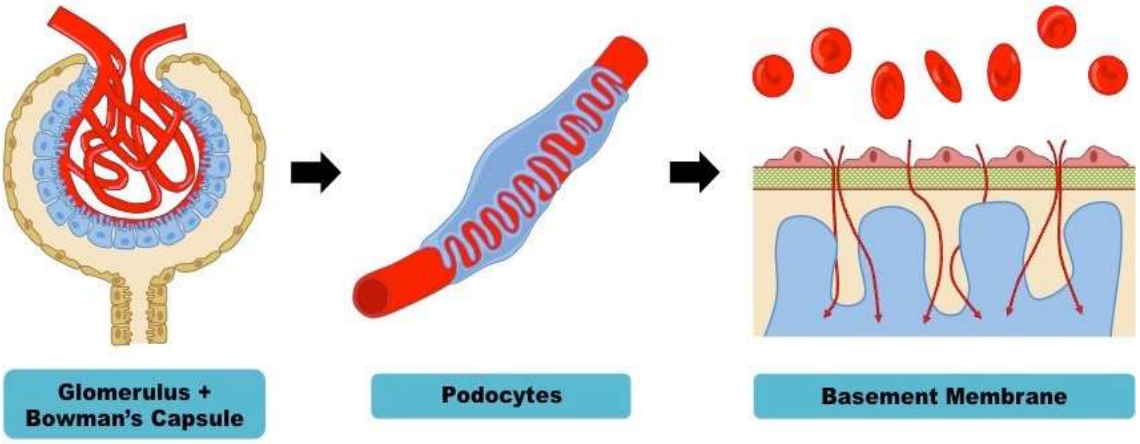


Figure 5. ***Structure of Glomerulus.*** *Glomerulus is made up of a bowman's capsule, which contains a single layer of parietal cells. Podocyte cell body forms the visceral layer. The afferent arteriole brings blood into the glomerulus and the efferent arteriole takes the blood away from the glomerulus. Mesangial cells are supporting cells between capillaries.*

The capillary endothelium is fenestrated throughout with the pores measuring between 70-90 nm diameter. The endothelium is surrounded by glomerular basement membrane along with specialized cells called podocytes. Podocytes have pseudopodia, which interdigitate to form filtration slits along the capillary wall. The filtration slits are about 25nm wide and the glomerular basement membrane has no pores.[(9)] The specialized cells present between glomerular basement membrane and basal lamina are called mesangial cells which are stellate shaped.



The mesangial cells are contractile in function, which regulates the glomerular filtration. It also secretes extracellular matrix, to take up immune complexes. The glomerular basement membrane functions by permitting neutral substances that are upto 4nm in diameter to pass through and totally excludes the substances that are greater than 8 nm.

JUXTAGLOMERULAR APPARATUS

Thick ascending limb of henle coming in contact with its own glomerulus specializes to form macula densa. The cells in the adjacent afferent arteriole is called juxtaglomerular cells which secretes rennin. The cells in between are the supporting cells and called lacis cells. The macula densa cells, juxtaglomerular cells and the lacis cells together constitute the juxta glomerular apparatus, which is involved in renin angiotensin aldosterone axis.

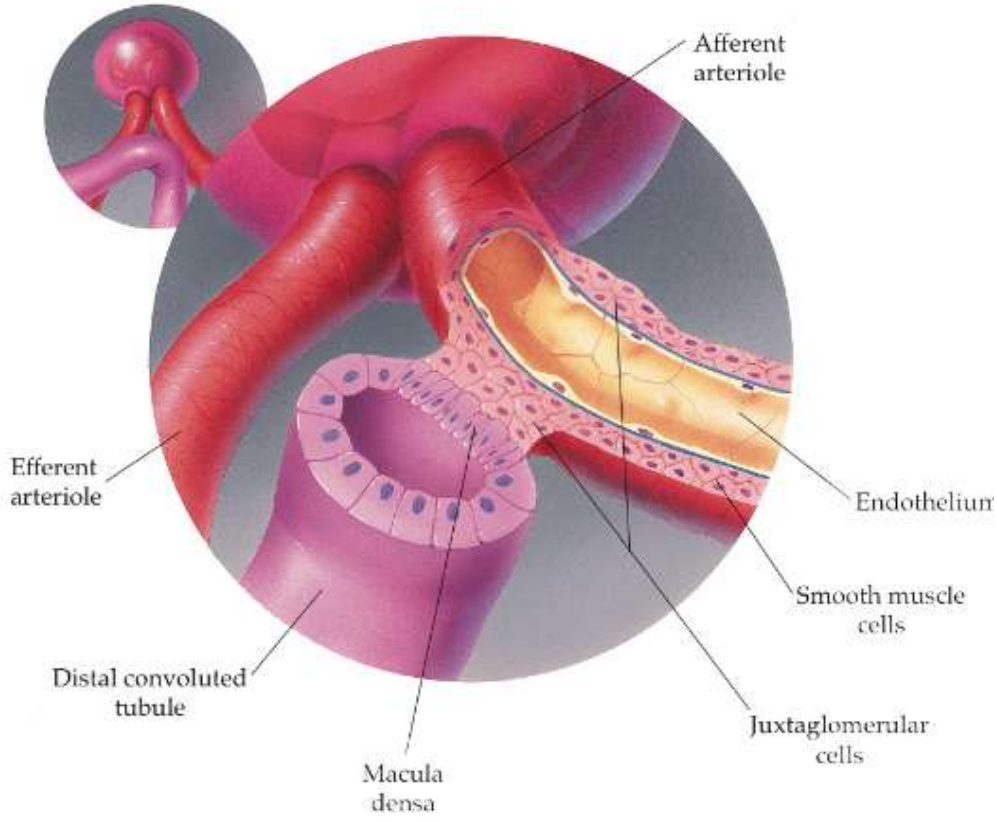


Figure 6. ***Structure of Juxta Glomerular Apparatus***

The blood vessels in the glomerulus consist of the afferent arteriole and efferent arteriole. Afferent arteriole is a short, direct branch of interlobular artery. The afferent arteriole forms a tuft in the glomerulus and comes out of the glomerulus as efferent arteriole. The efferent arteriole, after coming out of the glomerulus forms a network of capillaries around the tubules and is called peritubular capillaries.[(10)] The peritubular capillaries end as the interlobular vein. The efferent arteriole from juxta medullary glomerulus forms hair pin loops called the vasa recta.

RENIN ANGIOTENSIN SYSTEM

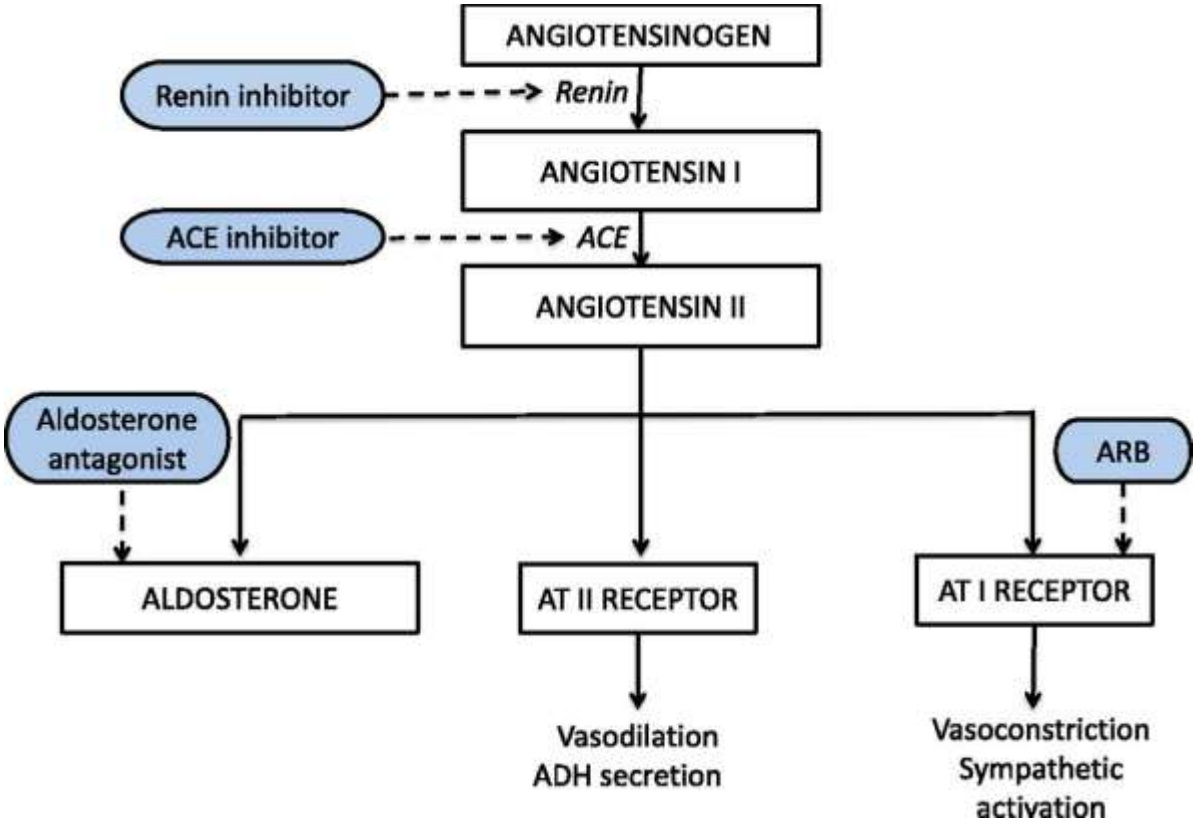


Figure 7. ***Renin Angiotensin Aldosterone System***

DIABETES MELLITUS

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia resulting from decreased insulin secretion or ineffective insulin action or both. Insulin is produced by beta cells in islets of langerhans, which is present in the pancreas. Human insulin gene is encoded by p13 locus on chromosome 11. Insulin is made up of 2 chains, bridged by a disulphide bridge, each containing 21 and 30 aminoacids. Insulin is stored as granules in beta cells and released by the process of exocytosis aided by neural, nutrients and hormonal factors. Insulin binds to insulin receptor and triggers tyrosine kinase activity and causes phosphorylation or dephosphorylation of certain proteins and enzymes in the cytoplasm. [11]

Diabetes mellitus can occur as a result of decreased production of insulin from the beta cells, or due to immune destruction of beta cells as well as from defective action of secreted insulin at the target tissues.

Insulin resistance can be due to[12]:

- Genetic disorders (Leprechaunism, lipoatropic diabetes)
- Immune disorder (Anti insulin and anti insulin receptor antibodies)
- Metabolic disorder (Obesity)
- Physiological (pregnancy, puberty)

DIABETES MELLITUS DIAGNOSTIC CRITERA

- Symptoms of diabetes plus random blood glucose level ≥200mg/dL or
- Fasting blood glucose ≥126 mg/dL or
- HbA1c ≥6.5%
- 2 hour blood glucose level ≥200 mg/dL after oral glucose tolerance test

COMPLICATIONS OF DIABETES MELLITUS

The complications of diabetes mellitus can be grossly classified as acute and chronic complications. While acute complications are a medical emergency, chronic complications occur due to uncontrolled hyperglycemia in blood over a prolonged period of time, which can be either microvascular or macrovacular.

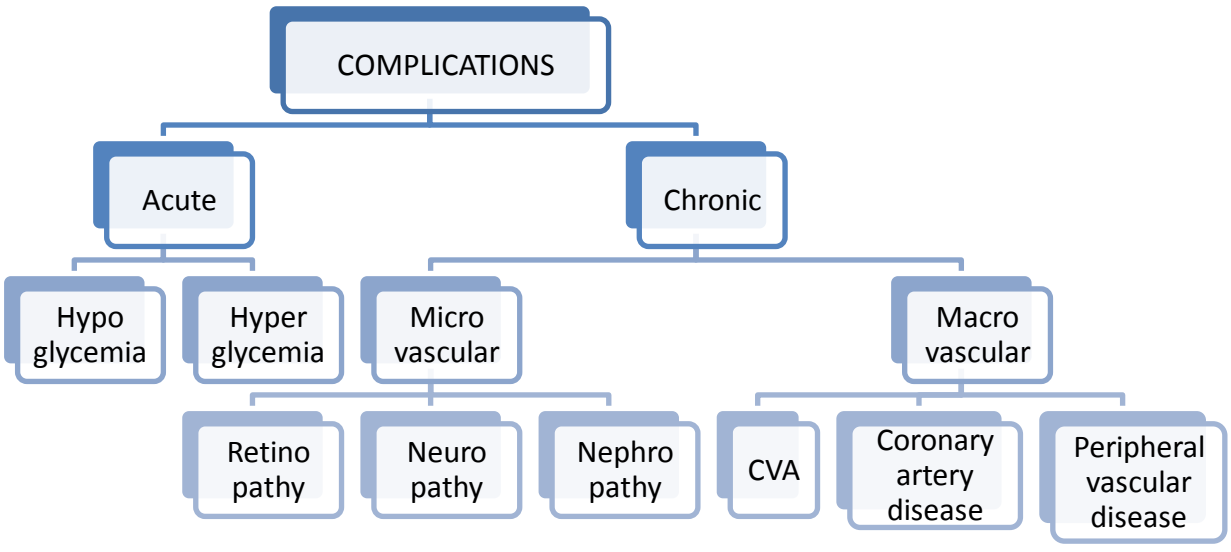


Figure 6. ***Complications of Diabetes mellitus***

PATHOGENESIS OF COMPLICATIONS

The chronic complications is caused by functional changes occurring at the cellular level, leading to structural changes that are reversible in early stages and then becomes irreversible causing end stage disease.

VASCULAR CHANGES	METABOLIC CHANGES
• Impaired contractility • Thickened basement membrane • Endothelial dysfunction • Accelerated atherogenesis	• Formation of advanced glycation end products • Reactive oxygen species production

Table 1. ***Pathogenesis of complications.***

CHRONIC KIDNEY DISEASE

Chronic kidney disease includes a spectrum of processes associated with abnormal kidney function and a progressive decline in glomerular filtration rate. The term end stage renal disease refers to a condition where the accumulation of toxins, fluid and electrolytes leads to uremic syndrome, which can lead to death unless treated as an emergency.[13] The development of chronic kidney disease is heralded by development of systemic hypertension in known diabetic or by symptoms of hypoglycemia occurring due to excessive action of insulin due to its diminished metabolism.

PATHOPHYSIOLOGY OF CHRONIC KIDNEY DISEASE

The key factors involved in the pathophysiology of chronic kidney disease are:

1. Initiating factor
2. Adaptive mechanism
3. Mal adaptation of the kidney function
4. Development of scarring in renal tissue.

- An initiating process which specific to the underlying etiology.
    - Genetically determined abnormality in kidney development
    - Immune complex deposition in certain type of glomerulonephritis
    - Toxin exposure in certain disease of renal tubules and interstitium
- A progressive mechanism involving hyperfiltration and hypertrophy of the remaining viable nephrons

Over a period of time, the compensatory hyperfiltration mechanism in remaining viable nephrons becomes maladaptive and predisposes to distortion of glomerular archietecture, abnormal podocyte function and disruption of filtration barrier leading to sclerosis and dropout of the nephrons.[14]

RAS system contributes to initial adaptive and hyperfiltration and to subsequent maladaptive hypertrophy and sclerosis.[15]

To stage chronic kidney disease, GFR has to be estimated. The equations for estimating GFR are applicable only if the patient is in a steady state of creatinine concentration. The equations used to measure GFR are:

1. MDRD - EQUATION FROM THE MODIFICATION OF DIET. IN RENAL DISEASE STUDY:

Estimated GFR (ml/min per $1.73m^2$) = $1.86 \times (\text{S Creatinine})^{-1.154} \times (\text{Age})^{-0.203}$

Multiplied by 0.742 for women

Multiplied by 1.21 for African ancestry

2. CKD – EPI equation

$GFR = 141 \times (\text{S Creatinine} / K, 1)^{\alpha} \times \text{Max}(\text{S Creatinine} / K, 1)^{-1.209} \times 0.993^{\text{Age}}$

Multiply by 1.018 for women

Multiply by 1.159 for African ancestry

Where, S creatinine is in mg/dL

K is 0.7 - females and 0.9 - males

α is -0.32 - females and -0.41 - males

min indicates the minimum of S Creatinine / K or 1

max indicates the maximum of S Creatinine/K or 1

KDIGO (KIDNEY DISEASE IMPROVING GLOBAL OUTCOME)

CLASSIFICATION OF CHRONIC KIDNEY DISEASE

PROGNOSIS OF CKD BY GFR and albuminuria. categories				PERSISTENT ALBUMINURIA CATEGORIES DESCRIPTION AND RANGE		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/d	30-300mg/d	>300mg/d
GFR categories (ml/mi/1.73m^2) description and range	G1	Normal to high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Figure 7. KDIGO classification of chronic kidney disease

ETIOLOGIES OF CHRONIC KIDNEY DISEASE

- Diabetic Nephropathy
- Glomerulonephritis
- Hypertension associated CKD

  (includes vascular and ischemic kidney disease and primary glomerular disease with associated hypertension)
- Autosomal polycystic kidney disease
- Other cystic diseases
- Tubule interstitial nephropathy

DIABETIC NEPHROPATHY

Diabetic Nephropathy is the most common cause of ESRD. Persistant albuminuria >300 mg/day or 200µg/min is the hallmark of diabetic nephropathy.[17] Diabetic nephropathy is diagnosed with persistant albuminuria along with any one: presence of diabetic retinopathy or absence of clinical or lab evidence of other kidney or renal tract disease.

The renal size is maintained in diabetes mellitus. The conditions of chronic kidney disease causing increased renal mass are amyloidosis, HIV nephropathy and polycystic kidney disease.

PATHOLOGY IN DIABETIC NEPHROPATHY

The term diabetic nephropathy is applied to the spectrum of lesions that occur concurrently in a diabetic kidney. The lesions that involve the glomeruli in a diabetic patient include 3 glomerular syndromes:

- Non-nephrotic proteinuria
- Nephritic syndrome
- Chronic renal failure

The morphological changes that occur in the glomeruli are:

- Capillary basement membrane thickening
- Diffuse mesangial sclerosis
- Nodular glomerulosclerosis also called Kimmelstiel – Wilson bodies.

PATHOGENESIS OF DIABETIC NEPHROPATHY

The state of insulin deficiency and resulting hyperglycemia is responsible for the biochemical alteration in the glomerular basement membrane. There is an increase in collagen type IV and fibronectin and decreased heparan sulphate proteoglycan, as well as increase in reactive oxygen species which damages the glomerular filter.[18]

Nonenzymatic glycosylation of proteins and formation of advanced glycation end products contributes to glomerulopathy. Hemodynamic alterations also contribute to the initiation and progression of diabetic glomerulosclerosis. Diabetes also causes hyalinizing arteriolar sclerosis, predisposes to pylonephritis, papillary necrosis and multiple tubular lesions.

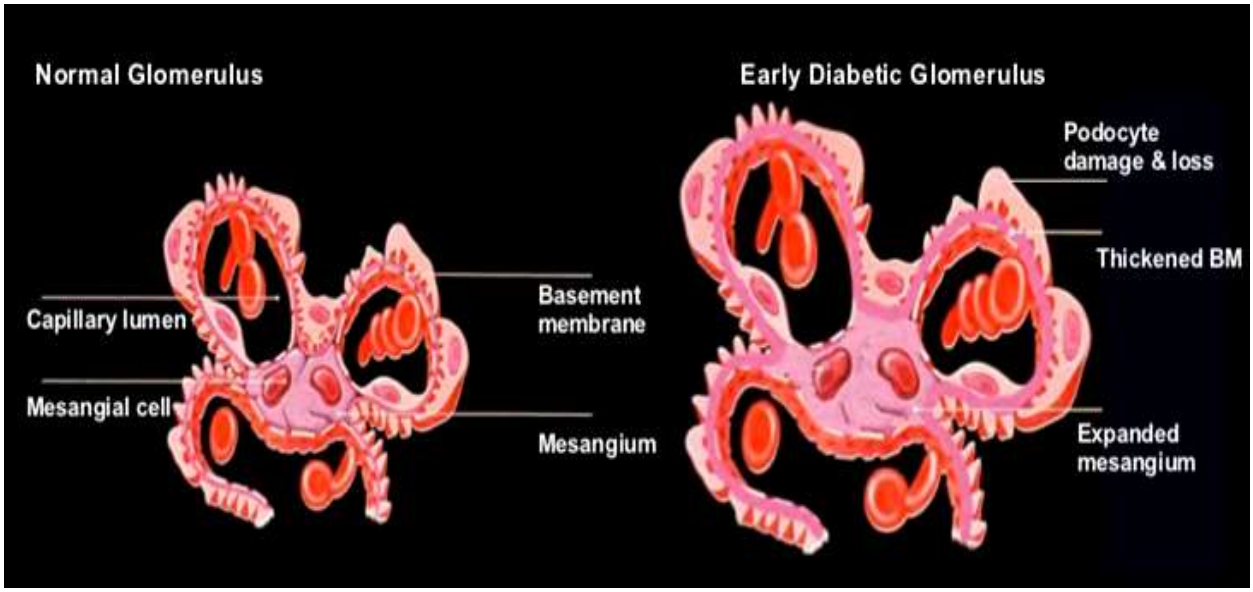


Figure 8. Pathology in diabetic nephropathy as compared with the normal glomerulus

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In diabetic nephropathy, the podocytes are damaged and there is a progressive loss in their structure and function. The basement membrane undergoes thickening, and filtration process is hampered. The mesangium expands and so unlike other chronic kidney diseases, the size of the kidneys are not decreased in diabetes mellitus.

Progression to diabetic nephropathy in diabetics is determined by genetic predisposition also [(19)]. The genetic factors are:

- Family history of diabetes mellitus
- Polygenic inheritance
- Angiotensin type 2 receptor gene on X chromosome
- Angiotensin converting enzyme gene
- Polymorphism of genes related to insulin resistance.

ALBUMINURIA

Microalbuminuria is defined as albumin in urine >30mg/day (20μg/min) and ≤300mg/day (200μg/min). Microalbuminuria denotes functional and potentially reversible abnormality.

Microalbuminuria is not tested with dipstick, but by ELISA, nephelometry, radioimmunoassay.

Causes of albuminuria:

- Urinary tract infection
- Physical exercise
- Hypertension, Obesity
- Congestive heart failure
- Uncontrolled diabetes mellitus

Risk factors for albuminuria:

- Familial
- Genetic predisposition – Pima Indians, Asians
- Poor glycemic control
- Non dippers
- Obesity, Smoking
- Increased waist hip ratio
- Male sex
- Hyperuricemia, Increased LDL and TGL

Proteinuria is a powerful predictor of cardiovascular events, of progressive loss of GFR and all cause mortality as compared to non-proteinuric patients.

New biochemical markers to predict the future development of microalbuminuria or decrease in GFR later on are:

- Urinary liver type fatty acid binding protein excretion
- Type IV collagen
- Increased serum TNF receptor 1 and 2

BIOCHEMISTRY OF UREMIA

With the decline in renal function, multiple toxins accumulate in the body. Urea and creatinine are the two measured toxins, while the other toxins that accumulate include water-soluble, hydrophobic, protein-bound, charged and uncharged compounds. Additional nitrogenous excretory products include guanidino compounds, urates and hippurates, products of nucleic acid metabolism, myoinositol, benzoates and indoles.

Uremic syndrome is also associated with abnormality of metabolic function. An abnormal metabolism of carbohydrates, fats and proteins occurs. There is also an alteration in the plasma levels of hormones like parathormone, FGF – 23, glucagon, vitamin D and sex hormones and prolactin. CRP levels are elevated along with other acute phase reactants and there occurs a fall in negative acute phase reactants such as albumin and fetuin.

There is also release of inflammatory mediators that causes a state of systemic inflammation, leading to its effects of appetite and producing malnutrition.

Thus, chronic kidney disease is associated with the malnutrition-inflammation-atherosclerosis/calcification syndrome. This state in turn leads to acceleration of vascular disease causing increased mortality and morbidity.

CLINICAL MANIFESTATION OF CHRONIC KIDNEY DISEASE AND UREMIA

- Fluid, electrolyte and acid base disorders
    - Fluid overload status
    - Metabolic acidosis
    - Hyperkalemia
- Disorders of calcium and phosphorus metabolism
    - Hypocalcemia
    - Hyperphosphatemia
- Cardiovascular abnormalities
    - Ischemic heart disease
    - Heart failure
    - Hypertension
    - Left ventricular hypertrophy
    - Pericardial disease
- Hematological abnormalities
    - Anemia
    - Abnormal hemostasis
- Neuromuscular abnormalities

    - Neuromuscular irritability
    - Autonomic neuropathy
    - Peripheral neuropathy
    - Restless leg syndrome
- Gastrointestinal and nutritional abnormalities
    - Uremic fetor
    - Gastritis
    - Peptic ulcer
    - Mucosal ulceration
- Endocrine – metabolic disturbances
    - Impaired glucose metabolism
    - Menstrual abnormalities
    - Infertility
- Skin manifestations
    - Nephrogenic fibrosing dermopathy

ANEMIA IN CHRONIC KIDNEY DISEASE

The morphological picture of anemia due to chronic kidney disease is normocytic normochromic picture. It is present as early as CKD stage 3 and almost universal by CKD4. Anemia serves as a risk factor for development of diabetic nephropathy and anemia occurs as a consequence of diabetic nephropathy.

CLINICAL MANIFESTATIONS

- Fatigue, Diminished exercise tolerance
- Angina, Heart failure
- Decreased cognition and mental acuity
- Impaired host defense against infections
- Growth impairment in children

PATHOGENESIS OF ANEMIA DUE TO CKD

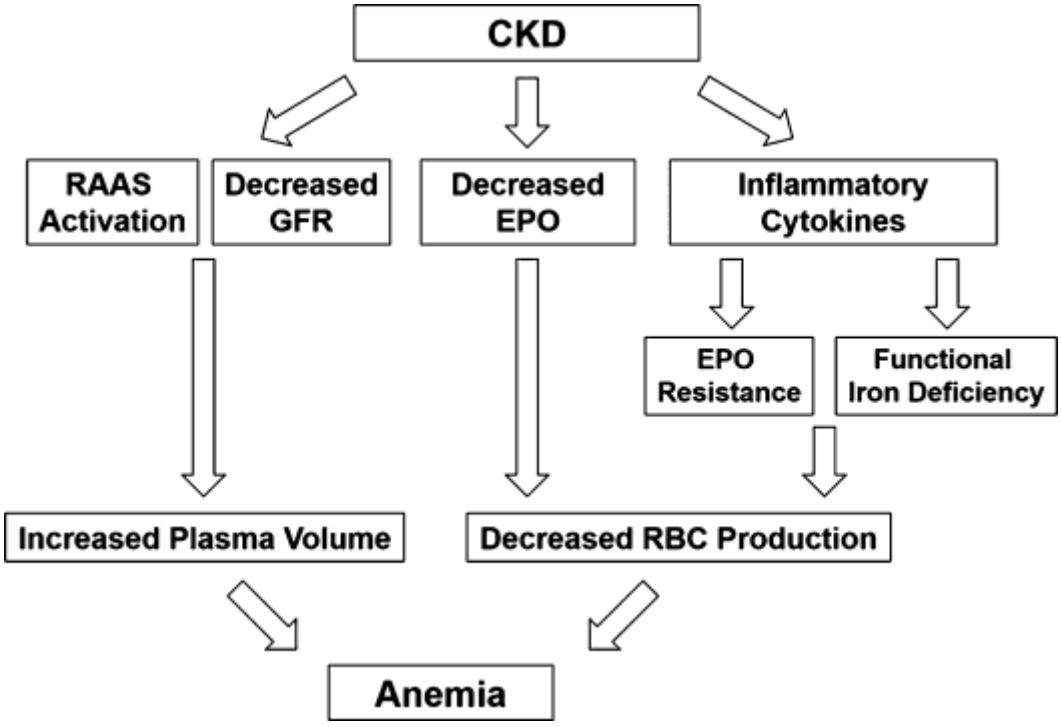


Figure 9. **Pathogenesis of Anemia due to chronic kidney disease**. CKD – Chronic Kidney Disease; RAAS – Renin Angiotensin Aldosterone System; GFR – Glomerular Filtration Rate; EPO – Erythropoietin; RBC – Red Blood Cell

PATHOPHYSIOLOGICAL CONSEQUENCES

- Decreased tissue oxygen delivery
- Increased cardiac output
- Ventricular dilation
- Ventricular hypertrophy
- Decreased exercise tolerance

CAUSES OF ANEMIA IN CHRONIC KIDNEY DISEASE

- Relative deficiency of erythropoietin
- Diminished red blood cell survival
- Bleeding diathesis
- Iron deficiency
- Folate or vitamin B_{12} deficiency
- Hyperparathyroidism
- Bone marrow fibrosis
- Chronic inflammation
- Hemoglobinopathy
- Co-morbid conditions : hypo/hyperthyroidism, pregnancy, HIV-associated disease, autoimmune disease, immunosuppressive drugs

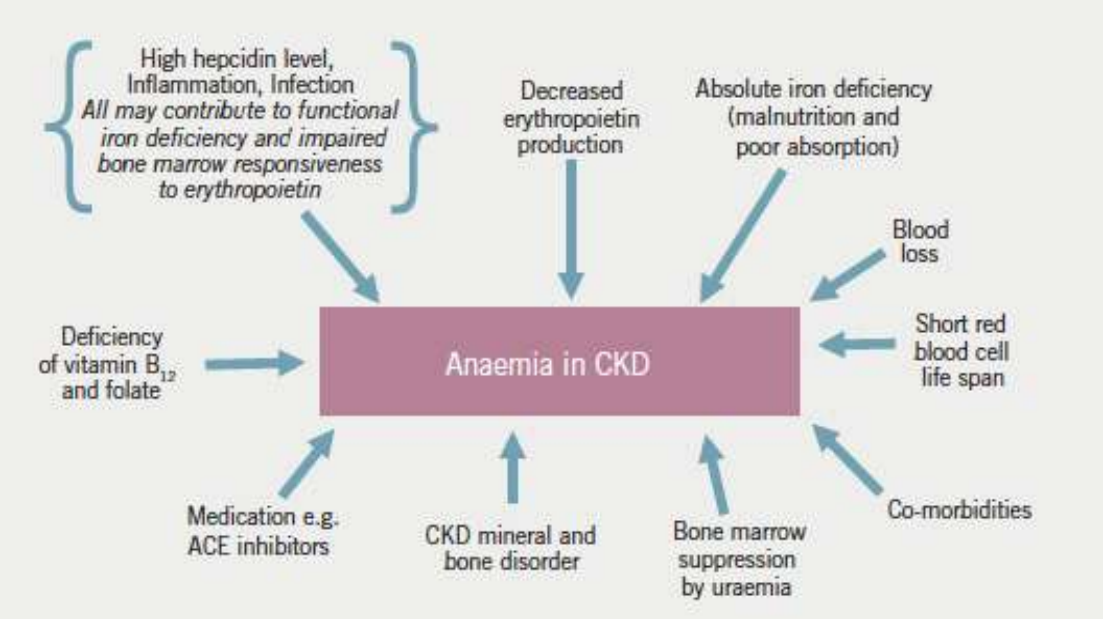


Figure 10. Causes of Anemia in chronic kidney disease

TREATMENT OF ANEMIA DUE TO CHRONIC KIDNEY DISEASE

Recombinant human erythropoietin stimulating agent is used to treat anemia due to CKD, provided adequate bone marrow iron stores are available. Iron, Vit B_{12} and folate supplementation must be given adequately. Anemia resistant to recommended doses of erythropoietin stimulating agents my be due to acute or chronic inflammation, inadequate dialysis, severe hyperparathyroidism, chronic blood loss or hemolysis, chronic infection or malignancy.

Blood transfusion is to be reserved for patients failing to respond to ESA, because it increases the risk of hepatitis, iron overload and transplant sensitization. Current practice is to target hemoglobin concentration of 10-11.5gm/dL

DIABETIC RETINOPATHY

One of the microvascular complications due to diabetes mellitus causing blindness is diabetic retinopathy. It is more common in type 2 than in type 1 diabetes mellitus. The hallmark of diabetic retinopathy is micro vascular occlusion and micro vascular leakage. Microvascular occlusion leads to hypoxia and causes release of growth factors, which leads to nevascularisation.

The factors that influence the natural history of diabetic retinopathy are:

- Effect of hyperglycemia
- Prolonged duration of diabetes mellitus
- Co – existing Hypertension
- Presence of nephropathy
- Pregnancy
- Genetic factors (HLA B15 – more incidence)
- Smoking

Factors that decrease the incidence of diabetic retinopathy are:

- Primary open angle glaucoma and High myopia
- Decreased ocular perfusion / Unilateral carotid artery stenosis

According to a recent study, 86% of diabetic patients with nephropathy had retinopathy, where as 24% of patients with retinopathy had nephropathy.

BIOCHEMICAL CHANGES IN DIABETIC RETINOPATHY

Excess glucose causes increased sorbitol production, which increases the activity of protein kinase, leading to pericyte loss and capillary leakage. Excess glucose also caused auto oxidation and free radical production, leading to endothelial damage and capillary leakage. Hypoxia due to decreased perfusion causes release of vascular endothelial growth factor causing angiogenesis. Microvascular leakage leads to formation of hard exudates, hemorrhage, and macular edema.

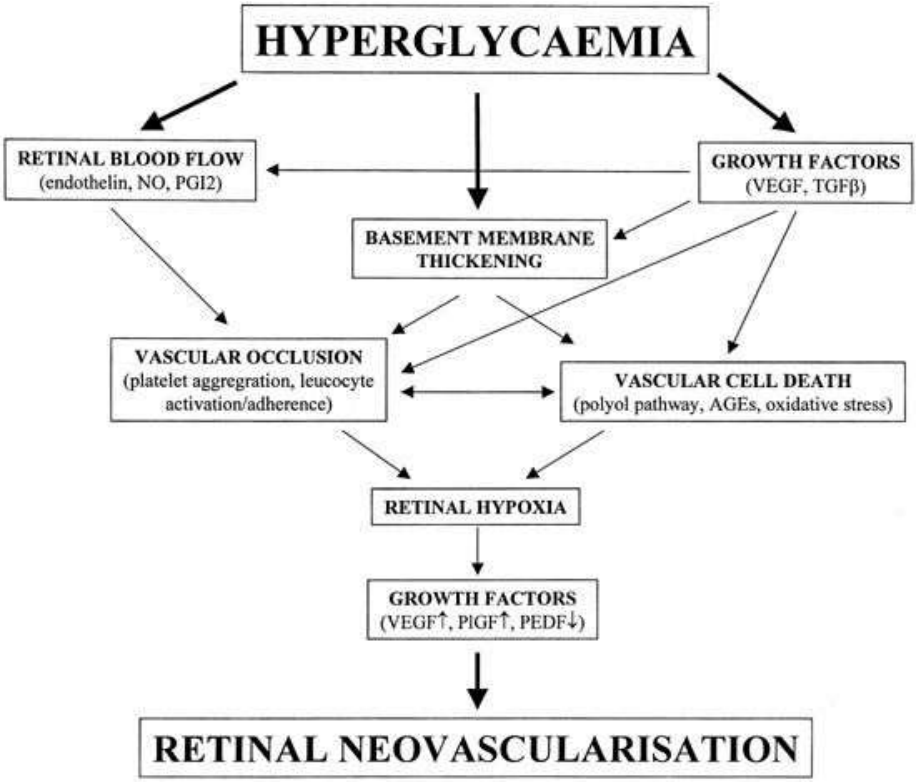


Figure 11. ***Pathogenesis of Diabetic retinopathy****. NO – Nitric Oxide; PGI2 – Prostaglandin I 2; VEGF – Vascular Endothelial Growth Factor; TGF β – Transforming Growth Factor β; AGE – Advanced Glycation End products*

CLASSFICATION OF DIABETIC RETINOPATHY

- Background diabetic retinopathy
- Preproliferative diabetic retinopathy
- Proliferative diabetic retinopathy
- Diabetic maculopathy

BACKGROUND RETINOPATHY

It consists of micro aneurysm, hard exudates and dot hemorrhages.

Microaneurysm

It is the earliest manifestation of diabetic retinopathy, but not pathognomic for diabetic retinopathy. Microaneurysms are 20 – 200 microns in size. They may bleed or hyalinize and fade.

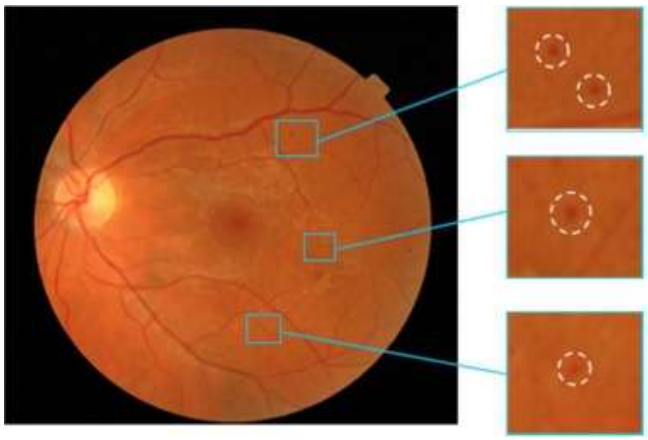


Figure 12. Microaneurysm in retina

Hard exudate

It is made up of lipoprotein and lipid laden macrophages seen mostly in macula. It can be focal or diffuse in the retina

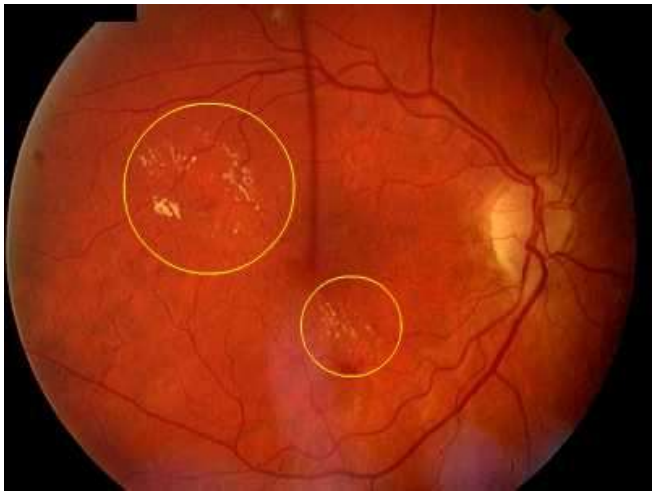


Figure 13. Hard exudates

Dot hemorrhage

It appears similar to microaneurysms, present in inner nuclear layer.

Figure 14. Dot hemorrhage

PREPROLIFERATIVE DIABETIC RETINOPATHY

Blot hemorrhage

It denotes the ischemic infarct of retina

Soft Exudate

It is a cotton wool spot, which indicates a nerve fibre layer infarct. In the absence of hypertension, >5 spots are taken as significant

Venous abnormalities

It consists of beading tortuous vessels and intraretinal microvascular abnormalities (IRMA)

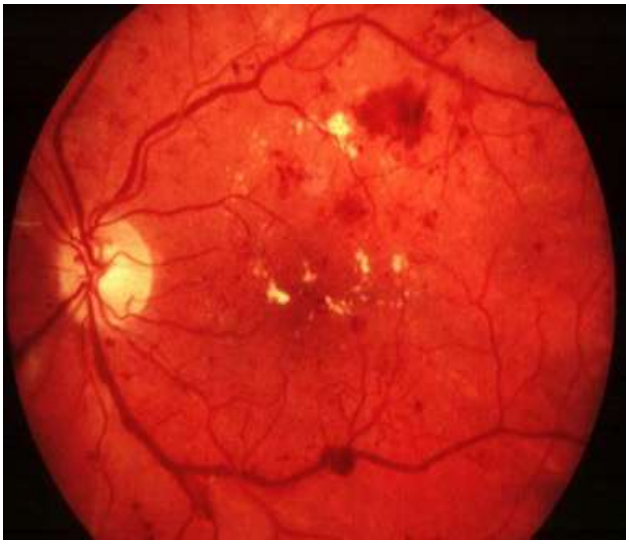


Figure 15. ***Preproliferative Diabetic Retinopathy****. Dot and blot hemorrhage, soft exudates and venous abnormalities are shown*

PROLIFERATIVE DIABETIC RETINOPATHY

It is manifested as neovascularisation in disc and elsewhere in retina. Neovascularisation on disc is more dangerous than that occurring on the retina. It is more dangerous because it may cause vitreous hemorrhage.

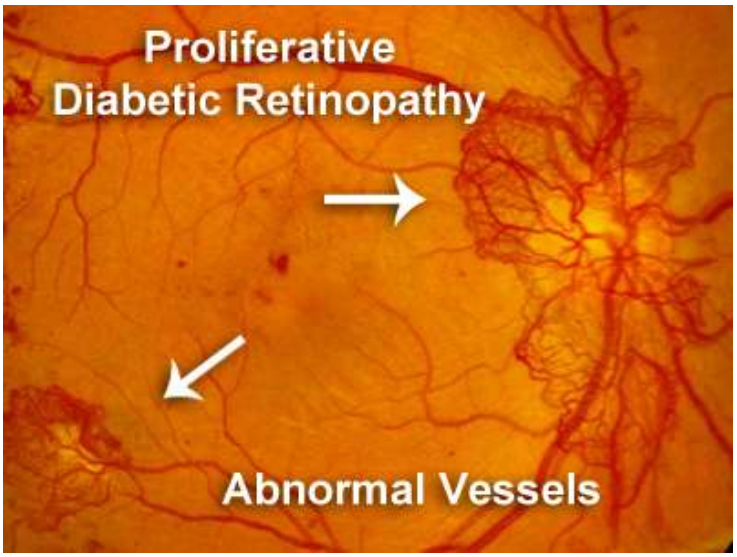


Figure 16. Proliferative diabetic retinopathy

Screening for diabetic retinopathy:

In type 1 diabetes, 5 years after diagnosis of diabetes mellitus and yearly thereafter is recommended.

In type 2 diabetes, screening must be made at the time of diagnosis and yearly thereafter.

ABBREVIATED EARLY TREATMENT DIABETIC RETIN0PATHY STUDY (ETDRS) CLASSIFICATION –

NONPROLIFERATIVE DIABETIC RETINOPATHY (NPDR)

CATEGORY	MANAGEMENT
NO DR	Review in 12 months
VERY MILD Microaneurysms only	Review in 12 months
MILD (any one of): • Microaneurysms • Retinal hemorrhages • Exudates • Cotton wool spots	Review range 6-12 months, depending on severity of signs, stability, systemic factors and patients personal circumstances
MODERATE • Severe retinal hemorrhages in 1-3 quadrants or mild IRMA • Significant venous beading in not more than 1 quadrant • Cotton wool spots	Review in approximately 6 months
SEVERE The 4-2-1 rule • Severe retinal hemorrhages in all 4 quadrants • Significant venous beading in ≥2 quadrants • Moderate IRMA in ≥1 quadrant	Review in 4 months
VERY SEVERE ≥2 of the severe criteria	Review in 2-3 months

ABBREVIATED EARLY TREATMENT DIABETIC RETIN0PATHY STUDY (ETDRS) CLASSIFICATION –

PROLIFERATIVE DIABETIC RETINOPATHY (PDR)

MILD-MODERATE • New vessels on the disc (NVD) <1/3 disc area • New vessels elsewhere (NVE) <1/2 disc area	Treatment considered according to severity of signs, stability, systemic factors and patient's personal circumstances If not treated, review in upto 2 months
HIGH-RISK • NVD >1/3 disc area • Any NVD with vitreous or preretinal hemorrhage • NVE >1/2 disc area with vitreous or preretinal hemorrhage	• Laser photocoagulation • Intraretinal anti-VEGF agents • Intravitreal triamcilone • Pars plana vitrectomy • Lipid lowering drugs
ADVANCED DIABETIC EYE DISEASE • Preretinal and/or intragel hemorrhage • Tractional retinal detachment • Tractinal retinoschisis • Rubeosis iridis (iris neovascularisation)	Pars plana vitrectomy

MATERIALS

&

METHODS

MATERIALS AND METHODS

This study is conducted in Government Royapettah hospital, Chennai for a duration of 6 months from April 2018 to Sep 2018. A proper ethical approval was obtained from the Institutional Ethical Committee. The study was conducted after getting written informed consent from all the Subjects involved in this study.

STUDY DESIGN	:	Cross sectional study
STUDY PERIOD	:	6 Months
STUDY AREA	:	Government Royapettah Hospital, Chennai
STUDY POPULATION	:	Patients with Type 2 Diabetes DM
SAMPLE SIZE	:	Total 200 diabetic patients
DATA COLLECTION	:	All the diabetic patients admitted to medical ward for any complaint were screened for hemoglobin level, nephropathy and retinopathy changes.

SAMPLE SIZE

Sample size calculated by using the formula:

$$N = 4pq/E^2$$

- 95% confidence interval
- Level of significance $p<0.05$

INCLUSION CRITERIA

Diabetics in this study will be defined by the American Diabetes Association as either

- Diagnosis by a physician before the survey, or
- Fasting plasma glucose (FBS) of >126 mg/dL or
- Postprandial blood sugars(2Hr)> 200 mg/dL

Anemia is defined by hemoglobin concentration

- In males <13g/dL
- In females <12g/dL

EXCLUSION CRITERIA

- Normocytic Normochromic anemia
- Chronic Kidney Disease Stage 3-5
- Fever
- Prolonged exercise
- Symptomatic UTI
- Non Diabetic Renal Disease
- Heart failure
- Uncontrolled Hypertension
- Type 1 Diabetes mellitus
- Gestational Diabetes mellitus
- Recent Surgery
- Allergy to drugs
- Glaucoma or family history of Glaucoma

METHODOLOGY

Inpatients with diabetes mellitus irrespective of the admitting complaints were chosen in this study after eliminating the patients who fall under exclusion criteria. After explaining the purpose of the study, written consent was obtained from the patients. The demographic history was obtained from each patient using a proforma.

All patients were assessed with FBS, PPBS and then included in the study. Hemoglobin concentration for each patient was obtained using an automated analyser. Peripheral smear study was made for all patients who were anemic and those with normocytic normochromic picture were eliminated from the study.

All the diabetic patients were tested for urine albumin by dipstick technique. All patients were also tested for 24 hour urinary protein estimation. After voiding the first early morning sample, urine was collected in a clean container starting from morning 8 am to next day morning 8 am. The collected sample was sent for protein estimation. The normal protein excretion is 150mg/day

Urine dipstick

It measures albumin concentration via a calorimetric reaction between albumin and tetrabromophenol blue producing different shades of green according to the concentration of albumin in the sample.

The interpretation of the test are:

- Negative
- Trace – between 15 and 30 mg/dL
- 1+ - between 30 and 100 mg/dL
- 2+ - between 100 and 300 mg/dL
- 3+ - between 300 and 1000 mg/dL
- 4+ - >1000mg/dL

Serum creatinine

Serum creatinine estimation made by Jaffe method. The principle with jaffe method of creatinine estimation is formation of creatinine-picrate complex (a yellow – orange complex).

The difference in absorbance at fixed times during conversion is proportional to the concentration of creatinine in the sample.

The normal creatinine level for adult males is 0.6-1.2 mg/dL and for females is 0.5 – 1.1 mg/dL.

With the above information, eGFR was calculated using the MDRD formula. Estimated GFR (ml/min per $1.73m^2$) = 1.86 x (S Creatinine)$^{-1.154}$ x (Age)$^{-0.203}$

Multiplied by 0.742 for women

Multiplied by 1.21 for African ancestry

Diabetic Nephropathy

Diabetic Nephropathy was diagnosed in the patients with evidence of macroalbuminuria and or the presence of diabetic retinopathy. Those patients with diabetic nephropathy were staged with eGFR values and those with stage 1 and 2 alone were included in the study. As anemia is a complication of chronic kidney disease that beings by CKD stage 3 and almost universal by stage 4, the patients with CKD stage 3 and above were excluded from the study.

Diabetic Retinopathy

Fundus examination was made all the patients using Welch Allyn direct ophthalmoscope. Fundus findings were recorded and the retinopathy changes were classified according to ETDRS classification.

STATISTICAL ANALYSIS

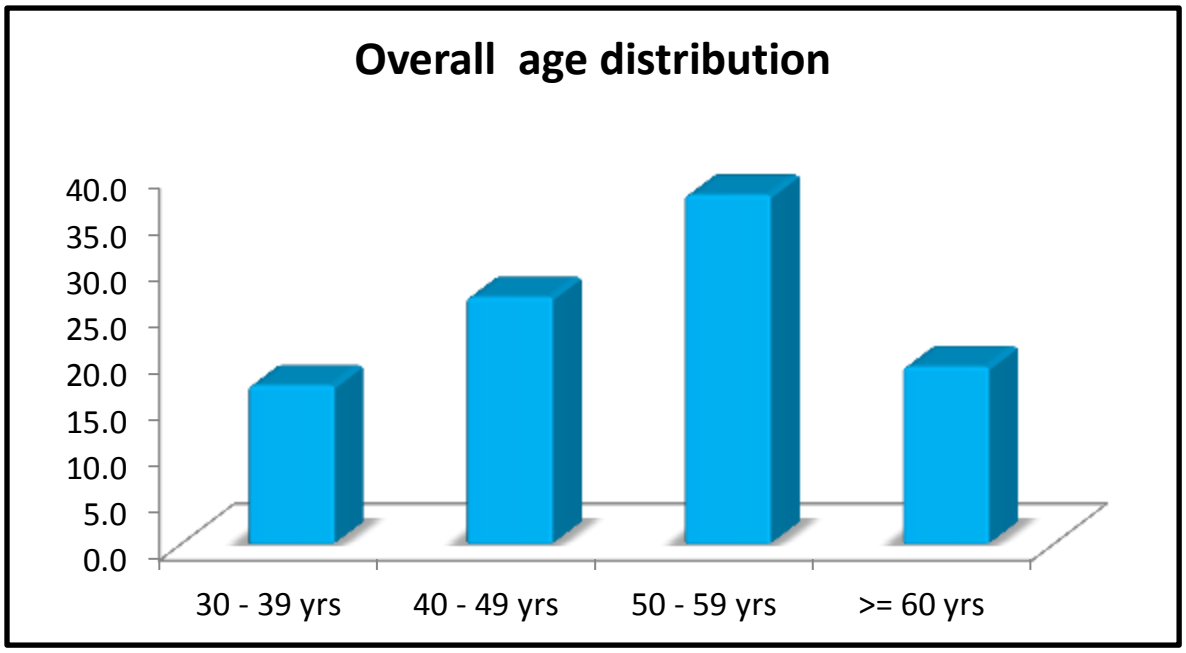
The collected data were analysed with IBM.SPSS statistics software 23.0 Version. To describe about the data descriptive statistics frequency analysis, percentage analysis were used for categorical variables and the mean & S.D were used for continuous variables. To find the significant difference between the bivariate samples in Independent groups the Unpaired sample t-test was used. To find the significance in categorical data Chi-Square test was used. In both the above statistical tools the probability value 0.05 is considered as significant level.

RESULTS
&
ANALYSIS

AGEWISE DISTRIBUTION OF THE STUDY POPULATION

AGE CATEGORY	FREQUENCY	PERCENTAGE
30 - 39 yrs	34	17.0
40 - 49 yrs	53	26.5
50 - 59 yrs	75	37.5
≥ 60 yrs	38	19.0
Total	200	100.0

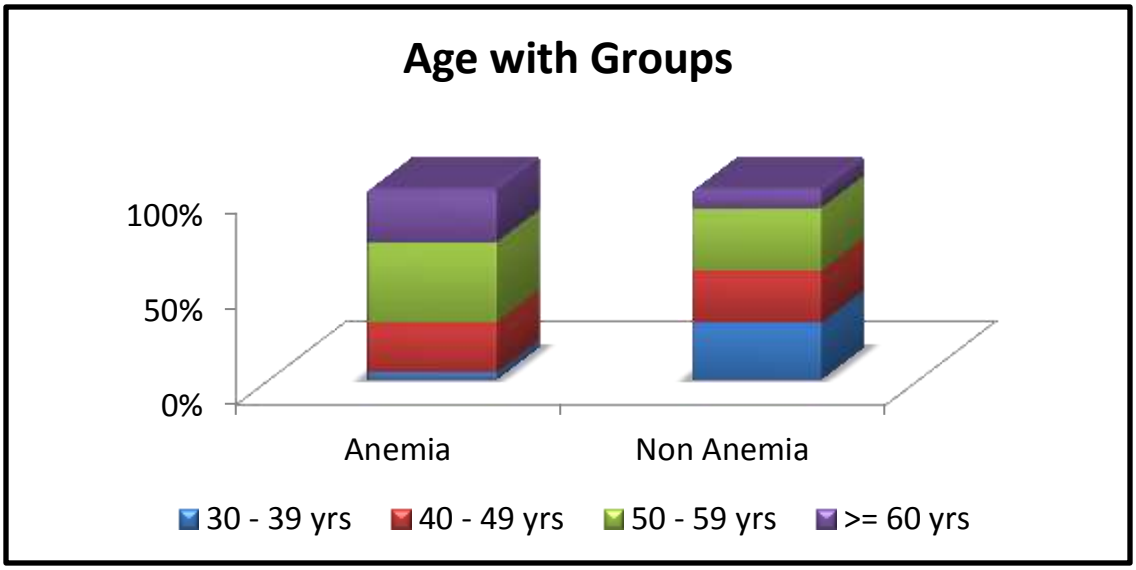
In this study, the study population was divided into 4 categories based on age. The maximum number of study population belonged to 50 – 59 year category and the group in 30-39 years were the minimum.



AGE WISE DISTRIBUTION OF BOTH STUDY GROUPS

AGE CATEGORY	GROUPS		TOTAL
	Anemia	Non Anemia	
30 - 39 yrs	4	30	34
40 - 49 yrs	26	27	53
50 - 59 yrs	42	33	75
>= 60 yrs	28	10	38
TOTAL	100	100	200

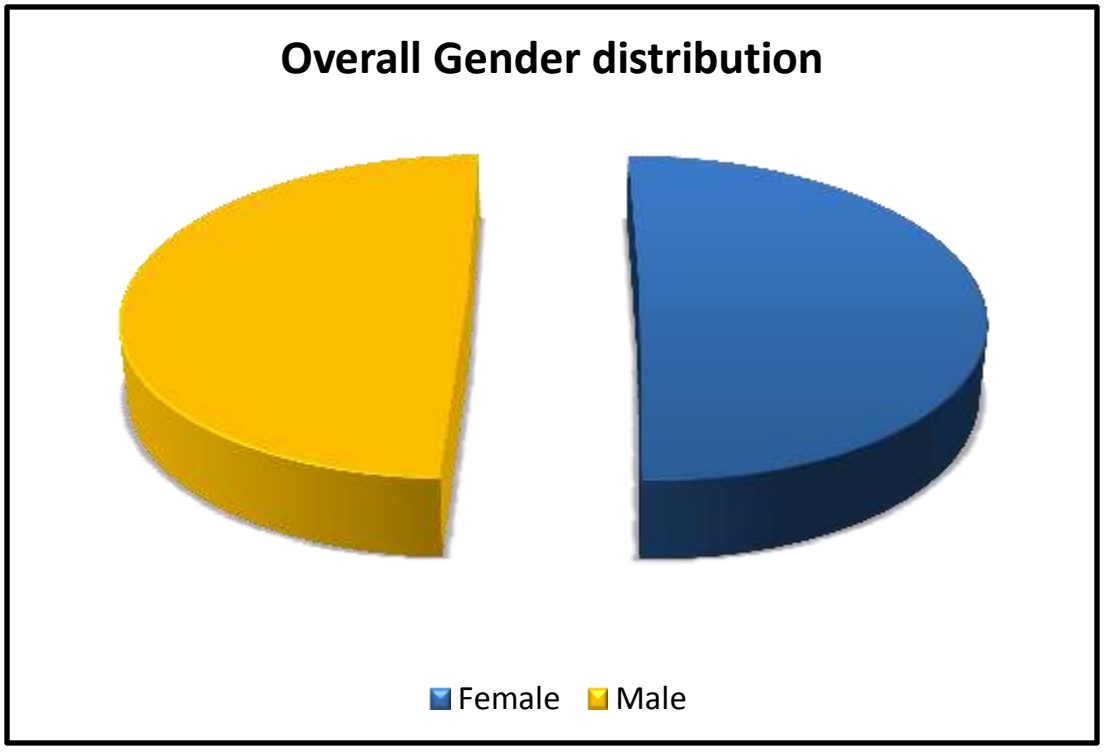
In our study, the study population in 2 groups – anemic and non-anemic were categorized according to age. In the anemic group, the population in 50-59years were the majority contributors followed by the age group category of ≥60years and the 30-39 years contributed the least. In the non-anemic category, the majority were from 50-59 years category followed by 30-39 years.



SEXWISE DISTRIBUTION OF THE STUDY POPULATION

SEX CATEGORY	TOTAL
Female	101
Male	99
Total	200

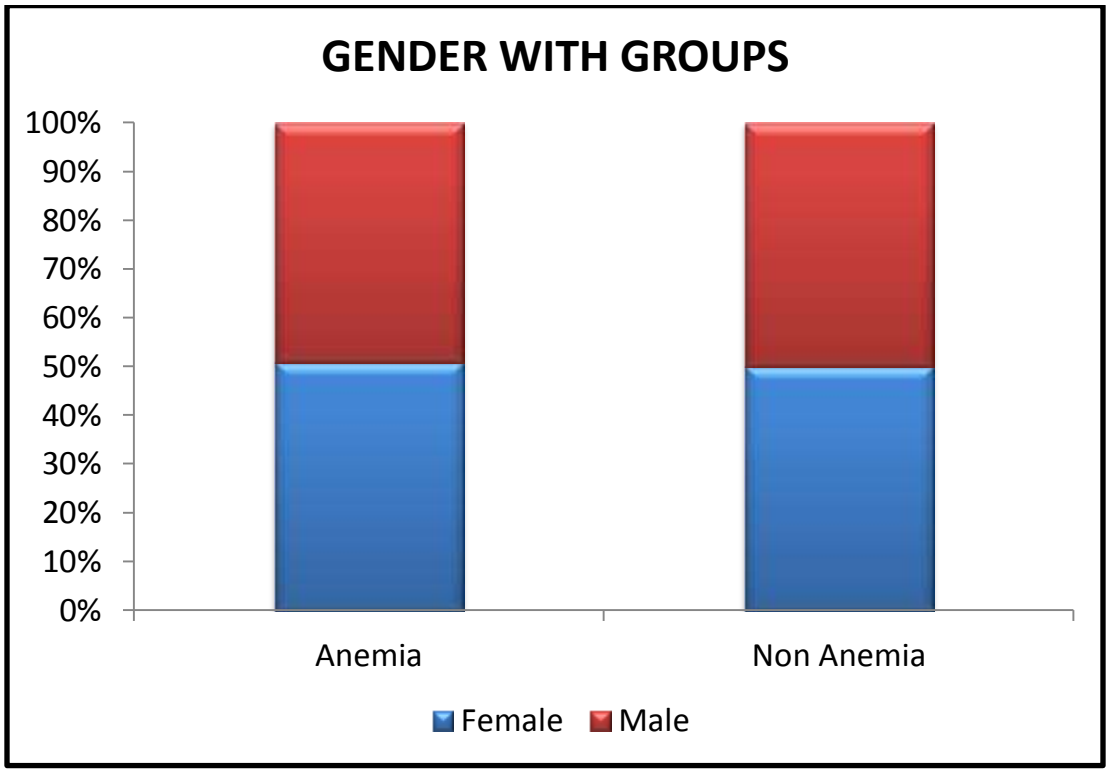
In this study, the study population consisted of almost equal males and females, with about 101 females and 99 males.



SEX DISTRIBUTION IN BOTH STUDY GROUPS

SEX CATEGORY	Anemia	Non Anemia
Female	51	50
Male	49	50
TOTAL	100	100

The study population in either group – anemic and non anemic consisted of almost equal males and females.



Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.020[a]	1	.888		
Continuity Correction[b]	0.000	1	1.000		
Likelihood Ratio	.020	1	.888		
Fisher's Exact Test				1.000	.500
N of Valid Cases	200				

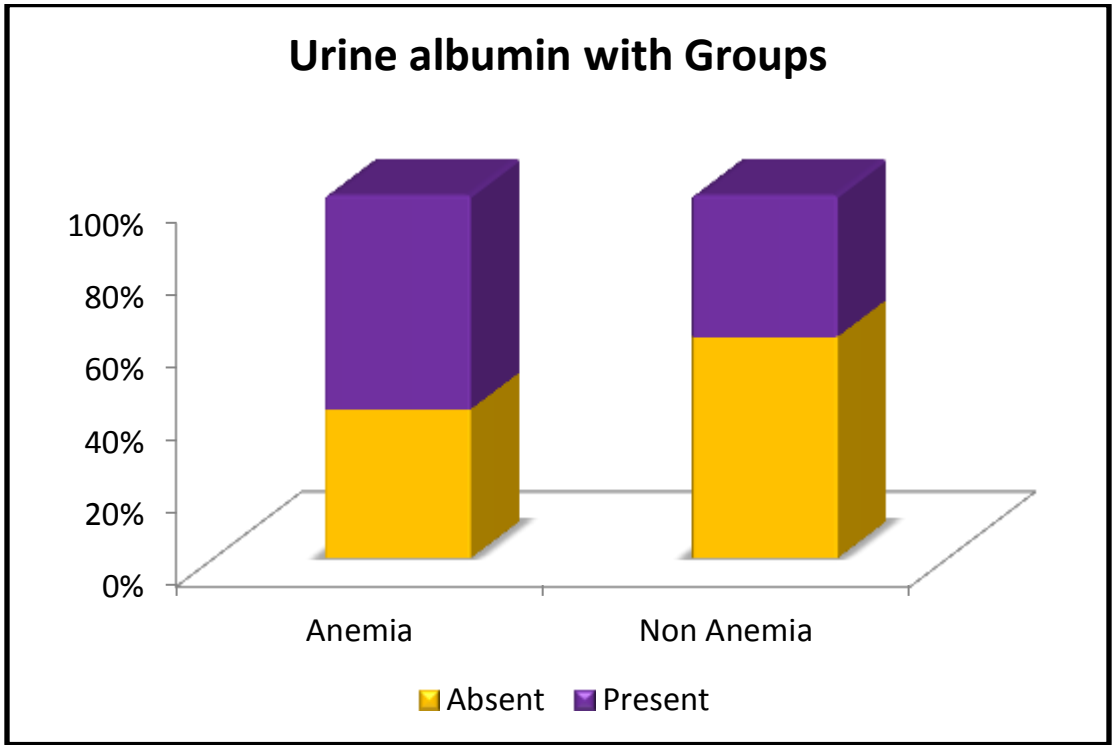
a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 49.50.

b. Computed only for a 2x2 table

URINE ALBUMIN EXCRETION IN BOTH GROUPS

URINE ALBUMIN	GROUPS		TOTAL
	Anemia	Non Anemia	
Absent	41	61	102
Present	59	39	98
TOTAL	100	100	200

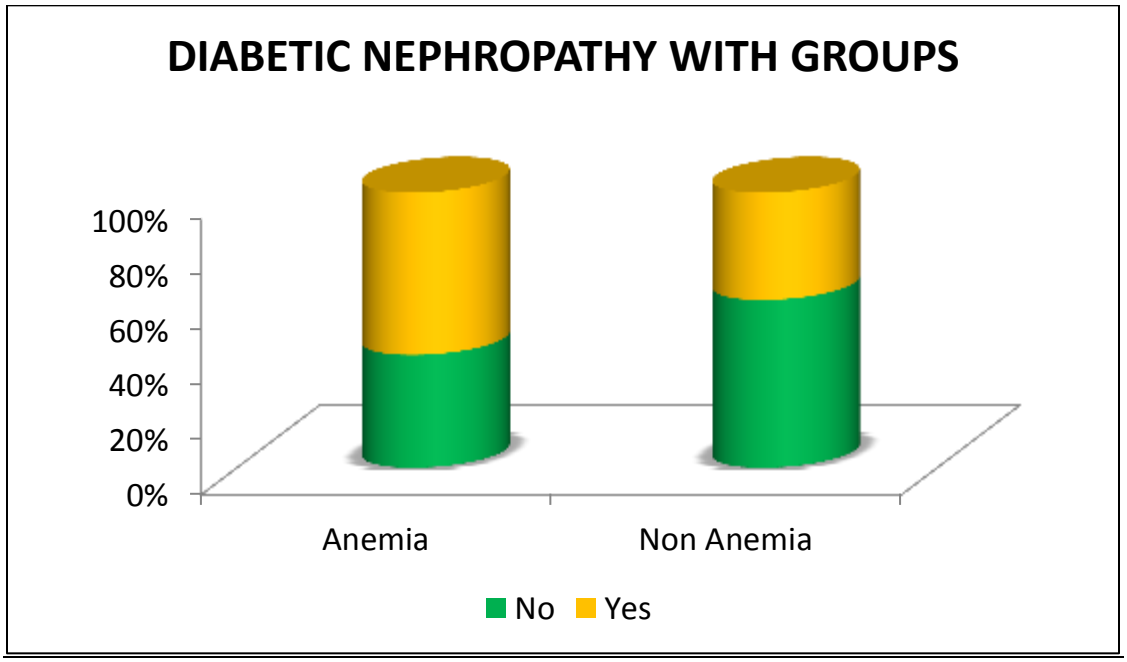
The total number of anemic patients with urine albumin (59) was greater than the non anemic patients with urine albumin (39)



DISTRIBUTION OF DIABETIC NEPHROPATHY PATIENTS IN BOTH GROUPS

DIABETIC NEPHROPATHY	GROUPS		TOTAL
	Anemia	Non Anemia	
No	41	61	102
Yes	59	39	98
TOTAL	100	100	200

In the anemic group, the total number of anemic patients with nephropathy (59) was greater than the patients without nephropathy (41). In the non-anemic group, the number of patients without nephropathy (61) was higher than the patients with nephropathy (39).



CHI-SQUARE TESTS

	Value	Df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	8.003[a]	1	.005		
Continuity Correction[b]	7.223	1	.007		
Likelihood Ratio	8.058	1	.005		
Fisher's Exact Test				.007	.004
N of Valid Cases	200				

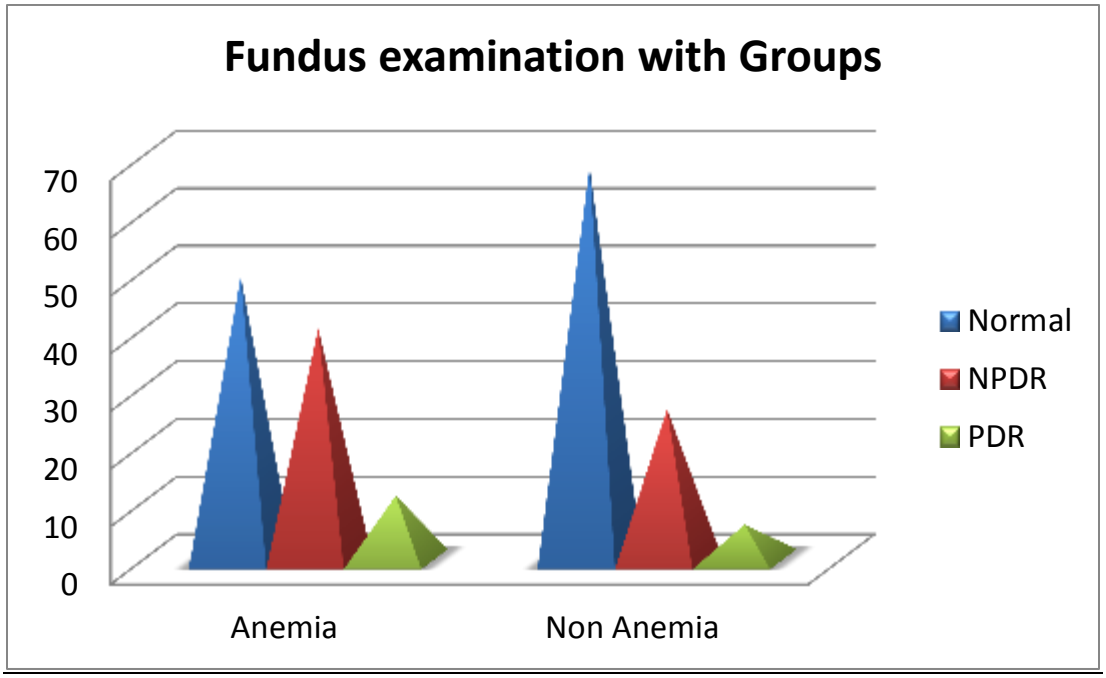
a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 49.00.

b. Computed only for a 2x2 table

FUNDUS EXAMINATION IN BOTH GROUPS

FUNDUS EXAMINATION	GROUPS		TOTAL
	Anemia	Non Anemia	
Normal	49	68	117
NPDR	40	26	66
PDR	11	6	17
TOTAL	100	100	200

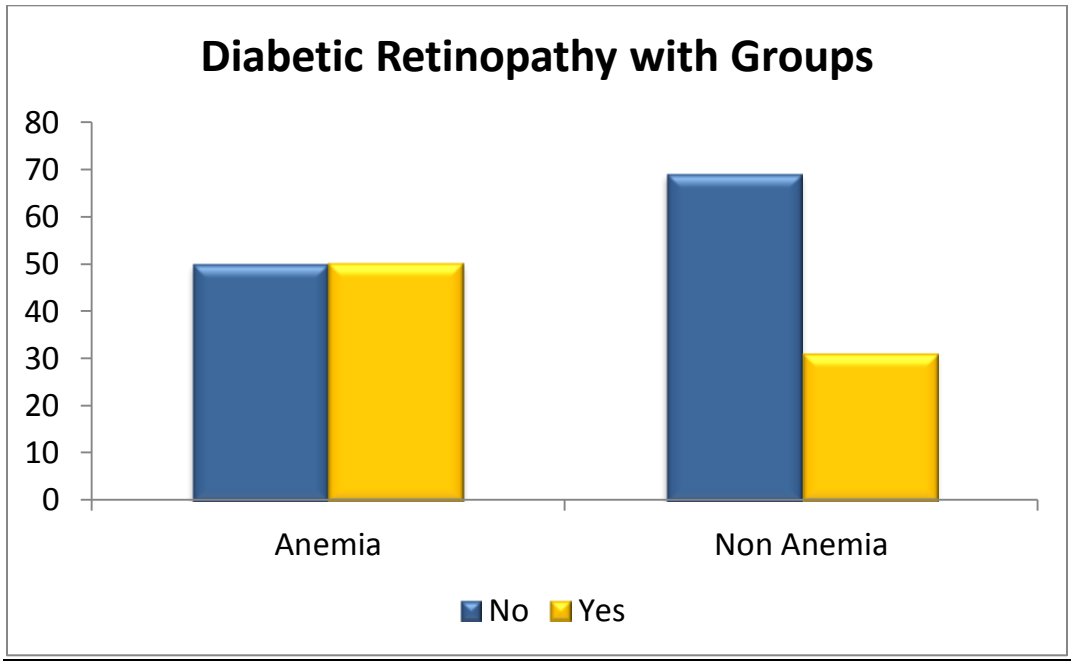
Fundus examination in anemic group showed normal interpretation in 49 patients, NPDR in 40 patients and 11 had PDR. In the non-anemic group, 68 patients had normal fundus examination, 26 had NPDR and 6 had PDR.



DISTRIBUTION OF DIABETIC RETINOPATHY PATIENTS IN BOTH GROUPS

DIABETIC RETINOPATHY	GROUPS		TOTAL
	Anemia	Non Anemia	
NO	50	69	119
YES	50	31	81
TOTAL	100	100	200

The number of patients having diabetic retinopathy was greater in the anemic group(50) than in the non-anemic group (31).



CHI-SQUARE TEST

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	7.490[a]	1	.006		
Continuity Correction[b]	6.723	1	.010		
Likelihood Ratio	7.545	1	.006		
Fisher's Exact Test				.009	.005
N of Valid Cases	200				

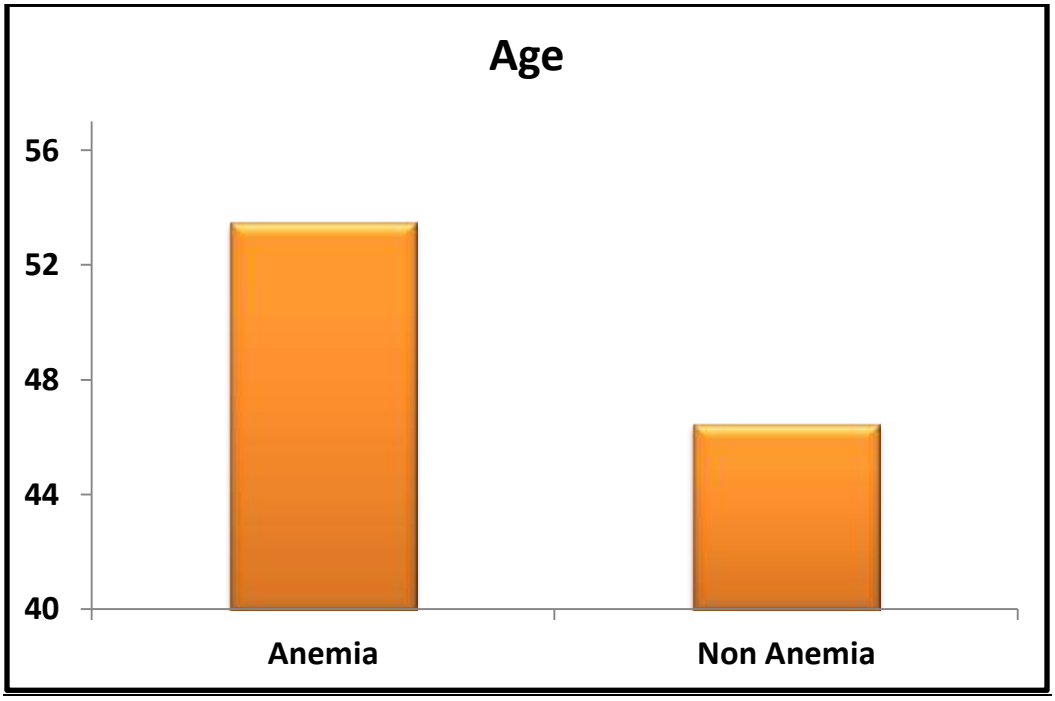
a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 40.50.

b. Computed only for a 2x2 table

MEAN AGE IN BOTH GROUPS

GROUP	AGE
Anemia	53
Non Anemia	46

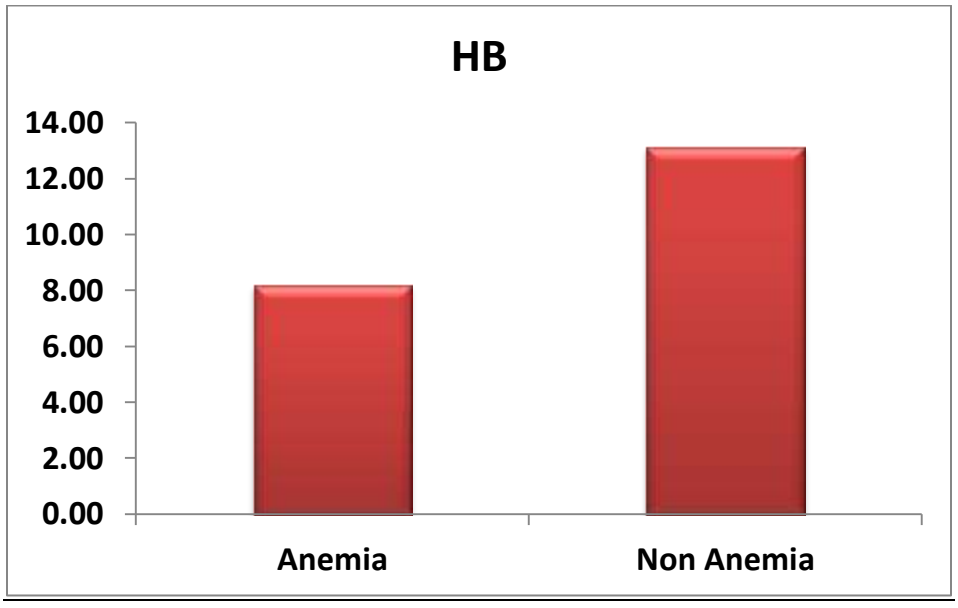
The mean age calculated among the anemic population is 53 years and among non-anemic group is 46 years.



MEAN HEMOGLOBIN IN BOTH GROUPS

GROUP	HEMOGLOBIN
Anemia	8.19
Non Anemia	13.14

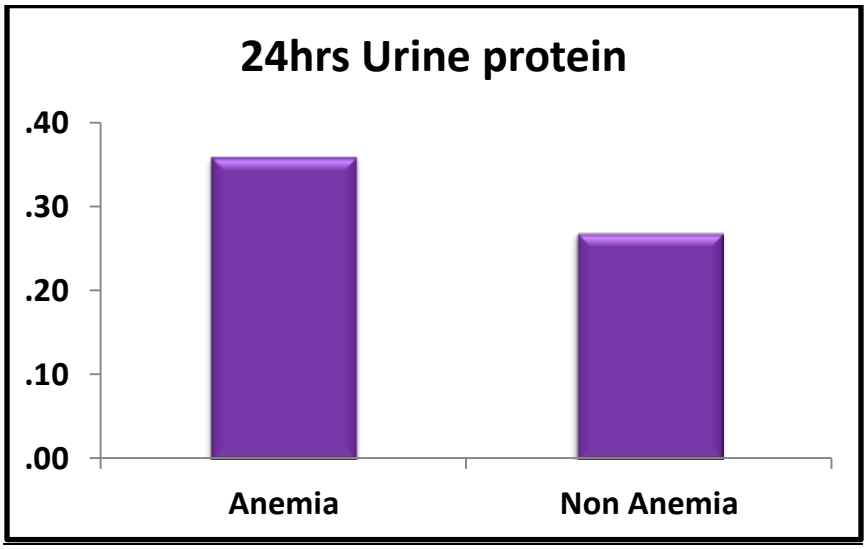
The mean hemoglobin in anemic population is 8.19g/dL. The mean hemoglobin concentration in non-anemic group is 13.14 g/dL



MEAN 24 HOUR URINARY PROTEIN ESTIMATION IN BOTH GROUPS

GROUP	24 HOUR URINARY PROTEIN ESTIMATION (GMS)
Anemia	0.36
Non Anemia	0.27

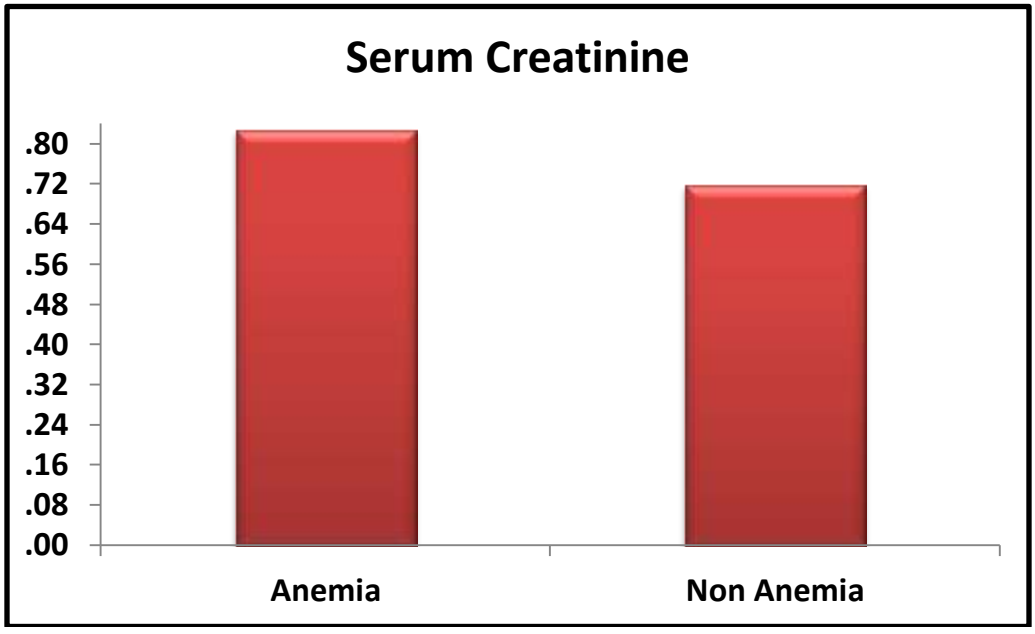
The mean amount of 24hours urinary protein estimation in anemic group is 0.36 grams and in non-anemic group is 0.27gms



MEAN SERUM CREATININE IN BOTH GROUPS

GROUP	SERUM CREATININE
Anemia	0.83
Non Anemia	0.72

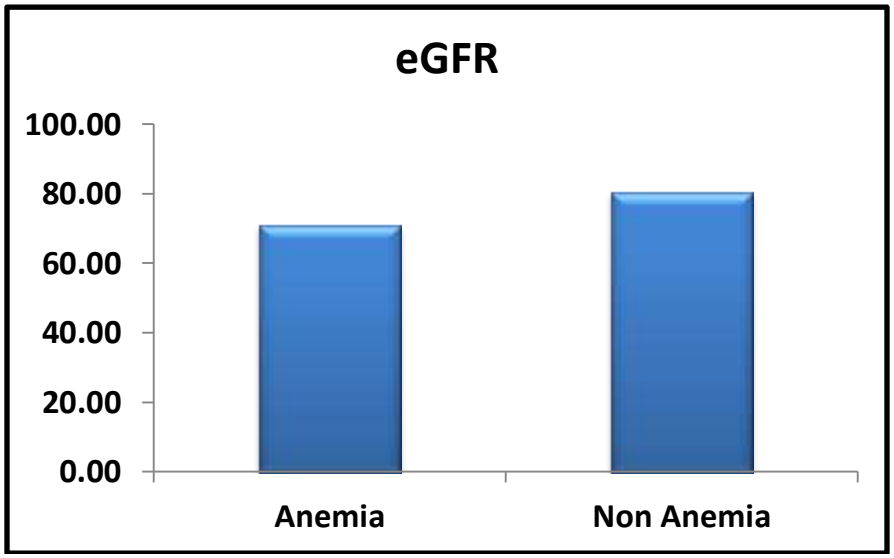
The mean serum creatinine in the anemic population is 0.83mg/dL and the mean creatinine value in non-anemic group is 0.72 mg/dL



MEAN eGFR IN BOTH GROUPS

GROUP	eGFR
Anemia	70.88
Non Anemia	80.44

The mean eGFR value calculated in anemic population is 70.88ml/min/1.73m^2, where as the mean eGFR in non anemic patients is 80.44ml/min/1.73m^2



GROUP STATISTICS

Groups		N	Mean	Std. Deviation	Std. Error Mean
AGE	Anemia	100	53.49	7.251	.725
	Non Anemia	100	46.44	9.688	.969
WEIGHT	Anemia	100	53.51	8.667	.867
	Non Anemia	100	49.91	11.935	1.194
HB	Anemia	100	8.186	.8968	.0897
	Non Anemia	100	13.137	.5702	.0570
24 HR URINE PROTEIN	Anemia	100	.3595	.29691	.02969
	Non Anemia	100	.2683	.26284	.02628
SERUM CREATININE	Anemia	100	.8280	.22567	.02257
	Non Anemia	100	.7160	.08844	.00884
eGFR	Anemia	100	70.8847	10.90736	1.09074
	Non Anemia	100	80.4370	16.65458	1.66546

INDEPENDENT SAMPLE TEST

		Levene's Test for Equality 0f Variances		t-test for Equality 0f Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
AGE	Equal variances assumed	17.192	.000	5.826	198	.000	7.050	1.210	4.664	9.436
	Equal variances not assumed			5.826	183.419	.0005	7.050	1.210	4.662	9.438
WEIGHT	Equal variances assumed	18.707	.000	2.441	198	.016	3.600	1.475	.691	6.509
	Equal variances not assumed			2.441	180.697	.016	3.600	1.475	.690	6.510
HB	Equal variances assumed	22.542	.000	-46.587	198	.000	-4.9510	.1063	-5.1606	-4.7414
	Equal variances not assumed			-46.587	167.809	.0005	-4.9510	.1063	-5.1608	-4.7412
24 HR URINE PROTEIN	Equal variances assumed	4.495	.035	2.300	198	.022	.09120	.03965	.01300	.16940
	Equal variances not assumed			2.300	195.130	.023	.09120	.03965	.01300	.16940
SERUM CREATININE	Equal variances assumed	19.177	.000	4.621	198	.000	.11200	.02424	.06420	.15980
	Equal variances not assumed			4.621	128.712	.0005	.11200	.02424	.06404	.15996
eGFR	Equal variances assumed	33.031	.000	-4.798	198	.000	-9.55234	1.99084	-13.47832	-5.62636
	Equal variances not assumed			-4.798	170.729	.0005	-9.55234	1.99084	-13.48218	-5.62250

DISCUSSION

DISCUSSION

In this study, the study population was divided into 4 categories based on age. The maximum number of study population belonged to 50 – 59 year category and the group in 30-39 years were the minimum.

In our study, the study population in 2 groups – anemic and non-anemic were categorized according to age. In the anemic group, the population in 50-59years were the majority contributors followed by the age group category of ≥60years and the 30-39 years contributed the least.

In the non-anemic category, the majority were from 50-59 years category followed by 30-39 years, while the least contribution was from ≥60 years category.

In this study, the study population consisted of almost equal males and females, with about 101 females and 99 males.

The study population in either group – anemic and non anemic consisted of almost equal males and females.

The total number of anemic patients with urine albumin (59) was greater than the non anemic patients with urine albumin (39)

Statistical analysis showed significant association between patients with anemia and urinary albumin excretion ($p<0.1$)

In the anemic group, the total number of anemic patients with nephropathy (59) was greater than the patients without nephropathy(41). In the non-anemic group, the number of patients without nephropathy (61) was higher than the patients with

nephropathy (39). However, there was also significant statistical association between people with nephropathy and anemia. ($p<0.1$)

Fundus examination in anemic group showed normal interpretation in 49 patients, NPDR in 40 patients and 11 had PDR. In the non-anemic group, 68 patients had normal fundus examination, 26 had NPDR and 6 had PDR.

The number of patients having diabetic retinopathy was greater in the anemic group(50) than in the non-anemic group (31).

There is also significant statistical association between patients with anemia and diabetic retinopathy.

The mean hemoglobin in anemic population is 8.19g/dL. The mean hemoglobin concentration in non-hemoglobin group is 13.14 g/dL

The mean amount of 24hours urinary protein estimation in anemic group is 0.36 grams and in non-anemic group is 0.27gms

The mean serum creatinine in the anemic population is 0.83mg/dL and the mean creatinine value in non-anemic group is 0.72 mg/dL

The mean eGFR value calculated in anemic population is 70.88ml/min/1.73m^2, where as the mean eGFR in non anemic patients is 80.44ml/min/1.73m^2

The statistical analysis also showed that there was no association between gender and the groups studied.

CONCLUSION

CONCLUSION

This study verifies that an association exists between low hemoglobin in diabetic patients with diabetic nephropathy

A positive association between low hemoglobin in diabetic patients with diabetic retinopathy is also established.

It is estimated that the prevalence of low hemoglobin in diabetic patients is about 51 in females and 49% in males.

Statistical analysis shows a significant association between low hemoglobin in diabetic patients and presence of diabetic nephropathy. There is also statistical significance between low hemoglobin in diabetic patients and presence of diabetic retinopathy.

Hence, diagnosis and treatment of low hemoglobin must be made at the time of diagnosis of diabetes mellitus in order to decrease the complications of diabetes mellitus.

SUMMARY

With medical advancement, the life expectancy is improving and so is the morbidity due to complications of long standing diabetes mellitus. Anemia is a serious public health problem as harmful as the epidemic of infectious disease, especially in developing countries like India. About 54% women and 23% men in India suffer from anemia (NFHS – 4). With both the problems occurring together in an individual, the development of complications due to diabetes are severe and much earlier. This study shows a positive correlation between patients with low hemoglobin and development of diabetic nephropathy as well as low hemoglobin with development of diabetic retinopathy. Hence, treatment of anemia must also be considered as a routine entity at the time of diagnosis of diabetes mellitus.

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ANNEXURE

MASTER CHART
ANEMIC GROUP

S.NO.	AGE	SEX	WT	HB	URINE ALBUMIN	24 HR URINE PROTEIN	SERUM CREATININE	eGFR	DN	FUNDUS	DR
1	58	M	50	9.7	P	0.5	0.9	63.271	Y	NPDR	Y
2	56	M	48	9	P	0.7	0.6	93.333	Y	Normal	N
3	60	M	52	7.9	P	1	0.8	72.222	Y	Normal	N
4	48	M	40	7.8	P	0.6	0.7	73.015	Y	Normal	N
5	40	M	58	7.2	P	0.5	1.3	61.965	Y	NPDR	Y
6	58	M	50	8.6	P	0.4	0.9	63.271	Y	Normal	N
7	60	M	52	9.4	P	0.5	0.7	82.539	Y	NPDR	Y
8	55	M	47	7.9	P	1.1	0.8	69.357	Y	NPDR	Y
9	43	M	53	6.9	P	0.9	1	71.407	Y	Normal	N
10	36	M	68	9.8	P	0.4	1.5	65.481	Y	NPDR	Y
11	30	M	70	7.1	P	0.6	1.7	62.908	Y	Normal	N
12	58	M	50	8.5	P	0.7	0.9	63.271	Y	NPDR	Y
13	60	M	52	6.8	P	0.6	0.8	72.222	Y	Normal	N
14	48	M	49	10.5	P	0.5	0.7	89.444	Y	NPDR	Y
15	42	M	78	8.6	A	0.1	1	106.16	N	Normal	N
16	60	M	52	6.9	P	0.7	0.9	64.197	Y	Normal	N
17	53	M	45	7.8	A	0.1	0.7	77.678	N	Normal	N
18	55	M	47	7.1	A	0.1	0.9	61.651	N	Normal	N
19	55	M	47	6.8	P	0.6	0.9	61.651	Y	NPDR	Y
20	58	M	50	6.8	A	0.1	0.8	71.180	N	Normal	N
21	59	M	51	7.4	P	0.5	0.8	71.718	Y	NPDR	Y
22	60	M	52	7.5	P	0.4	0.8	72.222	Y	NPDR	Y
23	50	M	79	7.4	P	0.5	1.5	65.833	Y	Normal	N
24	52	M	55	8.3	P	1.1	0.7	96.031	Y	NPDR	Y
25	50	M	53	8.4	A	0.1	0.8	82.812	N	Normal	N
26	45	M	65	8.6	A	0.05	1	85.763	N	Normal	N
27	56	M	48	9.8	A	0.06	0.9	62.222	N	NPDR	Y
28	60	M	52	7.4	A	0.1	0.8	72.222	N	Normal	N
29	42	M	87	7.9	P	0.2	1.9	62.324	Y	NPDR	Y
30	47	M	65	9.5	A	0.1	1.6	52.473	N	Normal	N
31	55	M	57	9.1	A	0.1	0.8	84.114	N	Normal	N
32	47	M	55	8.7	P	0.7	0.9	78.93	Y	NPDR	Y
33	60	M	52	8.4	P	0.1	0.8	72.222	Y	NPDR	Y
34	60	M	52	8.6	A	0.04	0.9	64.197	N	Normal	N
35	57	M	49	8.1	A	0.05	0.7	80.694	N	NPDR	Y
36	58	M	50	9.5	P	0.1	0.8	71.180	Y	NPDR	Y

37	60	M	52	9.4	A	0.1	0.8	72.222	N	Normal	N
38	45	M	60	7.8	A	0.11	0.7	113.09	N	NPDR	Y
39	60	M	52	8.2	A	0.12	0.9	64.197	N	Normal	N
40	60	M	52	7.6	P	1.1	0.8	72.222	Y	NPDR	Y
41	59	M	51	8.5	P	0.9	0.9	63.75	Y	Normal	N
42	41	M	80	8.6	P	0.4	1.1	100	Y	NPDR	Y
43	58	M	50	8.4	P	0.6	0.9	63.271	Y	NPDR	Y
44	60	M	52	8.6	A	0.1	0.8	72.222	N	Normal	N
45	60	M	52	9	P	0.6	0.9	64.197	Y	Normal	N
46	47	M	58	7.9	P	0.5	1.2	62.430	Y	NPDR	Y
47	60	M	52	7.8	A	0.1	0.9	64.197	N	Normal	N
48	53	M	45	6.1	P	0.7	0.8	67.968	Y	NPDR	Y
49	60	M	52	7.8	A	0.1	0.8	72.222	N	Normal	N
50	60	F	52	6.9	A	0.1	0.7	66.031	N	NPDR	Y
51	40	F	74	8.2	A	0.15	0.8	102.77	N	Normal	N
52	45	F	67	8.5	P	0.1	0.7	101.03	Y	NPDR	Y
53	60	F	52	6.7	P	0.5	0.7	66.031	Y	NPDR	Y
54	48	F	70	7.8	P	0.4	0.9	79.506	Y	Normal	N
55	60	F	52	7.8	P	0.5	0.7	66.031	Y	Normal	N
56	58	F	50	7.4	A	0.11	0.7	65.079	N	Normal	N
57	40	F	68	7.2	A	0.1	0.9	83.950	N	Normal	N
58	53	F	45	7.1	A	0.12	0.7	62.142	N	NPDR	Y
59	35	F	74	8	A	0.1	1	86.333	N	Normal	N
60	50	F	55	6.4	A	0.13	0.8	68.75	N	NPDR	Y
61	56	F	48	8.6	A	0.1	0.7	64	N	Normal	N
62	58	F	50	8.7	P	0.5	0.7	65.079	Y	PDR	Y
63	55	F	47	7.8	P	0.2	0.7	63.412	Y	Normal	N
64	59	F	51	7.9	P	0.7	0.7	65.571	Y	PDR	Y
65	60	F	52	9.3	A	0.15	0.7	66.031	N	Normal	N
66	47	F	49	9.1	A	0.12	0.8	63.291	N	NPDR	Y
67	60	F	52	9.5	A	0.11	0.7	66.031	N	Normal	N
68	55	F	47	9.3	P	0.1	0.7	63.412	Y	PDR	Y
69	60	F	52	9.4	A	0.12	0.7	66.031	N	Normal	N
70	60	F	52	9.5	A	0.1	0.7	66.031	N	Normal	N
71	60	F	52	9.4	P	0.5	0.7	66.031	Y	PDR	Y
72	57	F	49	8.9	P	1.1	0.7	64.555	Y	NPDR	Y
73	45	F	57	8.4	A	0.11	0.9	66.851	N	Normal	N
74	59	F	51	7.9	A	0.12	0.7	65.574	N	Normal	N
75	49	F	51	7.8	P	0.6	0.8	64.458	Y	PDR	Y
76	57	F	49	7.6	P	0.7	0.7	64.555	Y	PDR	Y
77	60	F	52	7.6	A	0.1	0.7	66.031	N	Normal	N

78	58	F	50	7.5	P	0.5	0.7	65.079	Y	NPDR	Y
79	58	F	50	7.3	P	0.1	0.7	65.079	Y	NPDR	Y
80	60	F	52	8.9	P	0.7	0.7	66.031	Y	PDR	Y
81	48	F	40	8.3	P	0.8	0.7	58.414	Y	NPDR	Y
82	50	F	42	8.1	A	0.1	0.6	70	N	Normal	N
83	46	F	58	7.8	P	0.6	0.9	67.308	Y	NPDR	Y
84	49	F	51	7.5	A	0.1	0.8	64.458	N	PDR	N
85	59	F	51	8.7	A	0.15	0.7	65.571	N	Normal	N
86	60	F	52	9.4	P	0.5	0.6	77.037	Y	NPDR	Y
87	56	F	48	9.6	P	0.6	0.7	64	Y	NPDR	Y
88	59	F	51	8.5	P	0.7	0.7	65.571	Y	Normal	N
89	60	F	52	8.6	A	0.1	0.6	77.037	N	Normal	N
90	48	F	40	7.8	P	0.1	0.6	68.148	Y	NPDR	Y
91	60	F	52	7.3	P	0.6	0.7	66.03	Y	NPDR	Y
92	49	F	41	7.2	A	0.1	0.6	69.092	N	Normal	N
93	59	F	51	8.5	A	0.11	0.7	65.571	N	Normal	N
94	37	F	54	8.4	P	0.5	0.8	77.25	Y	PDR	Y
95	51	F	43	8.6	P	0.1	0.7	60.746	Y	NPDR	Y
96	49	F	61	9	A	0.12	0.8	77.097	N	Normal	N
97	57	F	49	6.8	P	0.5	0.7	64.55	Y	PDR	Y
98	59	F	51	7.2	P	0.1	0.7	65.571	Y	NPDR	Y
99	55	F	47	8	P	0.6	0.7	63.412	Y	PDR	Y
100	42	F	57	9.5	P	0.1	0.8	77.583	Y	Normal	N

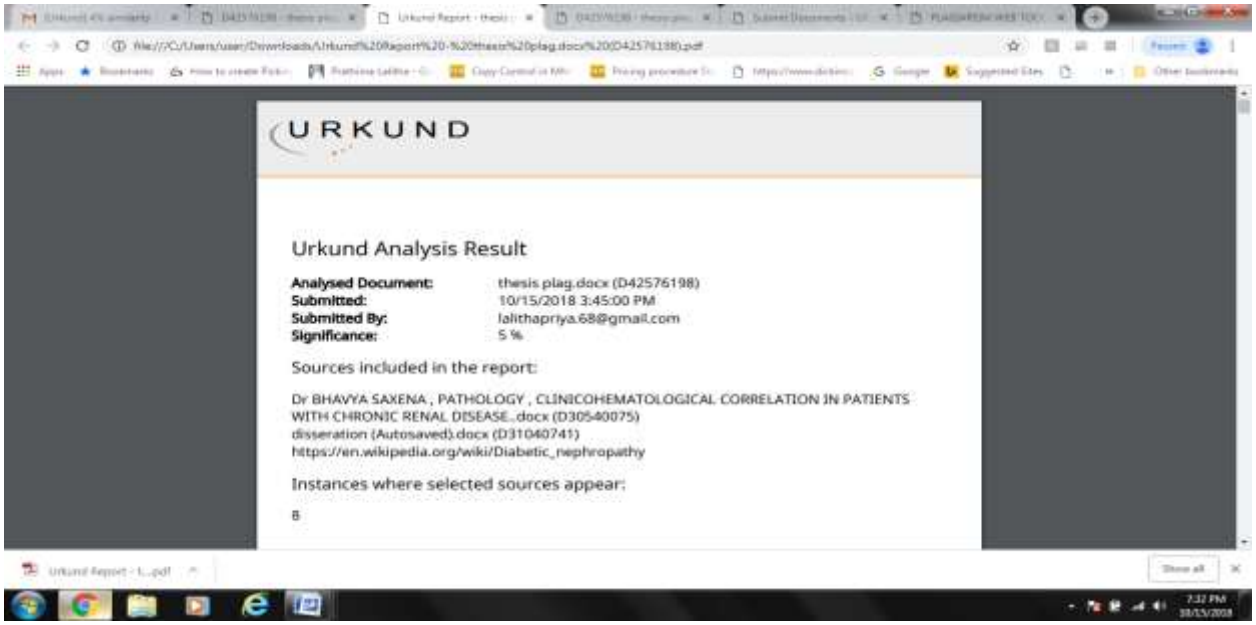
NON – ANEMIC GROUP

S.NO.	AGE	SEX	WT	HB	URINE ALBUMIN	24 HR URINE PROTEIN	SERUM CREATININE	eGFR	DN	FUNDUS	DR
1	35	M	50	12.7	A	0.12	1	72.917	N	Normal	N
2	56	M	43	12.9	A	0.1	0.8	62.708	N	Normal	N
3	60	M	48	13.4	A	0.13	0.8	66.667	N	Normal	N
4	48	M	55	12.4	A	0.1	0.6	117.130	N	Normal	N
5	40	M	46	13	A	0.1	0.8	79.861	N	Normal	N
6	58	M	34	12.6	A	0.15	0.6	64.537	N	Normal	N
7	60	M	43	12	P	0.7	0.7	68.254	Y	Normal	N
8	50	M	38	13	A	0.15	0.6	79.167	N	Normal	N
9	40	M	30	13.4	A	0.12	0.6	69.444	N	Normal	N
10	36	M	45	13.2	A	0.11	0.8	81.250	N	NPDR	Y
11	30	M	40	13.6	P	0.1	0.9	67.901	Y	Normal	N
12	38	M	35	13.6	A	0.12	0.7	70.833	N	NPDR	Y
13	35	M	30	12.8	A	0.1	0.7	62.500	N	Normal	N
14	48	M	54	13.7	P	0.5	0.7	98.571	Y	Normal	N
15	42	M	41	12.8	A	0.1	0.8	69.757	N	Normal	N
16	44	M	32	13.1	A	0.11	0.7	60.952	N	Normal	N
17	53	M	46	13	A	0.12	0.8	69.479	N	Normal	N
18	55	M	45	13.5	A	0.12	0.7	75.893	N	Normal	N
19	55	M	53	13.8	P	0.7	0.7	89.385	Y	NPDR	Y
20	58	M	48	14	A	0.1	0.9	60.741	N	Normal	N
21	59	M	56	12.6	P	0.5	0.7	90.000	Y	NPDR	Y
22	60	M	56	12.5	P	0.1	0.7	88.889	Y	Normal	N
23	50	M	54	12.3	A	0.1	0.9	75.000	N	Normal	N
24	52	M	45	13.2	P	0.8	0.7	78.571	Y	NPDR	Y
25	50	M	57	13.2	A	0.1	1	71.250	N	Normal	N
26	45	M	36	13.8	P	0.6	0.7	67.857	Y	Normal	N
27	56	M	48	13.7	A	0.1	0.7	80.000	N	NPDR	Y
28	60	M	41	13.5	A	0.15	0.7	65.079	N	Normal	N
29	42	M	56	12.8	P	0.5	0.8	95.278	Y	NPDR	Y
30	47	M	58	12.8	A	0.1	0.7	107.024	N	Normal	N
31	55	M	60	13.8	A	0.12	0.7	101.190	N	Normal	N
32	37	M	36	13.4	A	0.1	0.8	64.375	N	NPDR	Y
33	60	M	56	13.2	P	0.1	0.7	88.889	Y	Normal	N
34	60	M	56	14	P	0.6	0.7	88.889	Y	Normal	N
35	57	M	58	12.4	A	0.1	0.7	95.516	N	Normal	N
36	38	M	36	13.2	A	0.11	0.7	72.857	N	NPDR	Y
37	40	M	32	13.8	P	0.5	0.7	63.492	Y	Normal	N

38	45	M	35	13.2	P	0.1	0.7	65.972	Y	NPDR	Y
39	43	M	43	14.5	A	0.12	0.9	64.367	N	Normal	N
40	60	M	38	13.5	P	0.5	0.7	60.317	Y	NPDR	Y
41	30	M	32	13.6	A	0.1	0.8	61.111	N	Normal	N
42	41	M	36	13.5	A	0.1	0.7	70.714	N	NPDR	Y
43	58	M	38	12.8	P	0.1	0.7	61.825	Y	Normal	N
44	42	M	35	13.6	P	0.5	0.7	68.056	Y	Normal	N
45	34	M	30	13.6	P	0.7	0.7	63.095	Y	Normal	N
46	47	M	58	13.7	A	0.15	0.7	107.024	N	NPDR	Y
47	42	M	55	13.2	P	0.6	0.7	106.944	Y	Normal	N
48	53	M	35	12.5	A	0.12	0.6	70.486	N	NPDR	Y
49	55	M	48	12.6	P	0.4	0.9	62.963	Y	Normal	N
50	60	M	54	12.5	P	0.5	0.8	75.000	Y	NPDR	Y
51	35	F	56	13.2	P	1.1	0.7	116.667	Y	Normal	N
52	32	F	55	14.6	A	0.15	0.6	137.500	N	Normal	N
53	60	F	54	13.5	A	0.12	0.7	85.714	N	NPDR	Y
54	49	F	55	13.2	P	0.6	0.7	99.306	Y	Normal	N
55	52	F	45	13.1	P	0.7	0.6	91.667	Y	Normal	N
56	39	F	54	12.4	A	0.13	0.6	126.250	N	Normal	N
57	58	F	50	12.5	P	0.5	0.7	81.349	Y	Normal	N
58	58	F	60	13	A	0.1	0.6	113.889	N	NPDR	Y
59	59	F	48	13.4	P	0.7	0.7	77.143	Y	Normal	N
60	36	F	34	13	A	0.1	0.6	81.852	N	Normal	N
61	42	F	40	13.5	A	0.1	0.7	77.778	N	Normal	N
62	53	F	66	13.2	P	0.6	0.8	99.688	Y	Normal	N
63	55	F	66	13.7	A	0.1	0.7	111.310	N	Normal	N
64	50	F	50	12.8	P	0.5	0.7	89.286	Y	PDR	Y
65	45	F	78	12.3	A	0.1	0.7	147.024	N	Normal	N
66	56	F	47	14.8	P	0.5	0.7	78.333	Y	NPDR	Y
67	30	F	30	13.5	P	1.1	0.6	76.389	Y	Normal	N
68	33	F	53	13.5	A	0.1	0.6	131.273	N	Normal	N
69	32	F	35	14.5	A	0.05	0.7	75.000	N	Normal	N
70	56	F	60	12.8	A	0.06	0.7	100.000	N	Normal	N
71	32	F	54	12.8	A	0.1	0.6	135.000	N	Normal	N
72	45	F	35	12.5	P	0.2	0.6	76.968	Y	NPDR	Y
73	48	F	58	12.3	A	0.1	0.7	105.873	N	Normal	N
74	46	F	56	12.3	A	0.1	0.7	104.444	N	Normal	N
75	39	F	67	12.8	P	0.7	0.7	134.266	Y	PDR	Y
76	30	F	56	12.7	A	0.1	0.7	122.222	N	Normal	N
77	37	F	55	13	A	0.04	0.6	131.134	N	Normal	N
78	51	F	59	12.6	A	0.05	0.9	81.034	N	NPDR	Y

79	40	F	54	12.6	P	0.1	0.7	107.143	Y	Normal	N
80	57	F	58	12.5	A	0.1	0.7	95.516	N	PDR	Y
81	39	F	54	13.5	A	0.11	0.7	108.214	N	NPDR	Y
82	55	F	60	13.2	A	0.12	0.9	78.704	N	Normal	N
83	54	F	76	12	P	1.1	0.7	129.683	Y	NPDR	Y
84	49	F	44	13.5	A	0.1	0.7	79.444	N	PDR	N
85	40	F	56	13.2	P	0.4	0.7	111.111	Y	Normal	N
86	34	F	32	13.5	P	0.6	0.6	78.519	Y	Normal	N
87	46	F	76	12.5	A	0.1	0.8	124.028	N	NPDR	Y
88	38	F	56	12.5	P	0.6	0.7	113.333	Y	Normal	N
89	55	F	52	13	A	0.12	0.7	87.698	N	Normal	N
90	60	F	60	13.6	A	0.1	0.7	95.238	N	NPDR	Y
91	58	F	67	13.2	P	0.7	0.8	95.382	Y	Normal	N
92	30	F	34	13.1	A	0.1	0.6	86.574	N	Normal	N
93	37	F	54	13.4	A	0.1	0.6	128.750	N	Normal	N
94	44	F	65	13.5	A	0.15	0.8	108.333	N	PDR	Y
95	35	F	76	13.2	P	0.1	0.8	138.542	Y	NPDR	Y
96	57	F	80	13.9	A	0.1	0.7	131.746	N	Normal	N
97	35	F	42	12.5	P	0.4	0.7	87.500	Y	Normal	N
98	32	F	65	12.5	A	0.1	0.7	139.286	N	NPDR	Y
99	37	F	55	12.2	A	0.11	0.6	131.134	N	PDR	Y
100	35	F	65	13.6	A	0.1	0.7	135.417	N	Normal	N

PLAGIARISM REPORT



PROFORMA

NAME :

AGE/SEX :

IP/OP NO :

OCCUPATION :

DURATION OF DIABETES :

TREATMENT HISTORY :

SOCIOECONOMIC STATUS :

FBS :

PPBS :

HBA1C :

ANEMIA PROFILE

HB

PERIPHERAL SMEAR

MCV

MCH

ALBUMIN EXCRETION IN 24 HR URINE VOUME

SERUM CREATININE

eGFR

FUNDUS EXAMINATION

PATIENT CONSENT FORM

Study detail**: "A cross sectional study of low hemoglobin in diabetic population and its association with Nephropathy and Retinopathy"**
Study centre : KILPAUK MEDICAL COLLEGE, CHENNAI
Patients Name:
Patients Age :
Identification Number :
Patient may check ( ) these boxes

( ) I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction.

( ) I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected.

( ) I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study.

( )I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well-being or any unexpected or unusual symptoms.

( )I hereby consent to participate in this study.

( )I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical, radiological tests.

Signature/thumb impression:

Patients Name and Address: place date

Signature of investigator:

Study investigator's Name: place date