A STUDY ON GLUCOSE TOLERANCE IN NON-DIABETIC CHRONIC KIDNEY DISEASE

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CERTIFICATE

This is to certify that this dissertation titled "***A STUDY ON GLUCOSE TOLERANCE IN NON-DIABETIC CHRONIC KIDNEY DISEASE"*** submitted by **Dr. SURAJ P HARIDAS** to the faculty of General Medicine, The Tamilnadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the requirement for the award of MD degree branch I General Medicine, is a bonafide research work carried out by him under our direct supervision and guidance.

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DECLARATION

I**, Dr.SURAJ P HARIDAS,** solemnly declare that the dissertation titled ***"A STUDY ON GLUCOSE TOLERANCE IN NON-DIABETIC CHRONIC KIDNEY DISEASE"*** has been prepared by me. This is submitted to **The Tamilnadu Dr. M.G.R. Medical University, Chennai,** in partial fulfillment of the regulations for the award of MD degree (branch I) General Medicine.

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DEDICATED TO MY

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INTRODUCTION

Chronic kidney disease is one of the most common diseases in practice known for its morbidity and mortality.[1]

Chronic kidney disease (CKD) encompasses a spectrum of different pathophysiologic processes associated with abnormal kidney function, and a progressive decline in glomerular filtration rate (GFR). [2]

The varied etiology of chronic kidney disease are as follows:[3]

Disease	Proportion of ESRD
Congenital and inherited	5%
Renal artery stenosis	5%
Hypertension	5 – 25%
Glomerular diseases	10 – 20 %
Diabetes mellitus	20 -40%
Systemic inflammatory diseases	5%
Unknown	5 – 20 %

Glomerulonephritis was the most common cause of chronic kidney disease, not including diabetic nephropathy, followed by interstitial disease and benign arterionephrosclerosis. In patients with unidentified severe chronic kidney disease, renal biopsy provided an aetiological diagnosis.[4]

Chronic kidney disease has been staged based on the GFR as follows:[5]

Classification of Chronic Kidney Disease (CKD)

Stage	**GFR, mL/min per 1.73 m^2**
0	>90 With risk factors for CKD
1	>90 With demonstrated kidney damage (e.g., persistent proteinuria, abnormal urine sediment, abnormal blood and urine chemistry, abnormal imaging studies)
2	60–89
3	30–59
4	15–29
5	<15

Adapted from US National Kidney Foundation Kidney Disease Quality Outcomes Initiative Classification (American Journal of Kidney Disease) .

The term chronic renal failure applies to the process of continuing significant irreversible reduction in nephron number, and typically corresponds to CKD stages 3–5. The term end-stage renal disease represents a stage of CKD where the accumulation of toxins, fluid, and electrolytes normally excreted by the kidneys results in the uremic syndrome.[2]

The uremic syndrome and the disease state associated with advanced renal impairment involve more than renal excretory failure. A host of metabolic and endocrine functions normally undertaken by the kidneys are also impaired, and this results in anemia, malnutrition, and abnormal metabolism of carbohydrates, fats, and proteins. Furthermore, plasma levels of many hormones, including PTH, insulin, glucagon, sex hormones, and prolactin, change with renal failure as a result of urinary retention, decreased degradation, or abnormal regulation. Finally, progressive renal impairment is associated with worsening systemic inflammation. Elevated levels of C-reactive protein are detected along with other acute-phase reactants, while levels of so-called negative acute-phase reactants, such as albumin and

ferritin, decline with progressive renal impairment. Thus, renal impairment is important in the malnutrition-inflammation-atherosclerosis/calcification syndrome, which contributes in turn to the acceleration of vascular disease and comorbidity associated with advanced renal disease.

Glucose metabolism is impaired in CKD, as evidenced by a slowing of the rate at which blood glucose levels decline after a glucose load. Glucose intolerance can occur in chronic renal failure when GFR is less than 10–20 mL/min. Primarily, this is due to peripheral insulin resistance. Fasting glucose levels are usually normal or only slightly elevated. Therefore, patients can be either hyperglycemic or hypoglycemic depending on the predominant disturbance. Because the kidney contributes to insulin removal from the circulation, plasma levels of insulin are slightly to moderately elevated in most uremic patients, both in the fasting and postprandial states. Because of this diminished renal degradation of insulin, patients on insulin therapy may need progressive reduction in dose as their renal function worsens. Many hypoglycemic agents require dose reduction in renal failure, and some, such as metformin, are contraindicated when the GFR is less than half of normal.

There is increased prevalence of impaired glucose tolerance in chronic renal failure patients who are non diabetic patients, and at the background of this information this study was done.

REVIEW OF LITERATURE

Chronic kidney disease in India

Mani et al[6] in a study in Chennai, South India, estimated a prevalence of chronic renal failure of 0.16 per cent in the community in 2003; applying the Modification in Diet in Renal Disease (MDRD) equation for GFR estimation in 2005, 0.86 per cent were found to have a GFR <80ml/min/1.73 [m.sup.2] . Agarwal and co-workers [7] arrived at an estimate of 0.78 per cent for CKD, in a community-based sample in New Delhi defined by an elevated serum creatinine >1.8 mg/dl.

Estimates for the United States population extrapolated from the National Health and Nutrition Examination Survey (NHANES III) [8] data place the prevalence of CKD stages 4 and 5 (severe decrease in GFR) and CKD stage 3 (moderate decrease in GFR) at 0.4 per cent .

However, such direct comparisons with Western populations are not valid, since the equivalent GFR for a serum creatinine of 1.8 mg/dl in Indians may place the individual anywhere between CKD stages 2 to 4 depending upon gender and nutritional status.

Modi and Jha [9] reported from an urban population in the city of Bhopal, that the crude and age-adjusted incidence rates of end stage

renal disease (ESRD) were 151 and 232 per million population, respectively. ESRD incidence rates lend themselves more easily to international comparisons as the diagnosis is less susceptible to inaccuracies. These estimates are roughly similar to the US [8].

DISTURBANCES IN CARBOHYDRATE METABOLISM IN CKD

Disturbances in carbohydrate metabolism, especially glucose intolerance, are common in CKD patients, particularly in patients on dialysis[10].One major factor behind the reduced glucose tolerance in uremia is an impaired sensitivity to insulin (insulin resistance, IR) in peripheral tissues, mainly in skeletal muscle. The most common manifestation of IR is glucose intolerance. However, in addition to abnormalities in carbohydrate metabolism, as has been pointed out,[10] the IR syndrome is accompanied by an elevation in non-esterified fatty acids, abnormalities in visceral fat metabolism, elevated uric acid, elevated hematocrit, endothelial dysfunction, and abnormalities in glucocorticoids. In addition, there appear to be differences in the phenotypic expression of the syndrome between men and women and associated abnormalities in fat distribution.[10] Elevations in non-

esterified fatty acids, in turn, appear to contribute to glucose intolerance, hypertension, and increased arteriosclerosis.

GLUCOSE INTOLERANCE

Impaired fasting glucose is defined as fasting glucose >110mg% and < 126mg% which favours early onset of microvascular complications namely diabetic nephropathy , retinopathy , neuropathy even in the absence of overt diabetes mellitus.

Impaired glucose tolerance is defined as 2hours post glucose challenge blood glucose >140 mg % and <200 mg%. Impaired glucose intolerance favours early onset of macrovascular complications like coronary artery disease , cerebrovascular accident , peripheral vascular disease even in the absence of overt diabetes mellitus.

INSULIN RESISTANCE

Several factors are implicated in the pathogenesis of insulin resistance in chronic renal failure which include: uremic toxins, exercise tolerance, metabolic acidosis, secondary hyperparathyroidism, vitamin D deficiency etc

The characterization of IR in pre- dialysis patients dates back to classic studies from the late 1950s.[11,12,13]. Defronzo and colleagues,[11] in experiments using the euglycemic insulin clamp technique. They demonstrated that in 17 chronically uremic and 36 control subjects, IR reflected tissue insensitivity to insulin rather than suppression of hepatic glucose production by physiologic hyperinsulinemia or abnormalities in insulin-mediated glucose uptake by the liver.

Insulin resistance may have an important role in the development of atherosclerosis, which is the most common cause of morbidity and mortality in hemodialysis patients. [14,15,16]

IR and concomitant hyperinsulinemia occur regardless of underlying etiology of the kidney disease.. Evidence suggests that reduced insulin production results from beta cell insensitivity to glucose rather than functional exhaustion of beta cells.(17)Calcium and phosphate disturbances, including vitamin D therapy, significantly reduces insulin resistance in uremia, suggesting a role for hyperparathyroidism.

Factors implicated in the pathogenesis of insulin resistance in chronic renal failure are

1.UREMIC TOXINS: Hippurate and pseudouridine are specific for uremia and inhibit glucose utilization at concentrations found in sera of uremic subjects. Partially purified toxins from uremic sera, after hemodialysis therapy, ameliorate beta-cell response to hyperglycemia and increase tissue sensitivity to insulin.

Possible Causes of Insulin Resistance in Patients with Chronic Kidney Disease

Kidney related
Accumulation of nitrogenous wastes
Uric acid
Pseudo-uridine
NC-Asparagine
Kidney unrelated
Resistin
Adiponectin
Pro-inflammatory cytokines (e.g., TNF-alpha)
Free fatty acids

2.EXERCISE INTOLERANCE: Exercise intolerance is common among hemodialysis patients, and also it can be the cause of insulin resistance. Moderate endurance training program improved both the exercise tolerance and insulin sensitivity in patients on hemodialysis.

3.METABOLIC ACIDOSIS: Metabolic acidosis is frequent in uremia, but not in hemodialysis patients. Treatment of metabolic acidosis increases insulin sensitivity and insulin secretion, but significant degree of insulin resistance still exists in uremic patients.

4.SECONDARY HYPERPARATHYROIDISM: After surgical correction of hyperparathyroidism, in hemodialysis patients, glucose tolerance and insulin secretion increase without significant changes in insulin sensitivity. Defect in insulin release attributable to reduced ATP content in the pancreatic islets induced partially by high intracellular calcium, secondary to augmented PTH-induced calcium entry into cells.

5.VITAMIN D DEFICIENCY: Acute and chronic intravenous 1,25-Dihydroxycholecalciferol therapy corrects insulin resistance in dialysis patients, in absence of PTH suppression. These results are consistent

with the hypothesis that 1,25(OH)2 D3 deficiency is a primary factor of insulin resistance.

Dr Suleyman Turk et al Department of Nephrology, University Hospital, Selcuk University evaluated the effect of calcitriol treatment on glucose intolerance in uraemia and found that blood glucose significantly decreased after calcitriol treatment at 0, 30, 60, 90, and 120 min.These results seem to confirm that vitamin D influences pancreatic beta (β) cell secretion and suggest that calcitriol may improve glucose intolerance in uraemic haemodialysis patients. This effect of calcitriol is probably due to normalization of serum PTH and regulation of intracellular calcium concentration.

6.ERYTHROPOETIN Deficiency: Treatment with recombinant human erythropoietin (EPO) also appears to improve insulin sensitivity, although the mechanism is not well established. . ERYTHROPOIETIN THERAPY corrects insulin resistance beside anaemia.

Angiotensin-converting enzyme inhibitors have been shown to improve insulin resistance, hyperinsulinemia, and glucose intolerance in uremic patients.[18]

Insulin resistance has been postulated as an important factor in modulating the excess risk of cardiovascular disease. IR manifests with hyperinsulinemia, glucose intolerance, hyperglycemia, and dyslipidemia.[19] IR may also indirectly result in renal damage.[20] Several other possible factors have been implicated . The impact of accumulating nitrogenous waste products in the context of a progressively uremic environment over time in a patient with CKD has been supported by several studies. Both renal replacement therapy and a low protein diet improve insulin resistance. Accumulation of uric acid in renal failure also appears to be associated with insulin resistance, although causality remains to be proven. Pseudouridine, a nucleotide that accumulates in patients with progressive kidney failure, has been observed in rats to reduce glucose utilization in muscles isolated. N-carbamoyl-L-asparagine has been observed to selectively reduce insulin-mediated glucose uptake in adipocytes.[95] N-carbamoyl-L-asparagine, one of 15 carbamoylated amino acids, selectively reduced insulin-mediated glucose uptake in adipocytes. Carbamoylation of insulin also reduces its activity.

It is postulated that IR results in compensatory hyperinsulinism and that excessive insulin promotes the proliferation of renal cells and stimulates the production of other important growth factors such as insulin-like growth factor-1 and transforming growth factor beta.

An article published in The Lancet, Volume 292, Issue 7572, Pages 798-801 states that malnutrition in chronic renal failure leads to increased growth hormone which causes insulin resistance producing impaired glucose tolerance.Insulin resistance and hyperglycemia adds on to the morbidity leading to dyslipidaemia , increasing risk for atherosclerosis.

The uremic state described is attributable to the uremic toxins that may impair intracellular glucose utilization to produce hyper glycemia and cause insulin resistance. Non diabetic CKD patients usually have mildly elevated blood glucose levels and impaired glucose tolerance which does not require therapeutic reduction of blood glucose – S.shah, API TEXTBOOK OF MEDICINE 8th edition ,2008,vol1,73721

METABOLIC ACIDOSIS: Metabolic acidosis is frequent in uremia, but not in hemodialysis patients. Treatment of metabolic

acidosis increases insulin sensitivity and insulin secretion, but significant degree of insulin resistance still exists in uremic patients.

LIPID DISTURBANCES

Cardiovascular risk increases with each decrement in renal function. Lipoprotein composition with increased abundance of small dense LDL and HDL and reduced levels of more buoyant isoforms is similar to what is found in states of insulin resistance and in the metabolic syndrome (MS). In both cases, high triglyceride levels are associated with reduced HDL levels. Chronic kidney disease (CKD) associated with increasing insulin resistance results in decreased levels of apo A-I and apo A-II as a consequence of increased fractional catabolic rate (FCR), resulting from a predominance of small HDL particles. HDL maturation is impaired in CKD through decreased activity of lecithin:cholesterol acyltransferase (LCAT), and increased cholesterol ester transfer protein (CETP) activity in MS shuttles triglycerides back into HDL, thereby destabilizing it. Whether insulin resistance is entirely responsible for disorders of HDL metabolism in CKD, or whether the process is a result of unrelated pathophysiology, is currently unknown.[22]

Nonphysiologic concentrations of urea have been reported to increase levels of ROS. End-stage renal disease (ESRD) patients have increased levels of oxidative stress , and intracellular ROS induced by hyperglycemia increase protein modification by O-linked β-N-acetylglucosamine (O-GlcNAc) . Increased modification of key signaling molecules by O-GlcNAc was recently shown to cause reduced insulin signal transduction . Insulin resistance is a well-documented feature of ESRD, and the rate of death among hemodialysis patients is greater in those with more severe insulin resistance . The insulin resistance present in ESRD appears to start much earlier in the course of chronic kidney disease, when renal failure is subclinical . Although the cause of insulin resistance in chronic renal disease is unknown , several abnormalities associated with ESRD might interfere with insulin signaling. The concentrations of urea associated with CRF might drive insulin resistance by increasing ROS production, thereby increasing modification of insulin signaling molecules by O-GlcNAc.

PROTEINURIA AND GLUCOSE TOLERANCE

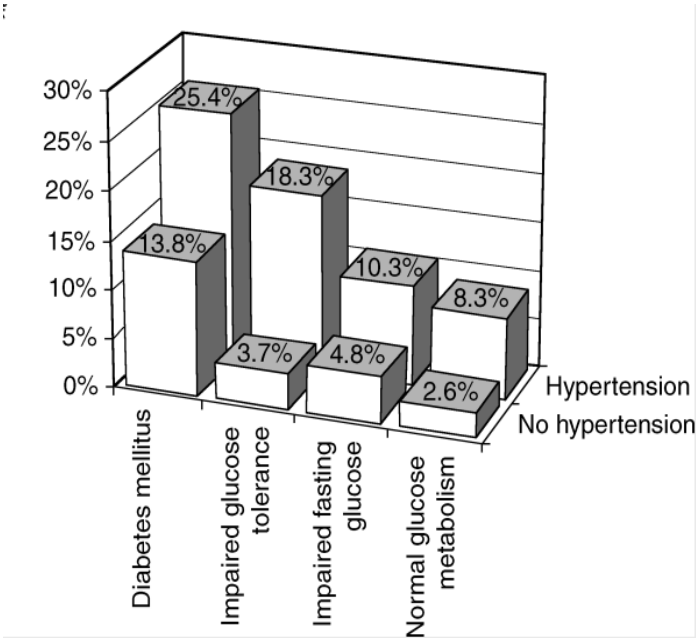
In a study conducted in Australia , The Aus Diab Kidney Study, 11,247adults of more than 25 years of age were screened between April 1999 and December 2000. Albuminuria was determined by urine albumin:creatinine ratio with normal ≤3.4 mg/mmol, microalbuminuria = 3.4 to 34 mg/mmol, and macroalbuminuria ≥34 mg/mmol. Proteinuria was determined by urine protein:creatinine ratio (mg/mg) with abnormal proteinuria ≥0.2 mg/mg, which approximates 250 mg/24-hour excretion

AUSDIAB[24] results showed that 7.2% of adult Australians in the community have diabetes. A portion (3.6%) knew they had diabetes, and 3.6% were undiagnosed. A percentage of adults (16.1%) had impaired glucose metabolism, 60% were overweight or obese, 61% had high cholesterol, and 29% had elevated blood pressure, with only 14% on treatment

The effect of hypertension and glucose tolerance on the prevalence of albuminuria demonstrated an enhancing effect. With increasing degrees of glucose intolerance there were increasing

amounts of albuminuria. However, when the effect of hypertension was also taken into account, microalbuminuria was increased at each degree of glucose intolerance in an incremental fashion, with 25.4% of people with diabetes mellitus and hypertension having albuminuria [25]

COMPARISON OF HYPERTENSION AND GLUCOSE TOLERANCE



Elevated urea in chronic renal failure (CRF) is considered to have negligible toxicity because Johnson et al. found in 1972 that in patients with far-advanced renal failure, blood urea concentrations of less than 50 mM (blood urea nitrogen [BUN] of 140 mg/dl) were well tolerated when blood urea concentration was maintained by adding urea to the dialysate solution and 30 years later, the HEMO study

showed that increasing urea reduction rate from 66% to 75% did not alter survival in patients with an increased dialysis dose. However, more recent data have demonstrated that survival of patients on daily hemodialysis is 2- to 3-fold greater than that of patients dialyzed less frequently. The observation that in an animal model of CRF-accelerated atherosclerosis, plasma urea was the only significant predictor of aortic plaque area fraction suggested to us that the high levels of urea found in chronic dialysis patients might play an important role in accelerated atherosclerosis in this group of patients.

Insulin resistance per se contributes to micro and macrovascular complications adding on to the morbidity of chronic kidney disease.

Impaired fasting glucose is defined as fasting glucose >110mg% and <126mg% which favours early onset of microvascular complications namely diabetic nephropathy , retinopathy , neuropathy even in the absence of overt diabetes mellitus.

Impaired glucose tolerance is defined as 2hours post glucose challenge blood glucose >140 mg % and <200 mg%. Impaired glucose tolerance favours early onset of macrovascular complications like coronary artery disease , cerebrovascular accident , peripheral vascular disease even in the absence of overt diabetes mellitus.

INSULIN RESISTANCE AND METABOLIC SYNDROME

Features of insulin resistance metabolic syndrome or syndrome X:

- Hyperinsulinaemia.
- Type II diabetes or impaired glucose tolerance.
- Hypertension.
- Low HDL and elevated triglycerides.
- Central obesity.
- Microalbuminuria.
- Increase fibrinogen.
- Increased plasminogen activator inhibitor 1.
- Elevated plasma uric acid.
- Increased sympathetic neural activity.

This is strongly associated with atherosclerosis and other macrovascular complications.

An article published in The Lancet, Volume 292, Issue 7572, Pages 798-801 states that malnutrition in chronic renal failure leads to increased growth hormone which causes insulin resistance producing impaired glucose tolerance.Insulin resistance and hyperglycemia adds

on to the morbidity leading to dyslipidaemia , increasing risk for atherosclerosis.

It s clear from the above discussion that there a wide array of metabolic derangements in chronic kidney disease and some of them contributing to insulin resistance leading to glucose intolerance which has its own detrimental effect on the existing pathology.

This study deals with the metabolic disturbance in glucose in chronic kidney disease patient and whether it has any bearing on lipid profile hypertension and severity of renal failure.

This study also takes into account whether oral glucose tolerance test has to be done as a routine investigation in chronic kidney disease patients adding to the battery of investigations. This study helps to analyse whether oral glucose tolerance test has any added advantage over the existing list of investigations in chronic kidney disease patients.

REVIEW OF ARTICLES

In a study at Copenhagen on, Pre-diabetes and arterial stiffness in uraemic patients found that of the 66 uraemic patients (41%) had pre-diabetes (IFG+IGT), and 39 had normal glucose tolerance. The uraemic patients were more insulin resistant with lower insulin

sensitivity index compared to healthy controls (6.1 ± 3 vs. 15 ± 7, P < 0.0001) but with no difference between patients with and without pre-diabetes. HbA1c and fasting plasma glucose was comparable in uraemic patients with and without pre-diabetes. In conclusion, a high prevalence of pre-diabetes, impaired insulin resistance, increased arterial stiffness of aorta as well as impaired augmentation index and vasodilatation was demonstrated in uraemic patients prior to kidney transplantation. Increased arterial stiffness of aorta and augmentation index were independently associated with age and blood pressure[26]

A study on Susceptibility to Hyperglycemia in Patients with Chronic Kidney Disease by, Walid Shehab-Eldin et al[27] ,showed that ,the prevalence of pre- diabetes was 40 percent . They proved that ,increased IR, rather than β-cell dysfunction, was the primary mechanism of pre- diabetes in CKD patients [27]

In another study by Kobayashi S et al ,they studied 39 subjects and using the hyperinsulinemic euglycemic glucose clamp technique was used to examine insulin sensitivity in patients without diabetes (n = 29) with different stages of renal function and study the metabolic abnormalities, such as apolipoprotein (Apo) profile or acidosis, associated with insulin resistance in patients with CKD and they found that, insulin resistance correlated linearly with decline in renal

function. Independent variables related to insulin resistance were bicarbonate and Apo A-/B levels in patients with CKD[28]. In yet another study from Department of Internal Medicine, University of Missouri-Columbia on the Relationship between Hyperinsulinemia, Hypertension and Progressive Renal Disease , found that impaired glucose tolerance and hypertension are important contributors to ESRD. they also found out that Obesity, especially the visceral type, is associated with peripheral resistance to insulin actions and hyperinsulinemia, which predisposes to development of diabetes. A common genetic predisposition to insulin resistance and hypertension and the coexistence of these two disorders predisposes to premature atherosclerosis. A constellation of metabolic and cardiovascular derangements, which also includes dyslipidemia, dysglycemia, endothelial dysfunction, fibrinolytic and inflammatory abnormalities, left ventricular hypertrophy, microalbuminuria, and increased oxidative stress, is referred to as the cardiometabolic syndrome. The components of this syndrome, individually and interdependently, substantially increase the risk of renal disease, cardiovascular disease (CVD) and mortality. Similar findings and cardiorenal risk factors can occur in subjects with android obesity without excess body weight. [29]

In a study at the Tulane University School of Medicine New Orleans, Louisiana on Insulin Resistance and Risk of Chronic Kidney Disease in Nondiabetic Adults identified a strong, positive, significant, and dose-response relationship among insulin resistance, insulin level, and risk of CKD among nondiabetic participants. This relationship was independent of age, gender, race, and other potential risk factors for CKD, such as BP, obesity, total cholesterol, education, physical activity, cigarette smoking, NSAID use, and alcohol

Consumption. In their study, a HbA1c level greater than or equal to 5.7% was associated with an elevated risk of CKD. These findings support the notion that intensive glycemic control in diabetics as well as a reduction of glycemic level in persons with an impaired fasting glucose may be important strategies for primary prevention of CKD and slowing the progression of CKD. [30]

A notable study done at the , University Magna-Graecia of Catanzaro, Catanzaro, Italy on One-Hour Postload Plasma Glucose Levels showed a link between postload hyperglycemia and kidney dysfunction, showed that , individuals with 1hPG ≥155 mg/dl had a worse cardiometabolic risk profile, exhibiting significantly higher body mass index, BP, triglycerides, and fasting insulin levels and lower

HDL, IGF-1 levels, and insulin sensitivity, than individuals with 1hPG <155 mg/dl. The Estimated GFR was significantly lower in individuals with 1hPG ≥155 mg/dl. These results showing a link between postload hyperglycemia and kidney dysfunction may have clinical implications. Lifestyle changes and pharmacologic treatment in individuals who are high risk for type 2 diabetes have been demonstrated to be effective in reducing the incidence of type 2 diabetes and cardiovascular risk factors. This suggests that performing OGTT with measurement of 1hPG levels may be useful to identify individuals who have NGT and in whom it would be important to measure renal function in addition to risk factors for CVD, because they could benefit from lifestyle change interventions and, possibly, pharmacotherapy to prevent or delay clinical adverse outcomes[31]

In another study on Insulin resistance and pancreatic beta-cell function in patients with hypertensive kidney disease, at Nara Medical University, Nara, Japan, HKD with moderate to severe renal dysfunction is associated with insulin resistance. Approximately 40% of HKD subjects were in an insulin-resistant state: only <10% of HTN subjects and ~10–30% of CKD-NT subjects were insulin resistant.[32]

Another study by Argani et al, showed that significant linear correlation was observed with body mass index and IGT only in hemodialysis patients. Glucose tolerance also had a significant correlation with triglyceride levels , in hemodialysis patients Also ,the glucose tolerance had significant relationship with higher serum cholesterol levels only in the renal transplant recipients.[33]

LIPID ABNORMALITIES

Hyperlipidemia and Long-Term Outcomes in Nondiabetic Chronic Kidney Disease showed , a higher level of serum triglycerides, fibrinogen, total homocyst(e)ine and proteinuria, and a lower level of serum high-density lipoprotein in the ESRD(+) group than in the ESRD(−) group. **.** These results suggest a limited role for dyslipidaemia in the progression of chronic renal disease to dialysis in CRF patients, in contrast with the powerful influence of proteinuria, baseline creatinine clearance and nephropathy type in predicting this progression.

There was no association of TG, HDL-C, and NHDL-C as continuous variables with all-cause or CVD mortality . There was a significant inverse association between HDL-C and kidneyfailure,

hyperlipidemia and Long-Term Outcomes in Nondiabetic Chronic Kidney Disease. [34]

In a study by Donald S. Silverberg et al on the effect of correction of anaemia in diabetics and non-diabetics with chronic renal failure ,by subcutaneous erythropoietin and intravenous iron, that the correction of the mild anaemia that was found in diabetics and non-diabetics with resistant CHF and mild to moderate chronic renal failure improved the cardiac function and patient functional status, stabilized the renal function and markedly reduced the need for hospitalization. [35]

AIMS AND OBJECTIVES

AIM :

To find out the prevalence of impaired glucose tolerance in non diabetic chronic kidney disease patients and to analyse its relation with other comorbidities of chronic kidney disease.

Objective:

1.To find out the prevalence of impaired glucose tolerance in patients with non diabetic chronic kidney disease.

2.To study its significance in relation to the severity of renal failure.

3.To study its correlation with other comorbidities like dyslipidemia, obesity , proteinuria,etc.

MATERIALS AND METHODS

Setting	:	Department of Medicine, Government Rajaji Hospital.
Design	:	Descriptive study.
Period of study	:	July 2010 To December 2010
Ethical approval	:	Obtained from ethical committee headed by Dean, Government Rajaji Hospital, Madurai.
Consent	:	Informed consent obtained from all patients
Statistical software	:	SPSS version 17.0

Study population: OP and IP patients in Medicine and Nephrology

i)Case:

- Inclusion criteria:

  Non diabetic chronic kidney disease patients.

- Exclusion criteria:

  1.Those not giving consent.

  2.Other chronic ailment.

  3.Patients with urinary tract infections.

  4.Bed ridden, terminally ill patients.

5.Patients on drugs altering the glycemic status like steroids phenytoin etc

ii.Control:

- Inclusion criteria:

  Non diabetic healthy patients.

- Exclusion criteria:

  1.Those not giving consent.

  2.Other chronic ailment or on treatment with drugs producing hyperglycaemia.

iii.Case definition:

Non diabetic chronic kidney disease patients → Pathological abnormalities or markers of damage including abnormalities in blood or urine tests or imaging studies(USG Abdomen) or GFR < 60ml/min/ 1.73 sq m for 3 months.

Sample size:140

Case 90 , control 50.

In this study 90 patients were studied , and 50 age and sex matched controls were taken. An informed consent was obtained from the patient, following which a meticulous history of the patient with regard

to CKD was taken,especially the presence of uremic symptoms , duration of CKD, Hypertension , drug history ,duration of treatment , intake of any steroids or other medications that could alter the glycemic status was also taken. History of other co-morbidities were also recorded.

The vital data especially the systolic BP and pulse pressure were carefully recorded, the fundus was examined to rule out cases with diabetic retinopathy. Patients with diabetic retinopathy were excluded from the study. In the general examination we looked especially for pallor, signs of failure ,puffiness of face, any markers of insulin resistance were noted. Anthropometric measurements were also taken inorder to calculate the BMI. A careful examination of all the systems were also done.,

Following examination a battery a investigations were done. All patients underwent the following blood investigations including blood sugar, urea, serum creatinine, Fasting lipid profile etc. Few urine investigations were also done which included ,urine albumin using heat coagulation test, urine Spot PCR, deposits were done . Those patients with Urinary tract infections were excluded from the study.

Thereafter eGFR was calculated from serum creatinine values using

1) Cockroft Gault equation [5]

$$\text{Creatinine Clearance} = \frac{(140\text{-age}) \times \text{body weight (kg)}}{72 \times \text{S.Creat (mg/dl)}} \times 0.85 \text{ (for women)}$$

2) MDRD formula[5]

Estimated GFR (mL/min per 1.73 m^2) = 1.86 x $(P_{Cr})^{-1.154}$ x $(age)^{-0.203}$

Multiply by 0.742 for women, Multiply by 1.21 for African Americans.

NKF-KDOQI staging of CKD was applied using MDRD formula and stage of CKD is determined. Once this was done, all the patients were subjected to a standard OGTT(oral glucose tolerance test)

STANDARD OGTT(WHO)

Preparation

The patient is instructed not to restrict carbohydrate intake for atleast 4 days before the test. The test should not be done during an illness, as results may not reflect the patient's glucose metabolism when healthy. A full adult dose should not be given to a person weighing less than 43 kg (94 lb), or exaggerated glucoses may produce a false positive result. The OGTT was performed in the morning as glucose tolerance can exhibit a diurnal rhythm with a significant decrease in the

afternoon. The patient is instructed to fast (water is allowed) for 8–12 hours prior to the tests.

Procedure

1. A zero time (baseline) blood sample is drawn.
2. The patient is then given a measured dose (below) of glucose solution to drink within a 5 minute time frame.
3. Blood is drawn at intervals for measurement of blood glucose levels .(blood was drawn at 1^{st} hour and 2^{nd} hour.)

Dose of glucose .

As in the WHO recommendation is 75g oral dose in all adults.

Interpretation of OGTT results

Fasting plasma glucose (measured before the OGTT begins) should be below 6.1 mmol/l (110 mg/dl). Fasting levels between 6.1 and 7.0 mmol/l (110 and 125 mg/dl) are borderline ("impaired fasting glycaemia"), and fasting levels are at or above 7.0 mmol/l (126 mg/dl) are diagnostic of diabetes.

The 2 hour OGTT glucose level should be below 7.8 mmol/l (140 mg/dl). Levels between this and 11.1 mmol/l (200 mg/dl) indicate

"impaired glucose tolerance"(IGT). Glucose levels above 11.1 mmol/l (200 mg/dl) at 2 hours confirms a diagnosis of diabetes.

1999 WHO Diabetes criteria - Interpretation of Oral Glucose Tolerance Test

Glucose levels	**NORMAL**		**impaired fasting glycaemia (IFG)**		**impaired glucose tolerance (IGT)**		**Diabetes Mellitus (DM)**	
Venous Plasma	Fasting	2hrs	Fasting	2hrs	Fasting	2hrs	Fasting	2hrs
(mmol/l)	<6.1	<7.8	> 6.1 & <7.0	<7.8	<7.0	>7.8	>7.0	>11.1
(mg/dl)	<110	<140	>110& <126	<140	<126	>140	>126	>200

All these tests were done in both the cases and the controls. All these patients were reviewed. All investigations reports were entered in the proforma, and tabulated in the excel spreadsheet.

According to the calculated GFR, patients were divided into stage 1 to 5 CKD. Thereafter each of the parameters were compared within the CKD groups and with the controls

All the datas were analysed using the SPSS software and a conclusion was arrived. The various statistical tools that were used were the chi-square test, the mean and standard deviation and the

independent sample T-test. The p value was obtained and then the parameters were said to be significant or not depending on the p – value. Graphs were made with these conclusions using the excel and the SPSS software.

RESULTS AND ANALYSIS

TABLE 1 :COMPARISION OF BASELINE DATA

Character	**Case n% (90)**	**Control n%(50)**
1.Age		
<30y	14 (15.6)	6 (12)
30 to 40	22 (24.4)	14 (28)
40 to 50	18 (20)	11 (22)
50 to 60	32 (35.6)	16 (32)
60 to 70	4 (4.4)	3 (06)
2.Sex		
Male	51 (56.7)	29 (58)
Female	39 (43.3)	21 (42)
3.CRF stage		
II	16 (14)	
III	11 (21)	
IV	30 (29)	
V	33 (36)	
4.BMI		
<18.5 underweight	14 (15.5)	10 (20)
18.5 – 24.9 normal	60 (66.6)	22 (44)
25 – 29.9 overweight	14 (15.5)	15 (30)
>30 obese	2 (2.2)	3 (6)
5.Prehypertension	57 (63.3)	0

6.Serum cholesterol		
<200	51 (56.6)	33 (66)
200 – 250	26 (28.8)	17 (34)
250 – 300	8 (8.8)	0
>300	5 (5.5)	0
7.serum triglyceride		
<150	66 (73.3)	18 (36)
150 – 200	5 (5.5)	22 (44)
200 – 250	12 (13.3)	10 (20)
>250	7 (7.7)	0
8.urine spot PCR		
<0.3	3 (3.3)	50 (100)
0.3 to 1.0	54 (60)	
1.0 to 2.0	29 (32.2)	
>2	4 (4.4)	
9.Urine albumin		
Nil	0	50 (100)
1+	53 (58.8)	
2+	15 (16.6)	
3+	22 (24.4)	

The above table shows the comparison of baseline data between the two study groups. This shows that, the groups are comparable with respect to age, sex , lipid profile and body mass index.

Figure 1, represents the age and sex distribution among the study groups. Figure 2 shows the stages of chronic kidney disease in the study population.

Figure 2, shows that , the major portion of the cases belonged to the stage 5 CKD,(38%) followed by 29,21,and 14% respectively in stages 4,3 and 2.

AGE DISTRIBUTION IN CASES AND CONTROLS

Figure 3 shows, a comparison of the age distribution in the cases and controls. The lowest age in the CKD group was 28, and in the control group was 26 ,and the highest was 67 and 68, respectively. The maximum number of cases in either groups fall into the 51-60 age group in either groups. The percentage wise distribution of the age was 12,28,22,32,6 in the age groups of <30,31-40,41-50,51-60,and 61-70 respectively. Similarly in the corresponding age groups , controls were 15.6,24.4,20,35.6,4.4 respectively.

This shows a similarity in the age distribution among cases and controls.

SEX DISTRIBUTION IN CASES AND CONTROLS

Figure 4, shows the sex distribution among cases and controls. There are 43.3% females in case group and 42% in the control group . Among the males it is 56.7% and 58 % in cases and controls respectively.

This shows that this study has a sex matched control group .

TABLE :2: COMPARISON OF 2 HR GTT TO STAGE OF CKD

			GTT-2Hr		
			< 140	>=140	Total
CKD Stage	2	Count	15	1	16
		Percent	25.4%	3.2%	17.8%
	3	Count	9	2	11
		Percent	15.3%	6.5%	12.2%
	4	Count	17	13	30
		Percent	28.8%	41.9%	33.3%
	5	Count	18	15	33
		Percent	30.5%	48.4%	36.7%
Total		Count	59	31	90
		Percent	100.0%	100.0%	100.0%
Chi square test		P value	.021		

This table shows a comparison of CKD stages to, 2hour glucose tolerance values. Of all the CKD patients, there was a statistically significant increase in the percentage of patients having IGT(i.e:>140) after a 2 hour glucose load, as the stage of CKD advances.(p=0.021). When there was only 3.2% and 6.5% cases with IGT in stages 2 and 3 CKD there was a significant rise to 41.9% and 48.4% respectively in CKD stages 4 and 5 respectively.

TABLE: 3 COMPARISON OF ONE HOUR GLUCOSE TOLERANCE TO CKD STAGE

			GTT_1h		
			<= 155	>155	Total
CKDStage	Stage 3	Count	8	3	11
		Percent	72.7%	27.3%	100.0%
	Stage 4	Count	20	10	30
		Percent	66.7%	33.3%	100.0%
	Stage 5	Count	13	20	33
		Percent	39.4%	60.6%	100.0%
Total		Count	41	33	74
		Percent	55.4%	44.6%	100.0%
Chi-square test		P value	0.43		

This table shows a comparison of one hour post glucose load blood sugar > 155 to the different CKD stages. There is a steady increase in the blood glucose more than 155 as the stage of CKD progresses. In stage 3 CKD when there were only 27 % in stage 3 CKD that progressively increased to 33.3% and 60.6% respectively in stages 4 and 5.

TABLE 4: RELATIONSHIP BETWEEN TOTAL CHOLESTEROL AND GLUCOSE INTOLERANCE IN CKD PATIENTS.

Serum cholesterol (mg%)	No of CKD patients	Impaired glucose tolerance	Percentage
<200	51	21	41.1
200 – 250	26	3	11.5
250 – 300	8	4	50
>300	5	3	60

The above table shows the relation between serum cholesterol and glucose intolerance in chronic kidney disease patients which shows that with increasing serum cholesterol, there is impaired glucose tolerance.

Figure 7 shows the relationship between serum cholesterol and glucose intolerance in chronic kidney disease patients.

TABLE 5: RELATIONSHIP BETWEEN SERUM TRIGLYCERIDE AND GLUCOSE INTOLERANCE IN CHRONIC KIDNEY DISEASE PATIENTS.

Serum triglyceride (mg%)	No of CKD patients	Impaired glucose tolerance	Percentage
<150	66	24	36%
150 – 200	5	3	60%
200 – 250	12	0	0
>250	7	4	57%

The above table shows the relation between serum triglyceride and glucose intolerance in chronic kidney disease patients which shows that with serum triglyceride > 150mg % there is increase in impaired glucose tolerance.

Figure 8 shows the relationship between serum triglyceride and glucose intolerance in chronic kidney disease patients

TABLE 6 : HDL AND IGT

HDL (mg %)	Total	Impaired glucose tolerance	Percentage
<40	4	4	100
40 – 45	80	26	32.5
>45	6	1	16.6

This table shows, the relationship between IGT and HDL values. It shows that, patients with IGT had lower levels of HDL.

Figure 9 shows the relationship between, IGT and HDL.

TABLE 7 : BMI AND IGT

Body mass index	No of CKD patient	Impaired glucose tolerance	Percentage
<18.5	14	5	35.7
18.5 – 24.9	60	19	31.6
25 – 29.9	14	5	35.7
>30	2	1	50

The above table shows the relation between body mass index and impaired glucose tolerance which does not show any significant relation between body mass index and glucose tolerance.

Figure 10 shows the relation between body mass index and glucose tolerance.

TABLE 8 : ALBUMINURIA AND IGT

Urine albumin	IGT%
1+	15%
2+	16%
3+	69%

TABLE 9 :

Albuminuria	Total	Impaired glucose tolerance	Percentage
1+	53	7	13.2
2+	15	4	26.6
3+	22	20	90.9

The above tables show relationship between , albuminuria and IGT. With worsening of albuminuria, the percentage of patients with IGT also increases.

Figures show the relationship between albuminuria and IGT.

TABLE 10 :

Spot PCR	Total	Impaired glucose tolerance	Percentage
<0.3	3	1	33.3
0.3 – 1	49	7	14.28
1 – 2	30	16	53.3
>2	8	7	87.5

This table shows the relationship between spot PCR and IGT. It shows that with worsening proteinuria glucose tolerance is also impaired.

Figure 13 shows the comparison of spot PCR to IGT.

TABLE 11: SEX AND IMPAIRED GLUCOSE TOLERANCE

Age	Total	IGT	Percentage
≤ 30 years	14	3	21.4
31 to 40 years	22	7	31.81
41 to 50 years	18	10	55.5
51 to 60 years	32	9	28.12
>60 years	4	1	25

This table shows the sex distribution of IGT among CKD patients. The prevalence of IGT is comparable between the sexes.

DISCUSSION

Disturbances in carbohydrate metabolism, especially glucose intolerance, is common in CKD patients, particularly in patients on dialysis. One major factor for the reduced glucose tolerance in uremia is an impaired sensitivity to insulin (insulin resistance, IR) in peripheral tissues, mainly in skeletal muscle. Glucose metabolism is impaired in CKD, as evidenced by a slowing of the rate at which blood glucose levels decline after a glucose load. The burden of CKD is increasing worldwide and it has doubled over the past 15 yrs.

In this study titled a study of glucose tolerance in non – diabetic CKD patients , we studied a total of 140 patients 90 belonging to the study group and 50 belonging to the control group.

AGE

For the 90 patients we studied, we had obtained 50 age matched controls. In our study the lowest age among patients in the cases group was 28 and in the control group was 26 ,and the highest was 67 and 68 respectively. The maximum number of patients observed were in the age groups of 31 to 40 and 51-60 age group. Our study correlates well with the findings of Indian literature. In a study by rao

et al in 1998, observed that the mean age of CKD patients was 38 which again correlates with our study.[38]

SEX

The sex distribution in our study was, 43.3% females in patients group and 42% in the control group and males contributed about 56.7% and 58 % in patients and controls respectively. It was sex matched with the control group. This shows that there was a slight male preponderance . This is again in concordance with a study by madhumathi et al [39]conducted at CMC Vellore which showed that there was no significant change in the sex ratio but for a slight male preponderance.

CKD STAGE

In this study , 36% of the patients were in stage 5 CKD, 29% patients were in stage 4 CKD ,and 21%,14% in stages 3 and 2 respectively, suggesting that most of our patients seek medical help at stage 5 CKD (1/3).

IGT IN CKD

In our study, there were no cases with IFG (impaired fasting glucose). In the GTT done 2 hours after a glucose load when there was only 3.2% and 6.5% cases with IGT in stages 2 and 3 CKD, there was a significant rise to 41.9% and 48.4% respectively in CKD stages 4 and 5 respectively, indicating that as the CKD stage progresses there is a progressive increase in the glucose intolerance which was statistically significant.(p=0.021). This was in concordance with a study on Susceptibility to Hyperglycemia in Patients with Chronic Kidney Disease by Walid Shehab-Eldin et al[27] ,which studied the prevalence of pre-diabetes in CKD patients and determine the contribution of insulin resistance (IR) versus β-cell dysfunction in patients with CKD . IR was assessed by homeostasis model assessment of insulin resistance (HOMA-IR) and β-cell function was assessed by proinsulin/insulin ratio and β-cell percent **.** The prevalence of PDM was 40 percent. He concluded that, increased IR, rather than β-cell dysfunction, is the primary mechanism of PDM in CKD patients.

In a study at Copenhagen[26] on , pre-diabetes and arterial stiffness in uraemic patients found that of the 66 uraemic patients 41%, had pre-diabetes (IFG+IGT), and 39 had normal glucose tolerance. The

uremic patients were more insulin resistant with lower insulin sensitivity index compared to healthy controls ($P < 0.0001$), but with no difference between patients with and without pre-diabetes. HbA1c and fasting plasma glucose were comparable in uraemic patients with and without pre-diabetes.

In yet another study by Kobayashi S et al[28] ,they studied 39 subjects and using the hyperinsulinemic euglycemic glucose clamp technique was used to examine insulin sensitivity in patients without diabetes (n = 29) with different stages of CKD, and found that, insulin resistance correlated linearly with decline in renal function. Independent variables related to insulin resistance were bicarbonate and Apo A-1/B levels in patients with CKD.

Thus it may be noted that as the renal function declines , the glucose tolerance becomes more impaired and the predominant mechanism being insulin resistance.

ONE HOUR POST-PRANDIAL GLUCOSE AND CKD

In our study, the prevalence of patients with one hour post glucose load showed ,there was a steady increase in the blood glucose more than 155, as the stage of CKD progresses. In stage 3 CKD, when there

were only 27 % patients with IGT, it progressively increased to 33.3% in stage 4 and 60.5% in stage 5 CKD.

These results were comparable to a notable study done at the , University Magna-Græcia of Catanzaro, Catanzaro, Italy[31], showed a link between post load hyperglycemia and kidney dysfunction . Individuals with 1hPG ≥155 mg/dl had a worse cardiometabolic risk profile, exhibiting significantly higher body mass index, BP, triglycerides, and fasting insulin levels and lower HDL, IGF-1 levels, and insulin sensitivity, than individuals with 1hPG <155 mg/dl. The Estimated GFR was significantly lower in individuals with 1hPG ≥155 mg/dl. These results showing a link between post load hyperglycemia and kidney dysfunction may have clinical implications. This suggests that performing OGTT with measurement of 1hPG levels may be useful to identify individuals who have NGT and in whom it would be important to measure renal function in addition to risk factors for CVD, because they could benefit from lifestyle change interventions and, possibly, pharmacotherapy to prevent or delay clinically adverse outcomes.

IGT and Proteinuria:

In the comparison between IGT and proteinuria, 69% of the cases with IGT had, 3+ albuminuria, whereas, only 16% cases had 2+ and 15% had 1+ albuminuria.

This is correlating with a study by Nelson et al earlier this year, where in they found that, subjects with imparied glucose tolerance were found to have a higher prevalance of abnormal albuminuria than those with normal glucose tolerance.

In a study by of Edward Kessle et al[41], found that , glucose tolerance worsens in individuals excreting 1.0 g or more proteinuria/ day and this can lead on to prediabetic state or have chemical diabetes. The increased proteinuria could reflect glomerular nephrosclerosis.

A role for insulin resistance in the pathogenesis of microalbuminuria has been suggested, because the severity of IR appears to correlate with the severity of microalbuminuria.[20.] Indeed, data suggests that this endothelial-dependent vasodilatation is abnormal in microalbuminurics and this is linked with insulin resistance - Brenner nephrology 8 th edition[2]

Proteinuria is an independent marker for the progression of CKD. When managing patients with CKD, we aim to retard, and—if possible—reverse the progression of renal disease, and also to prevent CKD-related complications such as bone and cardiovascular diseases. In a recent study by Alessia Fornoni et al[42], insulin resistance correlates with the onset and severity of albuminuria. This correlation has also been found in normotensive persons who do not have diabetes, suggesting that insulin resistance per se may cause albuminuria. This may be due to podocyte dysfunction.

HDL CHOLESTEROL AND IGT

An independent sample T-test was done on the samples and control groups and the test showed that the mean HDL value in the study group was 41.61 with a standard deviation of 1.852. whereas in the control group the mean HDL value was 46.8 with a standard deviation of 2.648. The HDL values ranged from 38 to 45 in the study group and 40 to 52 in the control group .

This shows a significant reduction of the HDL values when compared to the control group.(p=0.00).

This was in consonant with a study byVarun Chawla,et al[34] there was a significant inverse association between HDL-C and kidney failure.

This is because ,HDL maturation is impaired in CKD through decreased activity of lecithin:cholesterol acyltransferase (LCAT), and increased cholesterol ester transfer protein (CETP) activity in MS shuttles triglycerides back into HDL, thereby destabilizing it. Low HDL cholesterol levels is a prominent feature of insulin resistance syndrome.

In our study HDL cholesterol was found to decrease in cases of IGT.

TOTAL CHOLESTEROL AND IGT

In our study 53.8% of patients with serum cholesterol >250 had IGT, whereas only 31% of the patients <250 had IGT.

TRIGLYCERIDES AND IGT

In our study in patients with TGL >250, 57% of CKD patients had IGT, when compared 32.5% patients with IGT with TGL <250.

SEX AND IGT

There was no significant difference in glucose tolerance between the sexes.

BMI AND IGT

The comparison between body mass index and IGT showed that , most of the patients fell in the normal BMI category and among them, 31.3% had IGT. In the ill nourished with BMI less than 18.5,5 patients among the 14 in the group had IGT(35.7%). In the group with a BMI between 24.9 to 30 , 5 of the 14 people had IGT i.e 35.7%. In the obese individuals with a BMI more than 30 ,1 of the only 2 patients had IGT.

BMI correlates well with insulin resistance in general. This has been proved in various clinical and research studies.

On the contrary most of our CKD patients present with normal BMI even though IGT was documented. This IGT is mainly due to uremic toxins, hyperparathyroidism etc.

SUMMARY

This study titled a study of glucose tolerance in non diabetic CKD patients was conducted at the Govt Rajaji Hospital Madurai, between June and December 2010. The study was conducted on 90 non diabetic CKD patients after fulfilling the inclusion and exclusion criterias. An age and sex matched control group was also taken, consisting of 50 people. A relevant meticulous history was obtained ,with relevant examinations and thereafter they were subjected to a battery of investigations, most importantly a 2 hour GTT, with one hour value too, along with the renal parameters and fasting lipid profile.

From the study the following observations were made, which were consistent with various national and international studies.

1) Most CKD patients are in the age group of 31-40 and 51-60, showing a younger age group CKD unlike the western population, which could be attributed to the more frequent streptococcal infections.
2) There was not much of difference in the sex distribution in this study, it showed only a slight male preponderance which is consistent with various studies across communities.

3) Among the patients in this study,most of them belonged to stage 5 CKD (36%), followed by stage 4,3 CKD, probably because patients fail to seek medical attention at an earlier time.
4) IGT is more prevalent in stage 4 and 5 CKD. It was 48.4% in stage 5 CKD and 41.9% in stage 4 CKD. The predominant factor responsible for this was increased insulin resistance, and reduced insulin sensitivity, in CKD patients.
5) IGT can be taken as a marker of severity of renal failure like GFR.
6) One hour post glucose load was also more in higher stages of CKD . 60.5% of patients with stage 5 CKD had impaired one hour glucose intolerance. Individuals with one hour impaired glucose more than 155 have a worse cardiometabolic profile ,and these patients have ,also have worsening insulin insensitivity. These patients could benefit from lifestyle changes, interventions and, possibly, pharmacotherapy to prevent or delay clinically adverse outcomes.
7) The HDL-Cholesterol was found to be significantly lower in CKD patients when compared to the control group. This was as suggested by performing an independent variable T-test. The

mean HDL cholesterol was 41.61 in the study group compared to 46.8 in the control group.(p=0.00)

8) The BMI in this study didn't show any correlation with IGT. Most of the patients fell into the normal BMI group.
9) BMI does not help to identify patients with IGT in CKD population.
10) Most of our patients are malnourished and have normal or low BMI.
11) Severity of proteinuria correlates with abnormal glucose metabolism, and may predict progression of renal failure.

CONCLUSION

CKD is fast becoming a hidden epidemic as termed by madhumati rao et al[39], and true to the fact it is fast becoming a major cause of mortality in the Indian scenario.

Chronic kidney disease (CKD) has become one of the most important, chronic, noncommunicable disease epidemics in the world, including India. It is clear that treatment of CKD and its advanced stage, that is, end-stage renal disease (ESRD), is consuming a huge proportion of health resources in most of the country, and in India it is beyond the reach of the average Indian. Thus, it is crucial that prevention of CKD becomes an important goal of the medical fraternity, government, and public at large in any country, including India.

In conclusion there is a high prevalence of IGT in the non- diabetic CKD patients, as the disease advances apart from a range of other metabolic parameters. The IGT is mainly contributed by the increasing Insulin resistance and decreased insulin sensitivity in CKD patients. Indeed, it has been postulated that the excess cardiovascular mortality that heralds and then subsequently accompanies the development of

kidney failure may have at least part of its origins in the insulin resistance that develops.

The one hour post glucose load impaired glucose tolerance was also higher, as the renal function worsens. The one hour IGT may act as a better predictor of adverse cardiovascular outcome, henceforth its imperative that we screen all CKD patients with an OGTT. These patients with IGT may benefit from lifestyle modifications and possibly pharmacotherapy to prevent or to delay adverse outcomes.
Various lipid abnormalities also occur in the setting of CKD , the most noted being a significant reduction in the HDL-cholesterol fraction, which is in addition an important co-efficient of metabolic syndrome, and further adverse outcome.

Glucose tolerance also becomes impaired with worsening of proteinuria. Hence it is worthwhile in screening all patients with urine spot PCR , or microalbuminuria ,to catch the disease early, and thereby giving our patients a better outcome in life as well as a healthy one. Measures like adding ACE inhibitors or ARB's may be started early in the disease so as to delay the progression of CKD.

ABBREVIATIONS

ACE	Angiotensin Converting Enzyme
ARB	Angiotensin Receptor blockers
ATP	Adenosine Tri Phosphate
BMI	Body Mass Index
BP	Blood pressure
BUN	Blood urea nitrogen
CG	Cockroft Gault equation
CHF	Congestive Heart Failure
CKD	Chronic kidney disease
CRF	Chronic renal failure
CRP	C- reactive Protein
CVD	Cardiovascular disease
DM	Diabetes Mellitis

EPO	Erythropoietin
ESR	Erythrocyte Sedimentation Ratio
ESRD	End stage renal disease
FCR	Fractional catabolic rate
GFR	Glomerular filtration rate
HbA1c	Glycosylated Hb
HDL-C	High density lipoprotein Cholesterol
HKD	Hypertensive kidney disease
HOMA-IR	Homeostasis model assessment of insulin resistance
IFG	Impaired Fasting Glucose
IGF-1	Insulin Like Growth Factor 1
IGT	Impaired glucose tolerance
IP	Inpatients
IR	Insulin resistance
KDOQI	National Kidney Foundation Kidney Disease Quality Outcomes Initiative

LCAT	Lecithin:cholesterol acyltransferase
LDL-C	Low density Lipoprotein Cholesterol
MDRD	Modification of Diet in Renal Disease
MS	Metabolic syndrome
NGT	Normal Glucose tolerance
NHANES	National Health and Nutrition Examination Survey
NHDL-C	Non HDL Cholesterol
NSAID	Non steroidal anti inflammatory drugs
O-GlcNAc	*N*-acetylglucosamine
OGTT	Oral Glucose tolerance Test
OP	Out patients
PCR	Protein Creatinine Ratio
PDM	Pre Diabetes
PG	Post glucose
PTH	Parathyroid hormone

ROS	Reactive oxygen species
TG	Triglycerides
UTI	Urinary Tract Infections
WHO	World Health Organisation

FIGURE 1

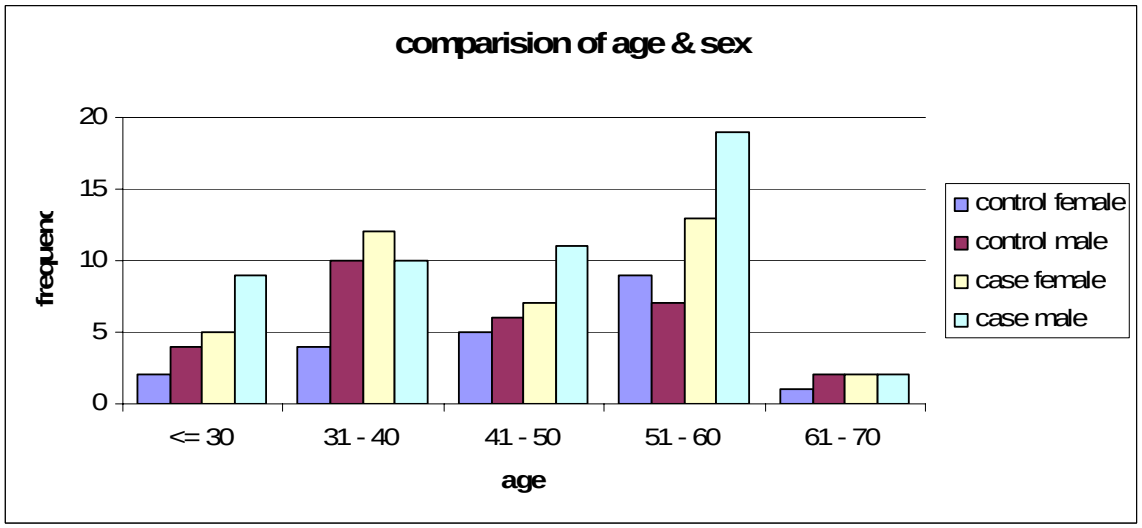


FIGURE 2

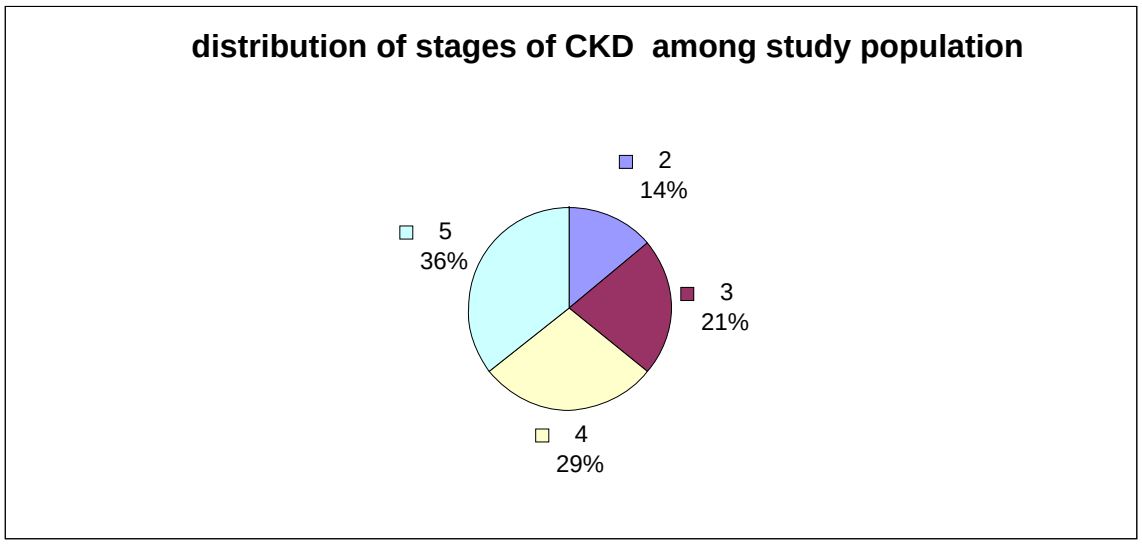


FIGURE: 3 AGE DISTRIBUTION IN CASES AND CONTROLS

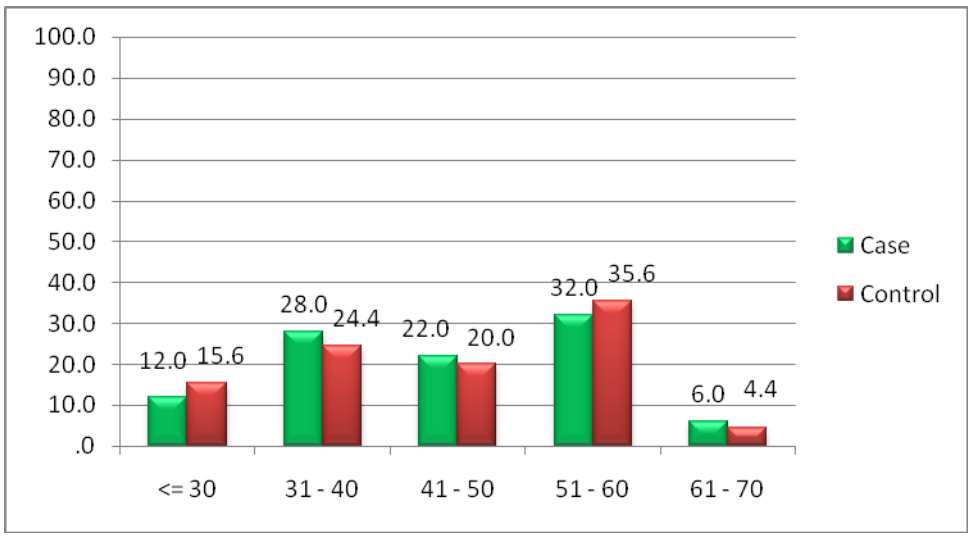


FIGURE : 4 SEX DISTRIBUTION IN CASES AND CONTROLS

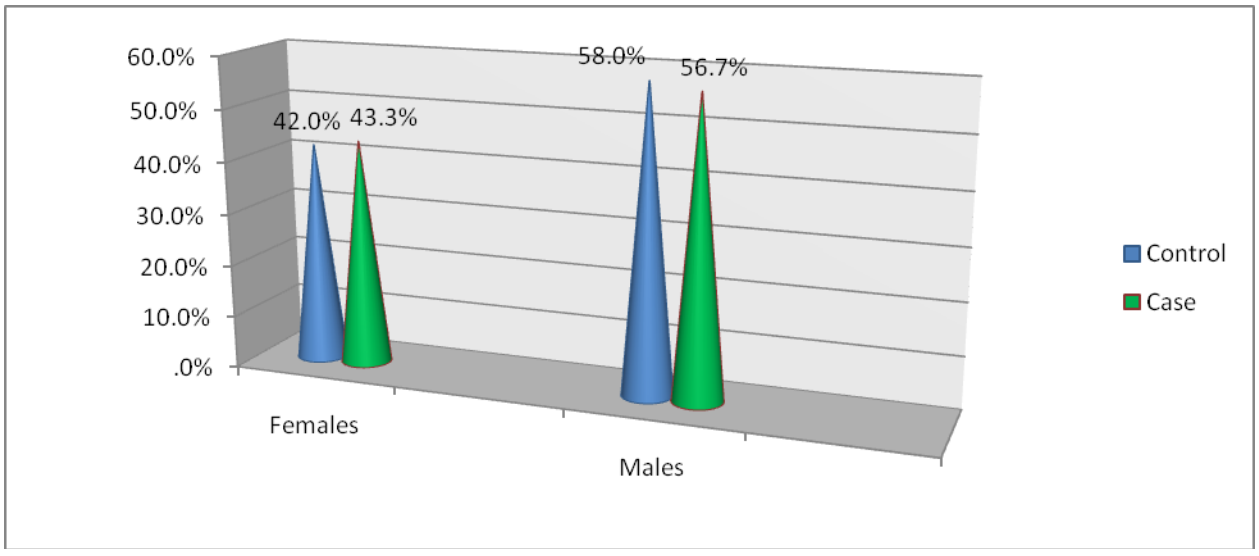


FIGURE:5 IGT ON 2 HR GTT TO STAGE OF CKD

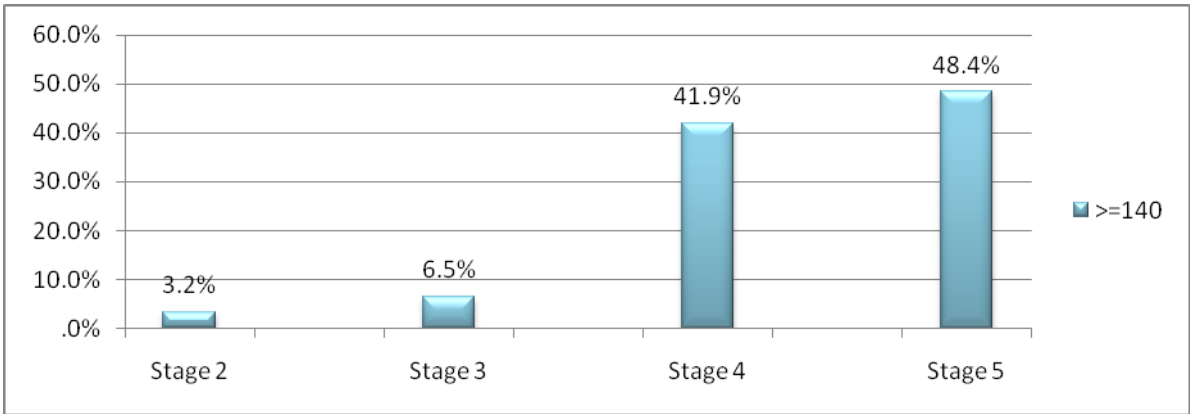


FIGURE 6: ONE HOUR POST –GLUCOSE LOAD TO CKD STAGE

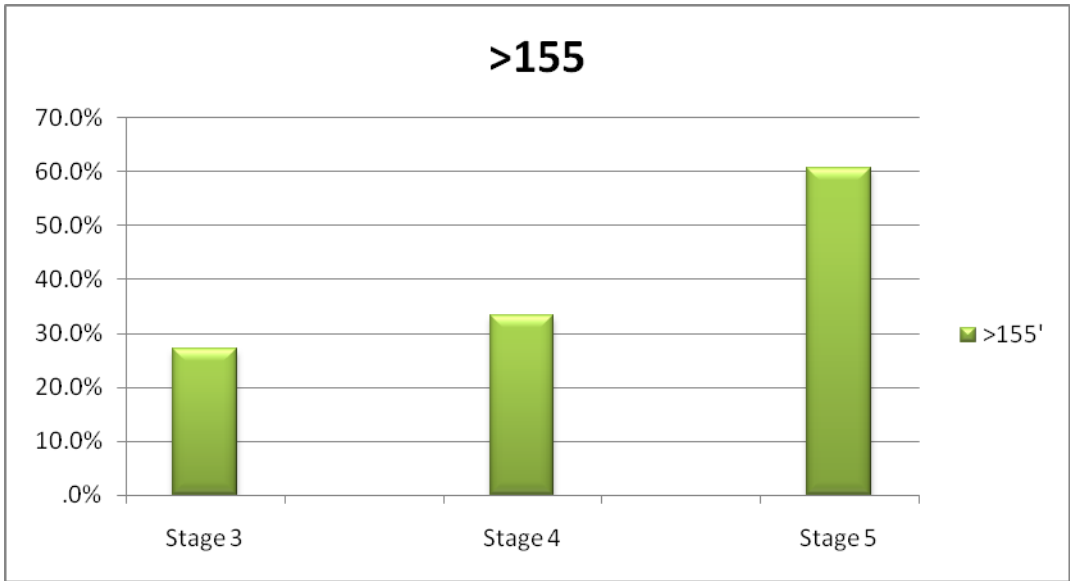


FIGURE 7

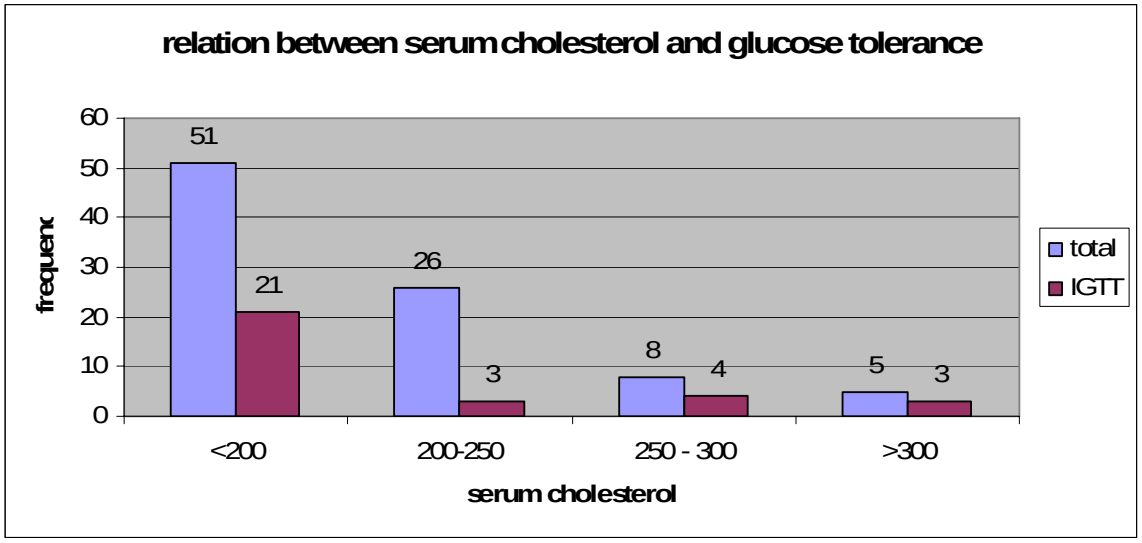

relation between serum cholesterol and glucose tolerance
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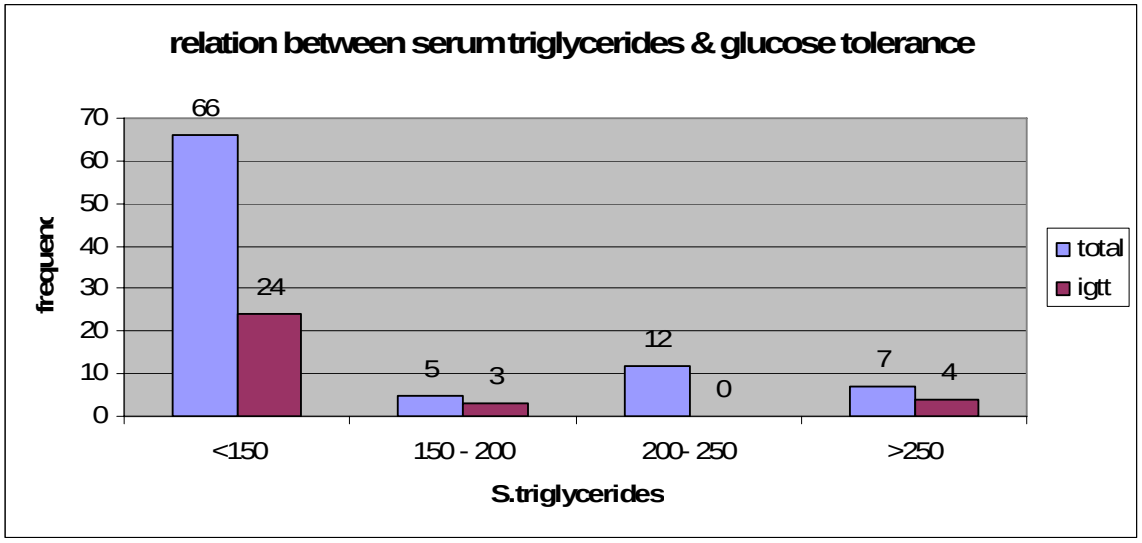
FIGURE 8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total
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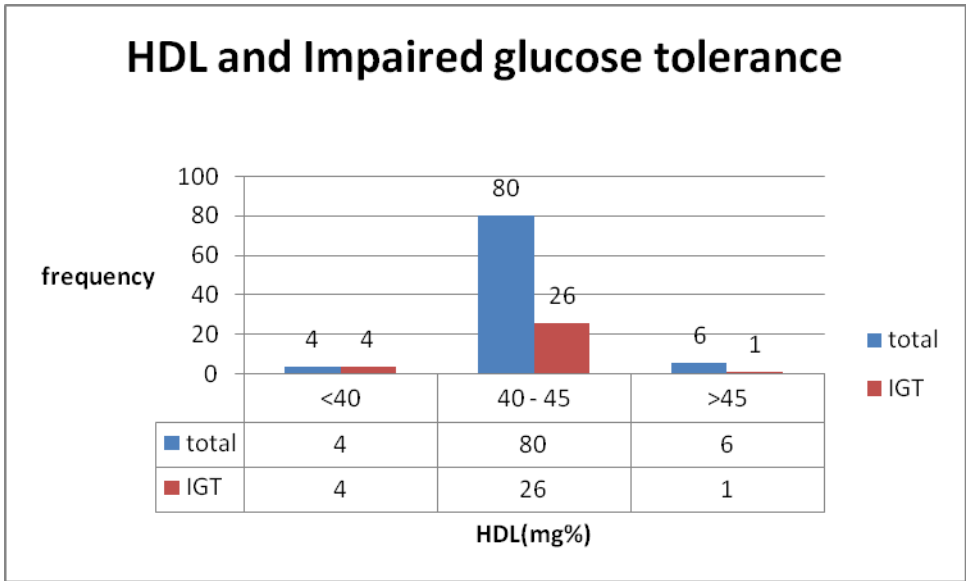
FIGURE 9 :


HDL and Impaired glucose tolerance
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80
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4
4
6
1
total
IGT
<40
40 - 45
>45
total 4 80 6
IGT 4 26 1
HDL(mg%)

FIGURE 10

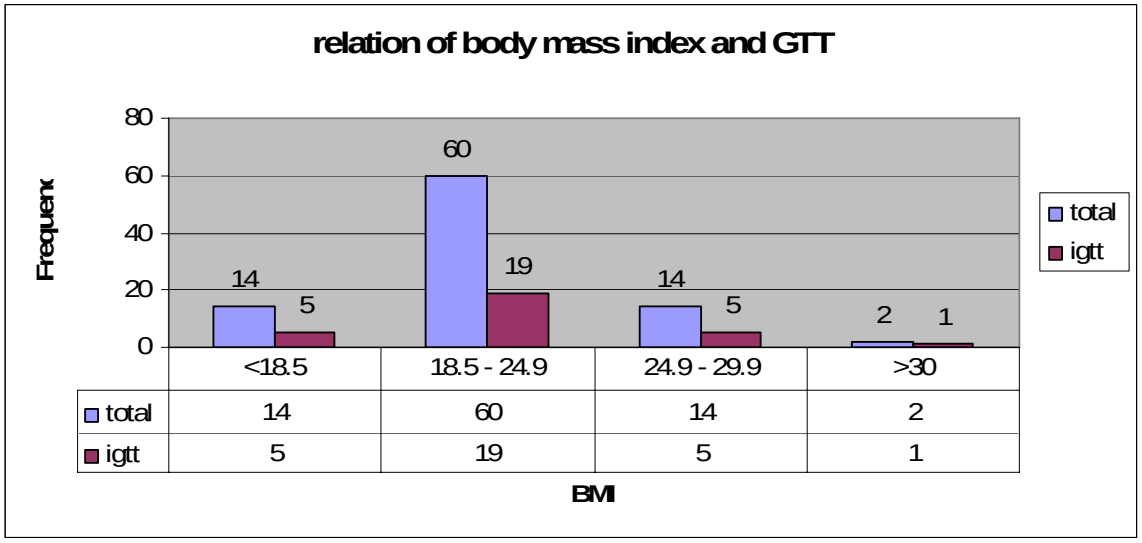

relation of body mass index and GTT
Frequency
80
60
40
20
0
14
5
60
19
14
5
2
1
total
igtt
<18.5
18.5 - 24.9
24.9 - 29.9
>30
total 14 60 14 2
igtt 5 19 5 1
BMI

FIGURE 11 : ALBUMINURIA AND IGT.

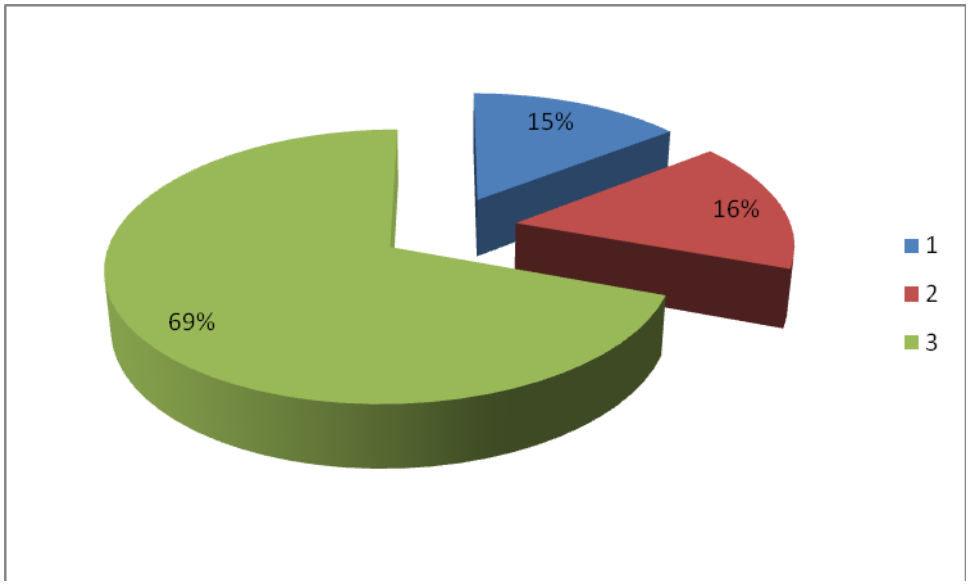


FIGURE 12

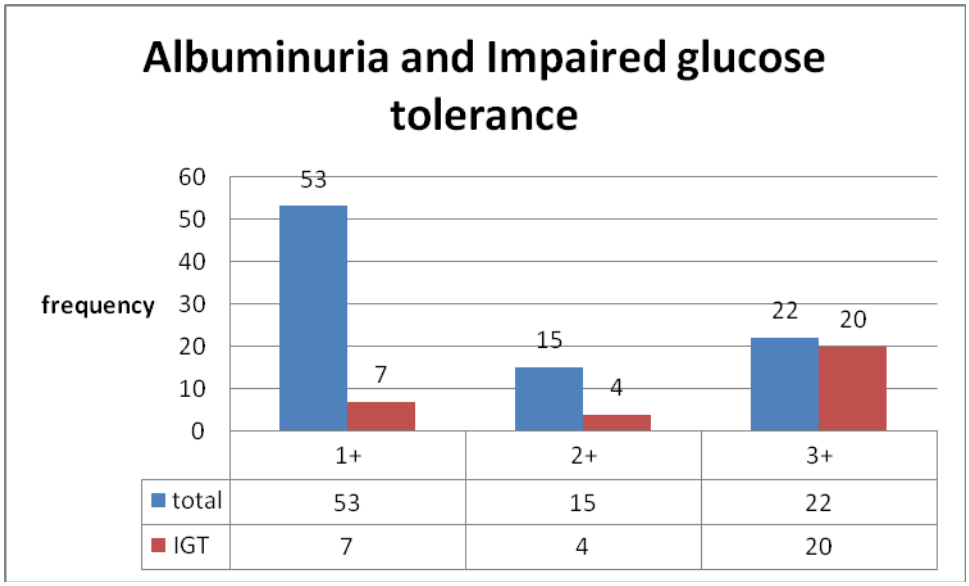


FIGURE : 13

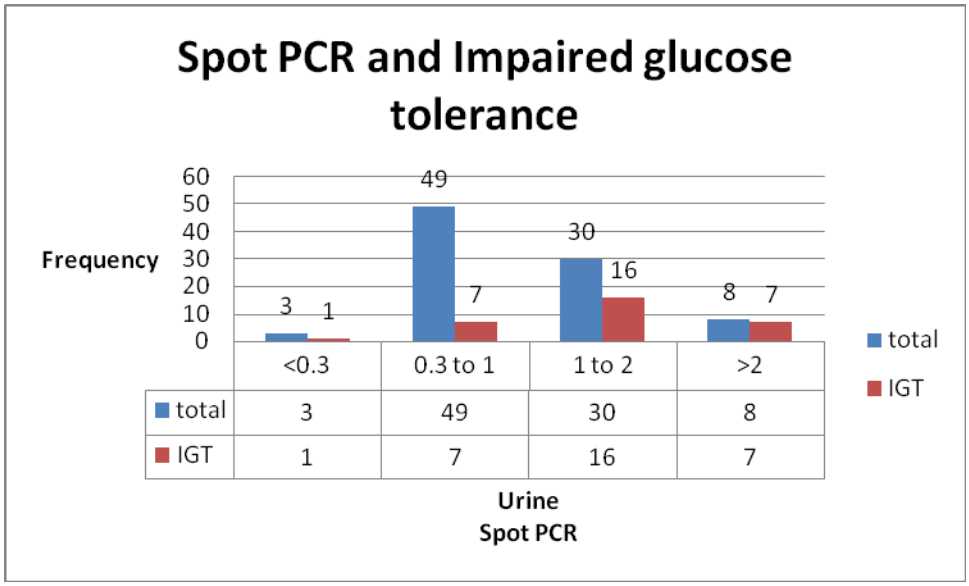
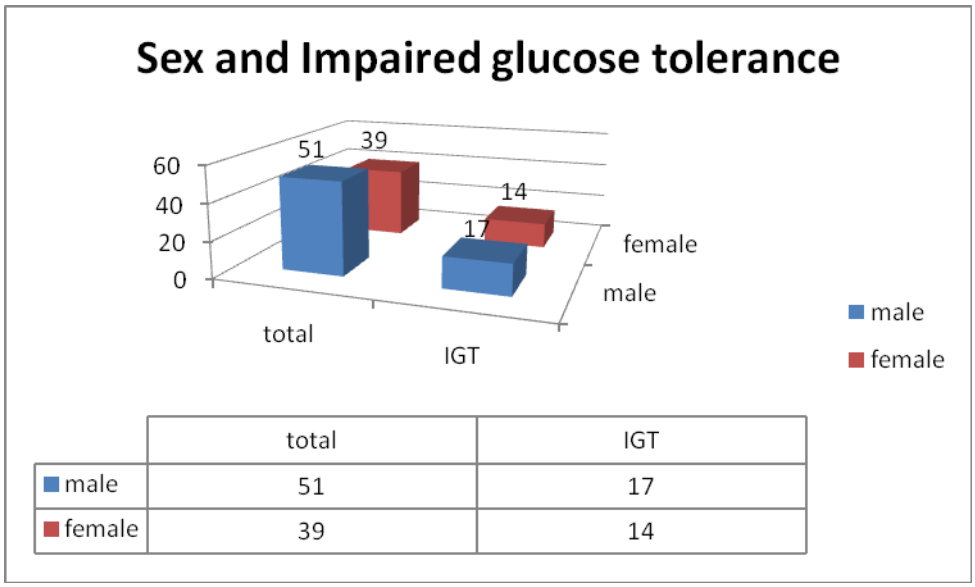

Spot PCR and Impaired glucose tolerance
Frequency
60
50
40
30
20
10
0
3
1
49
7
30
16
8
7
<0.3
0.3 to 1
1 to 2
>2
total
3
49
30
8
IGT
1
7
16
7
Urine Spot PCR
total
IGT

FIGURE 14



	total	IGT
male	51	17
female	39	14

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