Assessment of Therapeutic Efficacy of Anti-Hypertensive and Anti-Diabetic Drugs in Hypertensive Macroalbuminuric Type II Diabetic Patients

By

Dr. Tariq Mahmood

Department of Animal Sciences
Faculty of Biological Sciences
Quaid-I-Azam University
Islamabad
2006

In The Name Of

ALLAH

The Compassionate

The Merciful

Assessment of Therapeutic Efficacy of Anti-Hypertensive and Anti-Diabetic Drugs in Hypertensive Macroalbuminuric Type II Diabetic Patients

A dissertation submitted in the partial fulfillment of the requirements for the degree of Master of Philosophy

IN

ENDOCRINOLOGY

By

Dr. Tariq Mahmood

Department of Animal Sciences
Faculty of Biological Sciences
Quaid-I-Azam University
Islamabad
2006

CERTIFICATE

This is to certify that this dissertation, submitted by **DR. TARIQ MAHMOOD**, is accepted in its present form by the Department of Animal Sciences, Faculty of Biological Sciences, Quaid-I-Azam University, Islamabad as satisfying the requirements for the degree of **Master of Philosophy (Endocrinology)**

SUPERVISOR:

DR. IRFAN ZIA QURESHI

EXTERNAL EXAMINER:

CHAIRPERSON:

DR. M. SHAHAB

Dated: 8-11-2006

DEDICATED

TO

LALA JEE

ACKNOWLEDGEMENTS

ACKNOWLEDGEMENTS

All praise to Almighty Allah, The Most compassionate and Most merciful, Who is always there to shower His blessings upon me and gave me the strength to utilize the best of my abilities to complete this research work successfully.

I express my heartfelt gratitude to my supervisor. Dr. Irfan Zia Qureshi, Asst Professor, Biology Department, for his encouragement, keen interest, skillful guidance, valuable suggestions, constant support and enormous help through out the project.

I sincerely thank to Prof. Dr. Mrs. Samina Jalali Dean, Faculty of Biological Sciences, Quaid-I-Azam University who, since the inception of my admission provided opportunity and facilities for my research work.
I am obliged to Dr. M. Shahab, Chairperson, Department of Biology Quaid-I-Azam University for his co-operation during my study.

I covey my sincerest acknowledgements to Dr. Rehana Sukehara and Dr Shoiab Shafi, Head of Department, Medical unit I and II, Rawalpind General Hospital. Rawalpindi, for providing all the facilities during the research period.

I am extremely thankful to Dr. Rauf Niazi, Consultant, Department of Medicine Pakistan Institute Of Medical Sciences, Islamabad, for allowing me to work in his department.

I am grateful to Dr. Abbas Hayat, Head of Department Pathology, Rawalpindi General Hospital. Rawalpindi, in helping me with the investigations of my patients.

I owe special thanks to my wife Dr. Shireen Rafiq for her encouragement, pleasant company and helping me throughout the work.

Tariq Mahmood

TABLE OF CONTENTS

TABLE OF CONTENTS FOR TABLES

TABLE OF CONTENTS FOR FIGURES

Abbreviation

ACE Inhibitor	Angiotensin Converting Enzyme Inhibitor
ARB	Angiotensin Receptor Blocker
ANOVA	Analysis of Variance
BMI	Body Mass Index
BSR	Blood Sugar Random
CHD	Coronary Heart Disease
ESRD	End Stage Renal Disease
GFR	Glomerular filteration Rate
HB	Heamoglobin
IHD	Ischeamic Heart Disease
Kg/m^2	Kilogram per meter square
mm Hg	Millimeter of Mercury
mg/dl	Millligram per Deciliter
mmol/l	Millimols per Liter
NS	Non Significant
<	Less than
>	Greater than
P	Probability
RFT	Renal Function test
S.E	Standard Error
%	Percentage
n	Number
U.K	United Kingdom
WHO	World Health Organization
+1	>200mg
S.E.M	Mean ± Standard Error

ABSTRACT

The present prospective study was on 95, type II diabetic subjects registered at Rawalpindi General Hospital, Rawalpindi. The subjects selected were both males and females aged 35 – 75 years with known hypertension and macroalbuminuria. The study was designed to assess the efficacy of five different antihypertensive and two hypoglyceamic drugs in preventing the development of diabetic nephropathy and limiting its progression. All subjects were either on ACE inhibitors, tenormin, ACE inhibitors + ARB's, norvasc or capotin for hypertension and diaonil and glucophage or a combination of diaonil + glucophage for hyperglyceamia. The subject status was assessed through blood pressure, renal function tests, blood sugar random and lipid profile. The subjects were analyzed age-wise, gender-wise and drug-wise. All subjects were hypertensive, macroalbuminuric and hyperglyceamic, even though they were on drug treatment values of all parameters were above the normal levels. None of the subjects showed control over blood sugar random, blood pressure and renal function tests. Better response to drugs was the outcome in male subjects aged 49 – 61 years. Their BMI ($P<0.004$), serum urea ($P<0.03$) and serum creatinine ($P<0.003$) were significantly lower. In other age groups there was no difference between the two genders. On drug-wise comparison it was observed that ACE inhibitors were a better choice as compared to other antihypertensive agents. ACE inhibitors controlled the systolic blood pressure ($P<0.001$), blood sugar random ($P<0.029$), serum urea ($P<0.001$), serum creatinine ($p<0.005$) and serum potassium ($P<0.006$), significantly, in comparison with other antihypertensive drugs. Hypoglyceamic drugs behaved in a similar manner.

These observations suggest that ACE inhibitors lowered the renal funcion tests and can limit the progression of nephropathy. Quantification predicts the risk of disease progression. ACE inhibitors had renoprotective and as well as antihypertensive effect. The study therefore is a step forward but still leaves the question unanswered about renoprotective effect of ACE inhibitors.

Introduction

INTRODUCTION

Devastating nature of diabetes mellitus can be envisaged from the fact that the disease has become an epidemic in both developed and developing countries (WHO, 2004). A large population of the world is suffering from this disease, and the health care costs are increasing every year. The number of patients affected with type II diabetes is around 200 million, and it has been estimated that this will rise to around 366 million within the next 25 years (WHO 2004; Wild et al., 2004).

Diabetes UK reports that, at present in the United Kingdom there are 1.5 million people who are affected with the disease and about a million are still undiagnosed. It is expected that about 3 million people will be diabetic in the next few years (Colditz et al., 1997). While it is reported that 7% of world population suffers from diabetes (Anthony et al., 1999), and worldwide there are approximately 135 million cases known (King et al., 1998). This number is predicted to increase to 230 million by 2010 and 300 million by 2025 (Zimmet et al., 1995). In Pakistan the prevalence of diabetes mellitus was observed as 16.2% in men and 11.2% in women (Shera et al., 1991)

Diabetes is a life-long disease characterized by elevated blood sugar levels. Physiological reasons underlying are too little insulin characterized by impaired insulin secretion from pancreatic beta cells and or resistance to insulin in peripheral tissue, or both; body's production and use of insulin is impaired, causing sugar to build up in the blood stream above normal and excessive mobilization of body fats (Wild et al., 2004). It is further characterized by hyperglycemia, microangiopathy and neuropathy (Edwards et al., 1991).

CLASSIFICATION

Most common diabetic types are: type I, type II and gestational. Type II diabetes is also known as adult onset or non insulin-dependent diabetes mellitus (NIDDM), which is the most common form of diabetes (Wild et al., 2004). According to the

classification of American Diabetes Association, criteria for diagnosis of diabetes, has been listed into four major categories (Mayfield, 1998).

Type I	Absolute insulin deficiency
Type II	Insulin resistance with an insulin secretion defect
Type III	Maturity onset diabetes of young
Type IV	Gestational diabetes mellitus (GDM)

According to WHO diabetes is classified as:

Type I	insulin dependent diabetes mellitus (IDDM)
Type II	non-insulin dependent diabetes mellitus (NIDDM)
TypeIII	Maturity onset diabetes of young (MODY)
TypeIV	Gestational diabetes mellitus

DIABETIC NEPHROPATHY

The major underlying cause of type II diabetes is obesity, which is now occurring in epidemic proportion in both developing and developed countries (Kuczmarski et al., 1991). It has been Predicted in the United States where the problem of childhood obesity is even greater, that the child born there today has a one in three chance of developing type II diabetes during his or her life time (Barnett, 2005). A combination of obesity and family history accounts for 90% of etiological load in type II diabetes (Colditz et al., 1995).

Both environmental and genetic factors contribute towards course and complication of the disease. Diabetic disorder has been reported to run in families (Bell et al., 1987) and the genetic factors, which are considered to have a key role in the susceptibility towards diabetic nephropathy, have emerged a decade ago. The genetics of diabetic nephropathy and hypertension overlap each other. Genes involved in blood pressure regulation and genetic basis of hypertension is still unfolding (Viberti et al., 1987; Krolewski et al., 1988; Koren et al., 1998).

The risk of type II (NIDDM) diabetes increases with age and is considerably higher in fourth and fifth decade than in the elderly. Moreover, Type II diabetes mellitus is more common in females than in men (WHO 1980).

Diabetic nephropathy is a complication of diabetes in which kidneys lose their ability to function properly. This condition is characterized by microalbuminuria or proteinuria and accompanied with blood pressure.

Complications associated with type II diabetes include:

Microangiopathy (small vessel disease) such as diabetic retinopathy, as well as diabetic renal disease (nephropathy) are associated with increased cardiovascular morbidity and mortality. It is the most common cause of chronic renal failure (Borch-Johnson et al., 1985; Diabetes care and research in Europe, 1990).

In diabetes, 80% patients suffer from large vessel disease (macrovascular). They die prematurely, from cardiovascular disease, including coronary heart disease, stroke and peripheral vascular disease (Kannel and McGee., 1979; Stammler et al., 1993; Haffner et al., 1998; Fisher and Shaw., 2001).

Diabetic nephropathy is a clinical syndrome characterized by persistent albuminuria, decline in GFR, raised blood pressure and increased mortality due to cardiovascular disease (Parving et al., 1996). Diabetic nephropathy is associated with both types of diabetes. (Haak., 1997). Thus diabetic nephropathy is caused by a combination of microvascular and metabolic abnormalities (Lovell., 2000).

Renal disease is recognized as a complication of type I diabetes, with reported prevalence rate ranging from 24 – 40% (Anderson et al., 1983). The progressive deterioration of renal function leads to death from uraemia or cardiovascular disease with improved therapies for blood pressure control, particularly inhibitors of renin angiotensin system, the prevalence of this complication has reduced, although individuals with type I diabetes are generally at a risk of renal disease of around 20 – 25%. Renal diseases in type II diabetes are not diagnosed properly by non-specialists mainly because patients die from cardiovascular disease long before they develop

uraemia (Macleod et al., 1995). Quarter to one third patients with type II diabetes show evidence of renal disease defined as persistent proteinuria in association with hypertension (Remuzzi et al., 2002).

It is possible to detect the diabetic renal disease (incipient nephropathy) in the earlier phase because presence of microalbuminuria can be determined by measuring albumin excretion rate. Microalbuminuria is a strong predictor of later development of overt diabetic nephropathy (macroproteinuria) and is itself associated with a greatly increased risk of morbidity and mortality from cardiovascular disease. A number of studies have suggested that microalbuminuria may be present in up to 40% of patients with type II diabetes (Gall et al., 1997; Ritz, 2003., Adler et al., 2003).

Both microalbuminuria and overt macroproteinuria are commonly found at the diagnosis of diabetes, which shows that these patients had some degree of glucose intolerance for many years. About 50% patients diagnosed with type II diabetes show evidence of vascular complications particularly cardiovascular disease (UKPDS 1998).

A major finding of microalbuminuria in type II diabetic patients is that at least 5% of these patients develop overt diabetic nephropathy (macroalbuminuria) every year (Mogensen et al., 1984; Nelson et al., 1991). Renal protein leakage is associated with doubling or even trebling of mortality. Patients with type II diabetes who are normoalbuminuric have 40% chance of dying over a period of ten years, compared with an 80% chance in the same individual with microalbuminuria. Five years after diagnosis of microalbuminuria 35% patients die and this increases to 50% in overt diabetic nephropathy (macroproteinuria). Consequences of diabetic nephropathy include the need for dialysis (Jarret et al., 1984; Lacourciere et al., 2000; valmadrid et al., 2000; O`Donnel and Chowdhury., 2000; IDF, 2003).

PATHOGENESIS

The histological hallmark of diabetic nephropathy is diabetic glomerulosclerosis. In patients with renal diseases characterized by proteinuria, the initial damage to the kidney is usually followed by a progressive decline in the glomerular filtration rate.

This decline is due to changes in renal hemodynamics initiated by the loss of nephrons (Brenner et al., 1982). Hemodynamic changes cause the hydraulic pressure in glomerular capillaries to rise which leads to glomerular hypertension leading to progressive renal damage. High glomerular capillary pressure enlarges the radius of the pores in the glomerular membrane by the mechanism that is mediated at least in part by angiotensin II (Bohrer et al., 1977; Lapinski et al., 1996). This enlargement impairs the size selective function of the membrane so that the protein content of the glomerular filtrate increases, which in turn increases the endocytosis of protein by tubular epithelial cells, resulting in nephritogenic effect (Remuzzi and Bertain, 1990). A vicious cycle is then established in which changes in renal hemodynamics due to the loss of nephrons lead first to proteinuria and then to the loss of nephrons

The metabolic factors involved are glycation of tissue proteins, including collagen along with increase in various growth factors involved in collagen synthesis, with reduction in negatively charged proteoglycans and sialic acid resulting in the loss of glomerulus (O'Donnell et al., 2000).The basic lesion in the microvascular process is thickening of the capillary basement membrane with increased leakiness, which leads to the development of advanced glycation end-product where glucose chemically attaches to collagen. This is a generalized process and the leakiness of plasma proteins in one vascular bed often indicates similar abnormalities elsewhere. This explains that microalbuminuria is not just a risk factor for later development of chronic renal failure, but also points to 'bad' blood vessels elsewhere in the body, including cardiovascular system (O'Donnell et al., 2000).

NATURAL HISTORY

Functional changes within the kidney are followed by structural changes. More than one half of patients are hypertensive at diagnosis of type II diabetes. This problem progresses with time such that around 80% patients with type II diabetes develop hypertention, including all those with proteinuria (Ramsay et al., 1999; Barnett, 2005). At diagnosis, around one-fifth of patients with type II diabetes are already microalbuminuric and this proportion may rise to 30-40% over time. Without intervention, microalbuminuria converts to overt proteinuria in 5-10% of these patients each year (Gall et al., 1997; Ritz, 2003). Newly diagnosed patients with type

II diabetes have overt macroproteinuria. Overt persistant proteinuria is followed by a rise in serum creatinine levels and again, without intervention, end-stage renal disease (Adler et al., 2003).

DISEASE STAGES

Clinically, nephropathy in type II diabetes is recognized on the basis of micro- or macroalbuminuria, normally in association with hypertension, which, without intervention, leads to a progressive decline in renal function and massively increased risk of cardiovascular death. Nephropathy in Type II diabetes is divided into two stages normally incipient and overt nephropathy (Barnett, 2005).

Incipient nephropathy refers to the phase of microalbuminuria confirmed on the basis of albumin excretion rate of 20-200 micro-gram / minute. Small but increased protein leakage is associated with serious morbidity and mortality. At this stage the process can be reversed or stabilized (Barnett, 2005).

Overt nephropathy is associated with persistent proteinuria in a person with type II diabetes along with hypertension. It is associated with increased cardiovascular morbidity and motality and later development of end stage renal disease. Progression to renal failure can be slowed or even stabilized at this stage, but cannot be reversed. Overt proteinuria with leakage beyond 200 micro-gram / min tends to increase with time and is associated with other cardiovascular risk factors, dyslipidaemia and hypertension (Barnett, 2005).

Reduction of urinary protein levels by various medications and a low protein diet limits the decline of renal function in individuals with nondiabetic and diabetic nephropathies to the point that they show remission of the disease and regression of renal lesions (Remuzzi et al., 2006).

END STAGE RENAL DISEASE

Chronic kidney disease (CKD) is a worldwide threat to public health and approximately

1.8 million people are currently treated with renal replacement therapy, which consists

of kidney transplantation, hemodialysis, and peritoneal dialysis (Xue et al., 2001; Remuzzi et al., 2005). Diabetes is the most common cause of ESRD. Patients with diabetes and on renal replacement therapy have a worst outcome (USRDS. 2005). After 10-15 years of stable renal function, small amount of albumin appear in the urine of 20-40% of patients with both type I and type II diabetes is an early marker of nephropathy (Remuzzi et al., 2002; Ruggenenti et al., 2004). If left untreated 80-100% of microalbuminuric patients with type I, and 20-40% with type II diabetes progress to overt nephropathy, a syndrome of macroalbuminuria with declining GFR and increased cardiovascular morbidity (Nelson et al., 1991). At least two third of patients with overt nephropathy will die from cardiovascular disease before they progress to ESRD. While on dialysis 21% of these patients die within one year (Wolfe et al., 1999)

OBJECTIVES

To compare and contrast the effects of antihypertensive and hypoglyceamic drugs in Type II diabetic patients with special reference to diabetic nephropathy as demonstrated by renal functions.

Subjects And Methods

SUBJECTS AND METHODS

The study designed presently was prospective and carried out at Rawalpindi General Hospital, Rawalpindi. A total number of 95 subjects of both genders aged 35 – 75 years and suffering from diabetic nephropathy due to diabetes mellitus Type II, were included. The subjects were picked up randomly and were known hypertensives and had macroalbuminuria. Anthropomorphic and clinical data included: family history, past medical history, date of onset of diabetes mellitus, current diabetes status, cardiovascular disease, glycaemic control and current therapy, current hypertensive status i.e., both systolic and diastolic blood pressure and current hypertensive treatment, dyslipidaemic ststus and body mass index (BMI). The primary study objective was to compare and contrast the effects of antihypertensive and hyperglyceamic drugs in Type II diabetes mellitus and hypertension with macroalbuminuria. Secondary objectives aimed to assess levels of glycaemic and blood pressure control.

Exclusion criteria were: subjects with age less than 30 years, fever or urinary tract infection, positive leucocytes and nitrites indicative of significant bacteriuria or haematuria, chronic pylonephritus and stone production disease, or diabetic subjects with stitched kidneys.

BLOOD SAMPLING

Blood sampling was done to determine the baseline diabetic and nephropathic status. As it was not possible to take fasting samples, all samples were collected at random between 8.30 a.m. and 12.00 noon. 10ml periphral venous blood from the cubital vein was collected. 1ml blood was used to determine the blood sugar random and Hb%, remaining blood was used for determination of cholesterol, triglycerides, urea, creatinine and electrolytes, for which blood was centrifuged at 2000 revolutions for five minutes and serum thus obtained was stored at –20C until analysed.

ULTRASOUND

In order to provide information about the individuals kidney status, ultrasound was performed using a Toshiba ultrasound diagnostic system (Capsee model SSA-220 A). For transabdominal ultrasonography a convex abdominal probe of 7 MHZ frequency (model PVG-366V) was used. Transabdominal ultrasonography was performed to note gross abnormalities and the effect of diabetes on the kidney.

SERUM CHEMISTRY

Serum cholesterol, triglycerides, urea and creatinine were analyzed on fully automated chemistry analyzer, (Selectra E:). Commercially available kits were used to analyse the above parameters.

CREATININE

Commercial (AMP diagnostics, Austria) kit was used for determination of creatinine. Serum creatinine was measured by colorimetric, Jaffe's kinetic method, which is based on the fact that the rate of color formation is proportional to the concentration of the creatinine in the sample. The effect of the substance interfering, are reduced using the kinetic procedures. Normal range = 0.7 – 1.5mg/dl.

UREA

Commercial kit (cromatest of linear chemicals, Barcelona, Spain) used to determine serum urea. Urea is hydrolyzed by urease to ammonia and carbon dioxide. The ammonia is then converted to glutamate dehydrogenase in the presence of NADH and oxoglutarate. The reaction is monitered kinetically at 340 nm by rate decreased in absorbance not less than 1.100, resulting from the oxidation of NADH to NAD, proportional to the concentration of urea present in the sample. Normal range = 20 – 40mg/dl.

CHOLESTEROL

A commercial kit (Biocon fluitest, Hitachisysem Japan) used to determine serum cholesterol. Cholesterol is determined enzymetically using cholesterol estrase and cholesterol oxidase. Cholesterol esters are cleaved during the actionto give free cholesterol and fatty acid. Free cholesterol is converted by oxygen with the addition of cholesterol oxidase to cholest-4-en-3-1 and hydrogen peroxidase. Hydrogen oxidase forms a red dye stuff, under the catalytic action of peroxidase. The color intensity is directly proportional to the concentration of cholesterol and is determined photometrically by the lab system. Normal range = <200md/dl.

TRIGLYCERIDES

A commercial kit (pioneer diagnostics, USA) was used to determine serum triglycerides. Triglycerides are hydrolysed by lipases to release glycerol and fatty acid. Glycerol is converted by glycerol kinase into glycerol phosphate. This is then oxidized by glycerol phosphate oxidase to dihydroxy acetone phosphate. Hydrogen peroxide released during the action is exposed to phenol and 4 aminophenazole in the presence of peroxidase. A colored compound thus formed is measured. Normal range = 150 – 200 mg/dl.

ELECTROLYTES

Concentration of serum electrolytes, sodium (Na) and potassium (K) were estimated by flame photometry. Electrolytes like sodium (Na) and potassium (K) when excited (heated at high temperature) emit spectra with definite wavelengths (sodium at 589 nm and potassium at 671nm). The solution in which electrolytes are to be measured is sprayed on the flame with the help of an atomizer. The concentration of sodium and potassium is read as shown on the digital read out device of the instrument. Normal range, Na = 135 – 150 mmol/l, K = 3.5 – 5 mmol/l.

BLOOD SUGAR RANDOM

Blood sugar was estimated with the help of a glucometer (ACCU-CHEK, with test strips of Roche diagnostics). A drop of blood was applied to the application pad. Reading was displayed after 15 seconds on the glucometer screen, which was recorded. Normal range = 100 – 140 mg/dl.

URINE PROTEIN

Urinary proteins were estimated with the help of CYBOW strips (DFI CO., Ltd Korea). These reagent strips for urinalysis are for the rapid determination of proteins in the urine.

Fresh urine samples were collected in clean dry container. Reagent strips were inserted in the urine up to the test area for two seconds. The edge of the strip was drawn along the brim of the container to remove excess urine. If proteins are present in the sample, the color was changed from yellow to blue green. Test results were compared carefully with the color chart and measured.

BODY MASS INDEX

Body mass index is a reliable indicator of body fat. It was calculated by dividing body weight (Kg) with square of height in meters. Normal range = 18 – 25 J.

$$BMI = \frac{\text{Body wt (Kg)}}{\text{Height (m2)}}$$

BLOOD PRESSURE

Blood pressure was recorded using a standard method with mercury sphygmomanometer. Target blood pressure was taken as 120/70mmHg.

Drugs

Five different antihypertensive drugs and two hypoglyceamic drugs were used.

I Antihypertensive drugs

Zepres (ACE inhibitors) were used in a dosage of 5 – 20 mg/day.

Treatan (ARB's) were used in a dosage of 4 – 16 mg/day.

Tenormin (beta blocker) used in a dosage of 25 – 100 mg/day.

Norvasc (Calcium channel blocker) used in a dosage of 5 – 10 mg/day.

Capotin in a dosage of 25 –100 mg/day.

II Hypoglyceamic drugs

Daonil (Glibenclamide) 5mg tablets.

Glucophage (metformin) 250 – 1G tablets.

STATISTICAL ANALYSIS

For the purpose of data analysis and comparison these subjects were divided into groups age wise and drug wise. The values in tables and text are presented as mean ±SD (standard deviation). Student's t-test was used for exploratory comparison of initial parameters between male and female subjects. Excel and statistica statistical packages (statistica version SPSS 13. Stat Soft) were used for data analysis. Limit of significance was set at $P<0.05$. Comparison among different drugs, were made by single factor analysis variance (ANOVA) using Sigma Stat (version 2) to compare the variation of different parameters. Further, Dunken's and tukey's tests were applied to carry out the comparison among different treatment groups. P value (probability) less than 0.05 was considered significant

Percentage of few parameters was taken.

$$\text{Percentage of smokers} = \frac{\text{no of smokers}}{\text{Total no of subjects}} \times 100$$

$$\text{Percentage of stress} = \frac{\text{no of subjects effected with stress}}{\text{Total no of subjects}} \times 100$$

Percentage of exercise = $\frac{\text{no of subjects doing exercise}}{\text{Total no of subjects}} \times 100$

Percentage of restricted diet = $\frac{\text{no of subjects on restricted diet}}{\text{Total no of subjects}} \times 100$

Percentage of unrestricted diet = $\frac{\text{no of subjects on unrestricted diet}}{\text{Total no of subjects}} \times 100$

Percentage of drugs used = $\frac{\text{no of subjects using a drug}}{\text{Total no of subjects}} \times 100$

RESULTS

SUBJECTS

A total of 95 male and female diabetic subjects being treated for hypertension and hyperglyceamia were included in the present study. For comparison and data handling subjects were divided into different groups age wise and drug wise. Subjects taking antihypertensive drugs were divided into five groups, where ACE inhibitors were compared with other four antihypertensive drugs. Hypoglycemic drugs were divided into three groups and diaonil was compared with the other two.

GROUP I (35 – 48 years)

This group contained males (n = 7) and females (n = 13), with age range of 40–42 years. The period of illness was less in males as compared to females and ranged between 4.85 – 5.30 years.

Body Mass Index

Body mass index in males was lower as compared to females with no significant difference between the two (Table 1).

Heamoglobin

Heamoglobin concentration was 11.57±0.95 (mg/dl) in males, which was non-significantly ($P>0.05$) greater than the females 10.30±0.31 (mg/dl) (Table 1).

Blood Sugar Random

Blood sugar random was less in males as compared to females but it remained non-significantly different between the two genders (Table 1).

Blood Pressure

Blood pressure was higher in females as compared to males. Diastolic blood pressure of males was significantly ($P<0.05$) lower than the females in contrast, systolic blood pressure showed no significant difference between the two genders (Table 2).

Renal Function Tests

Serum urea concentration was greater in males as compared to females in this group without any marked difference between the two (Table 3). Serum creatinine was almost similar in males and females and ranged between 1.12 – 1.37 (Table 3). Serum sodium in males was 138.85±1.18 (mmol/l), which was higher as compared to females 135.38±0.83 (mmol/l). There was statistically significant ($P<0.026$) difference in the sodium concentration between the male and female subjects. Values for serum potassium concentration and macroalbuminuria were almost similar in both male and female with no significant difference (Table 3).

Lipid Profile

Serum cholesterol levels were higher in males 219.71±17.47 (mg/dl) as compared to females 199.38±11.66 (mg/dl) but the difference between the two was non-significant. Serum triglycerides concentration in males was less as compared to females but this parameter also remained non significantly different when a gender comparison was made (Table 4).

Significantly greater percentage of males (71%), were smokers as compared to females (15%). Almost all males (100%) were under stress and only 43% were doing regular exercise as compared to females who were under stress (77%) and only 30% among them were doing exercise (Fig 1). The percentage of males taking unrestricted diet i.e. all types of food were 100% as compared to females among whom 54% were on restricted diet while 46% were on unrestricted diet.

Table 1

BMI, heamoglobin and blood sugar random of both male and female subjects in Group I (35yrs – 48yrs)

Parameters	Males (n=7)	Females (n=13)
BMI (Kg/m^2) *(Normal range: 18 – 25)*	24.47±1.35	26.60±1.40
Hb (mg/dl) *(Normal range: M 13 –17 mg/dl) (F 12 – 15 mg/dl)*	11.57±0.95	10.30±0.31
Blood sugar random (mg/dl) *(Normal range 100 – 140 mg/dl)*	209.42±27.09	236.84±21.76

All values are given as mean ± standard error (S.E.M).
BMI=Body Mass Index.
Hb= heamoglobin

Table 2

Systolic and diastolic blood pressure in Group I (35 – 48yrs) of males and female.

Parameters	Male (n-7)	Female (n-13)
Blood pressure		
Systolic (mm Hg) *(Target BP: 120 mm Hg)*	142.14±5.75	152.30±6.78
Diastolic (mm Hg) *(Target BP: 70 mm Hg)*	89.28±3.16	98.07±2.00*

All values are given as mean ± standard error (S.E.M)

*P<0.05 shows significantly higher diastolic blood pressure in female subjects.

Table 3

Renal function tests in type II diabetic males and females of Group I (35 – 48yrs)

Parameters	Males (n=7)	Females (n=13)
Urea (mg/dl) *(Normal range: 20 –40 mg/dl)*	45±5.52	35.38±2.68
Creatinine(mg/dl) *(Normal range: 0.7 – 1.5 mg/dl)*	1.12±0.22	1.37±0.21
Sodium (mmol/l) *(Normal range: 135 –150 mmol/l)*	138.85±1.18	135.38±0.83*
Potassium (mmol/l) *(Normal range: 3.5 –5 mmol/l)*	3.58±0.08	3.63±0.15
Macroalbuminuria *(Normal range: 0)* (+1=200micro g/min)	1.50±0.24	1.50±0.19

All values are given as mean ± standard error (S.E.M).
*P<0.026 show significantly lower serum sodium in females

Table 4

Lipid profile in type II diabetic males and females of Group I (35 – 48 yrs)

Parameters	Males (n=7)	Females (n=13)
Cholesterol (mg/dl) *(Normal range <200 mg/dl)*	219.17±17.47	199.38±11.66
Triglycerides (mg/dl) *(Normal range <200 mg/dl)*	217.46±8.92	228.46±20.93

All values are given as mean ± standard error (S.E).

Fig. 1 Smoking, stress and exercise percentage in subjects suffering from Type II diabetes, in Group I (35 – 48) years.

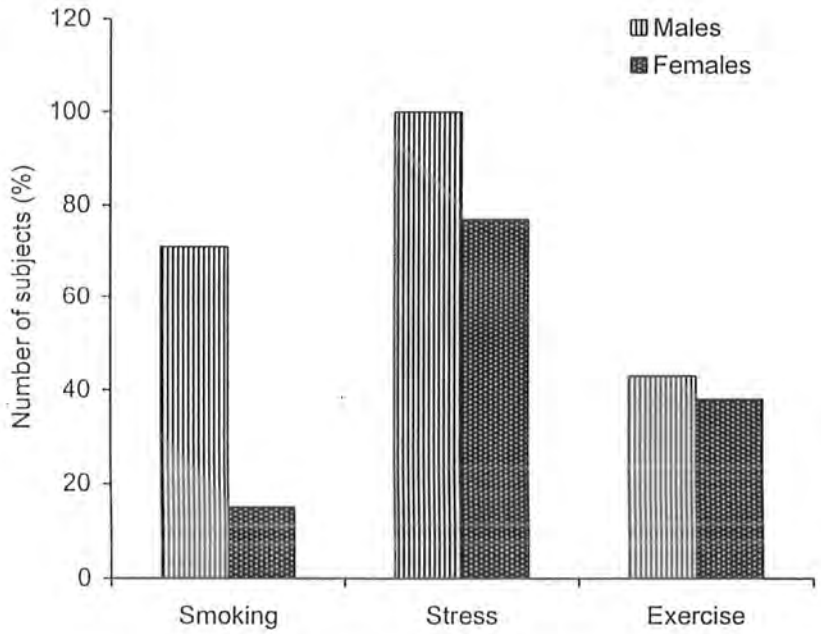
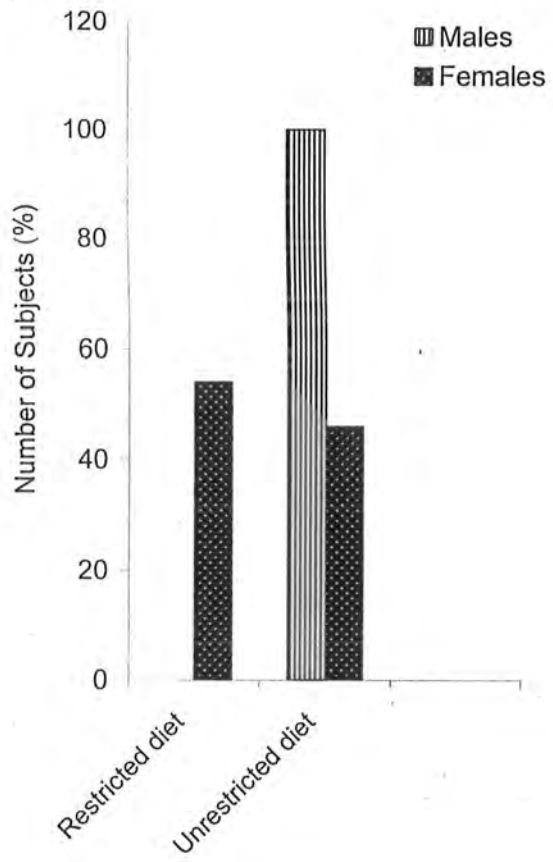


Fig. 2 Percentage of subjects taking restricted and unrestricted diet with Type II diabetes
in Group I (35 – 48) years.



Antihypertensive drugs

Majority of subjects were taking ACE inhibitors, out of which 41% were males and 23%were females. Capotin was the second common drug, in use of Group I, in which 30% males and 31% females were taking it. The percentage of males and females taking norvasc was found to be 29% and 15% respectively. Tenormin and ACE inhibitor+ARB's were not being used by the males while 16% females were using tenormin and 15% were on ACE inhibitors+ARB's (Fig 3).

Hypoglyceamic drugs

Combination of diaonil and glucophage was in use of majority of females (61%) where as only 42% males were taking this combination. Diaonil was in use of 29% males and 31% females. Glucophage was the least used drug as the females taking this drug were only 8% on the contrary 29% males were taking glucophage (Fig 4).

Fig. 3 Male and female subjects taking anti-hypertensive drugs with Type II diabetes in Group I (35 – 48) years.

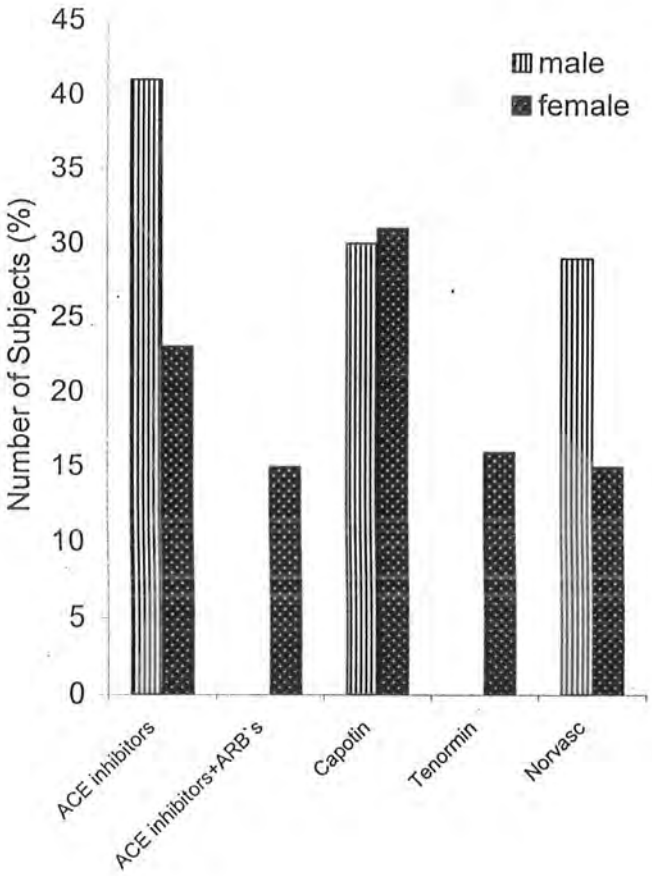
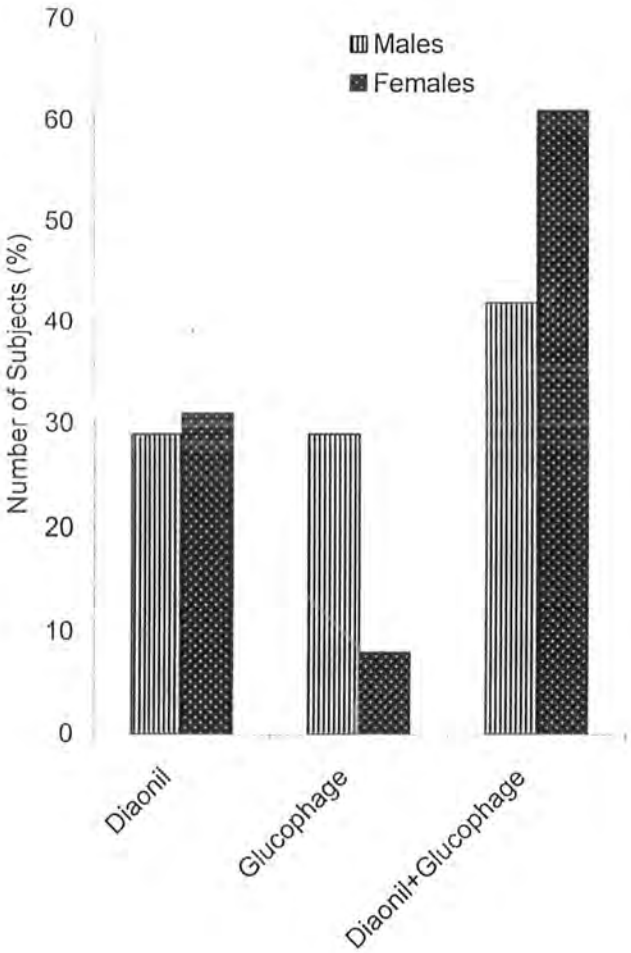


Fig. 4 Percentage of male and female subjects taking hypoglycemic drugs with Type II Diabetes mellitus, in Group I (35 – 48) years.



GROUP II (49 – 61 years)

This group contained (n=31) females and (n=25) males with age ranging between 52 – 53 years. The mean age of females was significantly (P<0.01) higher than the males. The period of illness ranged between 10 – 11 years showing no significant difference between the two genders.

Body Mass Index

Mean body mass index in males was 26.0.73±0.73 (Kg/m^2), which was significantly (P<0.004) lower than the mean BMI in females 28.31±0.79 (Kg/m^2) (Table 5).

Heamoglobin

Heamoglobin levels of male subjects were 10.79±0.27 (mg/dl) while those of female subjects were 10.01±0.26 (mg/dl). There was a significant difference (P<0.05) in the heamoglobin content of male and female subjects (Table 5).

Blood Sugar Random

BSR was 290.32±11.79 mg/dl in males, which was higher as compared to females 278.87±10.20 mg/dl but the difference was non significant (P>0.05) (Table 5).

Blood Pressure

Mean systolic and diastolic blood pressure in males and females was almost comparable only showing a slight rise in the females but did not show any significant (P>0.05) difference with those of males.

Renal Function Tests

Serum urea concentration in females was 42.08±1.96 mg/dl, which turned significantly greater (P<0.035) than the males (36.58±1.64 mgdl) (Table 7). Serum creatinine was higher 1.58±0.09 mg/dl in females as compared to males 1.22±0.08 mg/dl with the difference being markedly significant (P<0.003) (Table 7). Serum sodium was almost similar between male and female subjects (Table 7) while serum potassium levels were greater in males 4.32±0.12 (mmol/l) as compared to females 3.73±0.11 (mmol/l) showing a significant difference between male and female diabetics (P<0.002) (Table 7). Macroalbuminuria presented no significant difference between male and female diabetics (Table 7).

Lipid Profile

Serum cholesterol and triglycerides (Table 8), showed no marked difference when mean values of the two parameters were compared between males and females.

Significantly greater percentage of males (84%), were smokers as compared to less number of females (10%). 84% males were under stress and an almost equal number of females (87%) were under stress. A greater percentage of females (42%) were doing regular exercise as compared to males (36%) (Fig 5). The percentage of males on unrestricted diet i.e. all type of food, was 72% as compared to females (65%) while those on restricted diet were 28% and 35% respectively (Fig 6).

Table 5

BMI, Heamoglobin and blood sugar random of both male and female subjects in Group II (49 – 61yrs)

Parameters	Males (n=25)	Females (n=31)
BMI (Kg/m^2) *(Normal range: 18 – 25)*	26.±0.73	28.31±0.79*
Hb (mg/dl) *(Normal range: M 13 –17 mg/dl) (F 12 – 15 mg/dl)*	10.79±0.27	10.01±0.26
Blood sugar random (mg/dl) *(Normal range: 100 – 140 mg/dl)*	290.32±11.79	278.87±10.20

All values are given as mean ± standard error (S.E.M).
BMI=Body Mass Index.
Hb=Heamoglobin
*(P≤0.004) shows significantly higher BMI in female subjects.

Table 6

Systolic and diastolic blood pressure in Group II (49 – 61yrs) of males and females.

Parameters	Males (n=25)	Females (n=31)
Blood pressure		
Systolic (mm Hg) *(Target BP: 120 mm Hg)*	143.20±3.53	147.90±2.85
Diastolic (mm Hg) *(Target BP: 70 mm Hg)*	90.20±1.94	95.16±1.30

All values are given as mean ± standard error (S.E.M)

Table 7

Renal function tests in type II diabetic male and female subjects of Group II (49 – 61 yrs).

Parameters	Male (n=25)	Female (n=31)
Urea (mg/dl) *(Normal range: 20 –40 mg/dl)*	37.45±1.74	42.08±1.96*
Creatinine(mg/dl) *(Normal range: 0.7 – 1.5 mg/dl)*	1.30±0.09	1.58±0.09**
Sodium (mmol/l) *(Normal range: 135 –150 mmol/l)*	138.62±1.04	139±1.36
Potassium (mmol/l) *(Normal range: 3.5 –5 mmol/l)*	4.32±0.12	3.73±0.11***
Macroalbuminuria *(normal range: 0) (+1 >200 micro g/l)*	1.36±0.12	1.50±0.11

All values are given as mean ± standard error (S.E.M).
*P<0.035 shows significantly higher levels serum urea in females.
**P<0.003.shows significantly higher levels serum creatinine in females.
***P<0.002 shows significantly higher levels serum potassium in females.

Table 8

Lipid profile in type II diabetic males and females of Group I (49 – 61 yrs)

Parameters	Males (n=25)	Females (n=31)
Cholesterol (mg/dl) *(Normal range <200 mg/dl)*	221.92±8.14	217.66±8.12
Triglycerides (mg/dl) *(Normal range <200 mg/dl)*	242.29±13.08	236.83±11.17

All values are given as mean ± standard error (S.E.M).

Fig. 5 Percentage of smoking, stress and exercise in subjects with Type II diabetes mellitus in Group II (49 – 61 yrs).

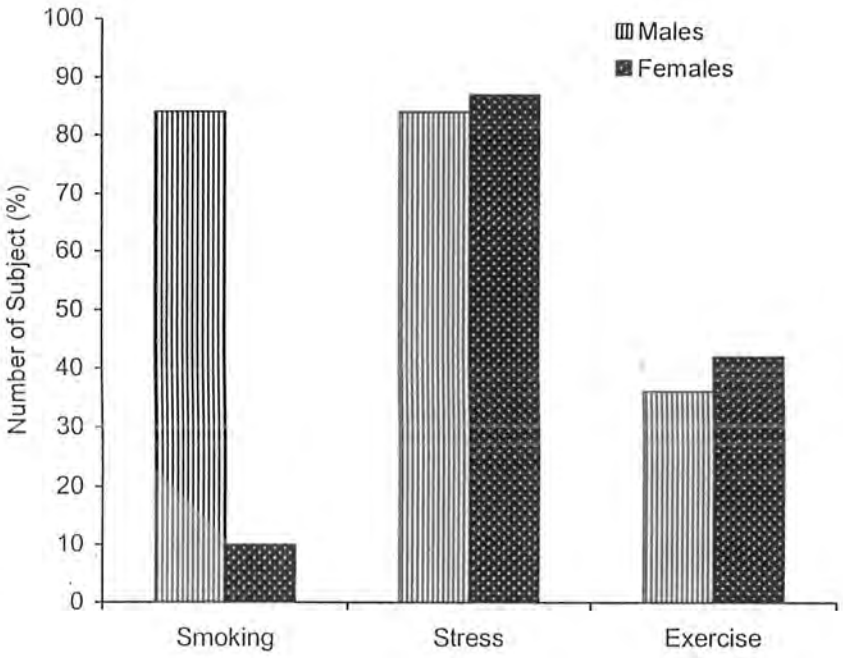
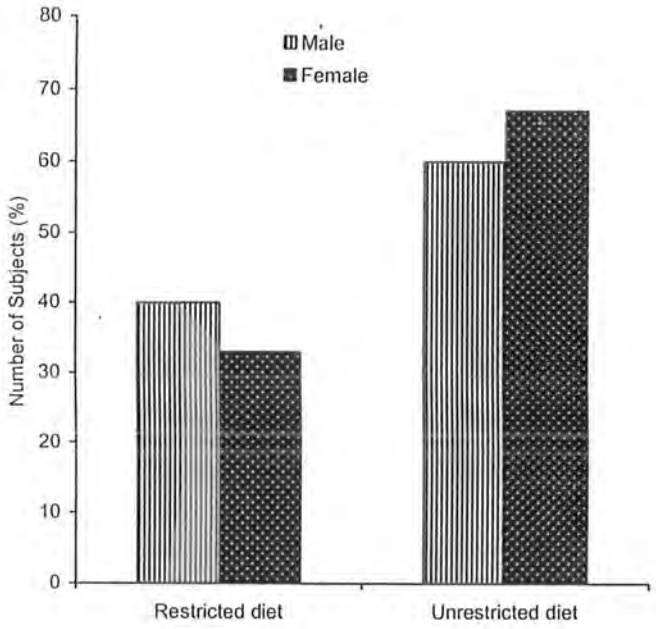


Fig. 6 Percentage of subjects taking restricted and unrestricted diet in Type II diabetes Group II (49 – 61yrs)



Antihypertensive drugs

Majority of subjects were taking ACE inhibitors, out of which 32% were males and 26%were females. Capotin was the second common drug in use of Group II, in which 12% males and 42% females were taking it. The percentage of males and females taking norvasc was 8% and 3% respectively. Tenormin and ACE inhibitor+ARB's being used by the males was 20% and 24% while in females it was 13% and 16% respectively (Fig 7).

Hypoglyceamic drugs

Combination of diaonil and glucophage was in use by the majority, females (67%) and males (44%). Diaonil was in use of 28% males and 23% females. Glucophage was the least used drug by the females as its percentage was found to be 10% in females while 28% males were taking this drug (Fig 8)

Fig. 7 Percentage of male and female subjects taking antihypertensive drugs in Type II Diabetes mellitus Group II (49 – 61 yrs).

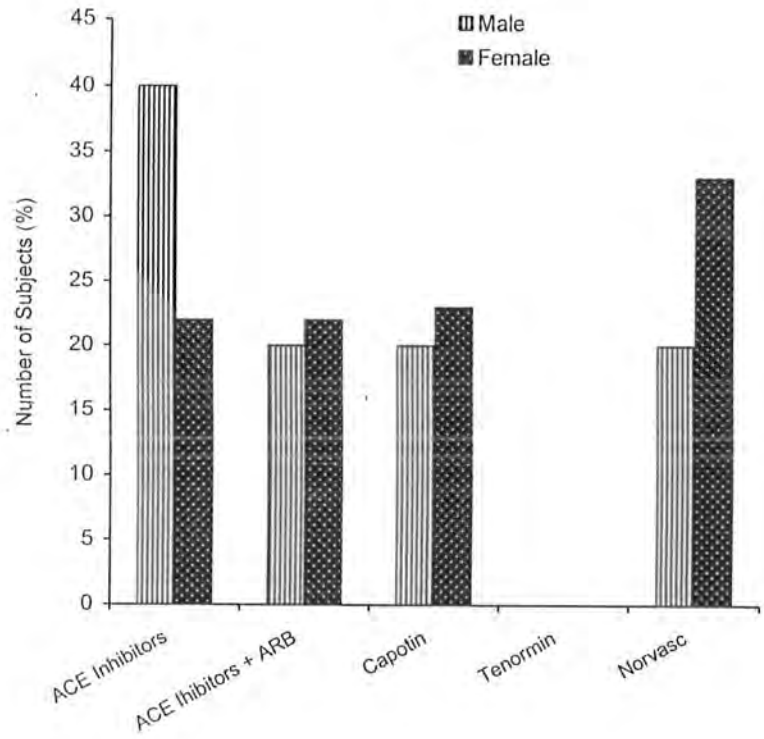
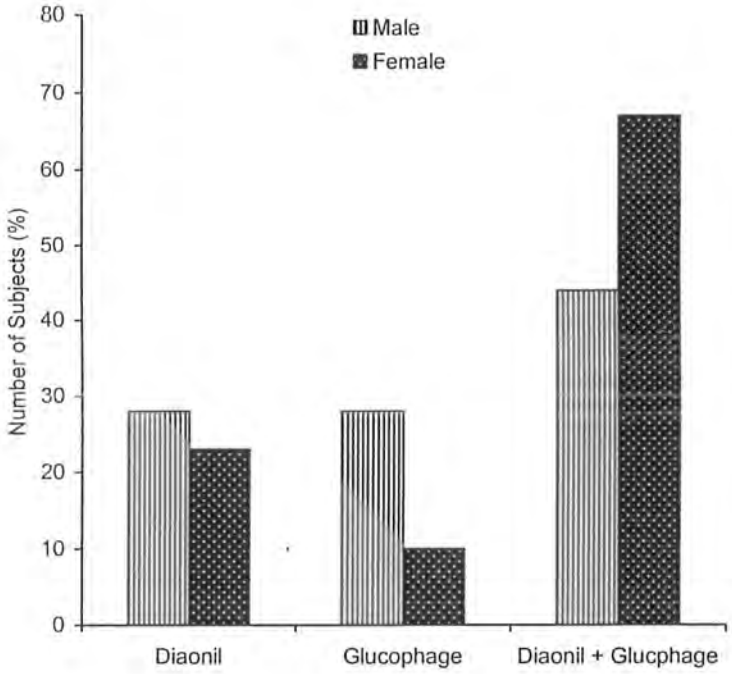


Fig. 8 Percentage of male and females subjects taking hypoglycemic drugs in Type II diabetes mellitus in Group II (49 – 61 yrs).



GROUP III (62 – 75 years)

This group contained (n=5) males and (n=9) females whose ages ranged between 66 – 70 years. The onset of diabetes mellitus was between 14 – 24 years and females showing an early onset of diabetes.

Body Mass Index

BMI of females in this group was higher but remained non-significantly (P>0.05) different as compared to males (Table 9).

Heamoglobin

Heamoglobin levels of males were 10±0.89 mg/dl while those of females were 10.40±0.51 mg/dl. There was no significant difference (P<0.05) in the heamoglobin concentration of male and female subjects (Table 9).

Blood Sugar Random

BSR was 290.20±39.90 mg/dl in males, which was higher as compared to females 248±24.03 mg/dl but the difference was not significant (P>0.05) (Table 9).

Blood Pressure

Mean systolic and diastolic blood pressure in males and females shown in (Table 10). Systolic and diastolic blood pressures were almost the same, only showing a slight rise in the females. Difference between males and females was however non-significant (P>0.05).

Renal Function Tests

Serum urea was 39.80±3.32 mg/dl in males while in the females it was 35.50±2.68 mg/dl but the difference between the two genders was non significant (P>0.05) (Table 11). Serum creatinine was higher 1.42±0.17 mg/dl in males as compared to females 1.23±0.12 mg/dl with no difference (P>0.05) (Table 11), whereas both electrolytes did not show any significant difference between males and females (Table 11). Macroalbuminuria presented no significant difference between males and females (table 11).

Lipid Profile

Serum cholesterol and triglycerides (Table 12), showed no marked differences between the mean values of the two parameters between male and females.

Significantly greater percentage of males (20%), were smokers as compared to females (11%). All males (100%) were under stress as compared to females (67%). A greater percentage of females (78%) were doing regular exercise as compared to males (60%) (Fig 5). The percentage of males on unrestricted diet i.e. all types of food was 60% as compared to females (67%) while those on restricted diet were 40% and 33% males and females respectively (Fig 6).

Table 9

Age, period of illness and body mass index of both male and female subjects in Group III (62yrs – 75yrs)

Parameters	Male (n–5)	Female (n-9)
BMI (Kg/m^2) *Normal range (18 – 25)*	25.22.±2.20	26.66±1.72
Hb (mg/dl) *Normal range (M 13 –17) mg/dl* *(F 12 – 15) mg/dl*	10±0.89	10.40±0.51
Blood sugar random (mg/dl) *Normal range (100 – 140) mg/dl*	290.20±39.90	248±24.03

All values are given as mean ± standard error (S.E).
BMI Body Mass Index.

Table 10

Systolic and diastolic blood pressure in Group III (62 – 75yrs) of males and female

Parameters	Male (n-25)	Female (n-31)
Blood pressure		
Systolic (mm Hg) *Target BP (120) mm Hg*	157±13	167.22±6.67
Diastolic (mm Hg) *Target BP (70) mm Hg*	96±2.44	97.77±2.37

All values are given as mean ± standard error (S.E)

Table 11

Renal function tests in type II diabetic male and female subjects of group III (62 – 75) years.

Parameters	Male (n-25)	Female (n-31)
Urea (mg/dl) *Normal range (20 –40) mg/dl*	39.80±3.32	35.50±2.68
Creatinine(mg/dl) *Normal range (0.7 – 1.5) mg/dl*	1.42±0.17	1.23±0.12
Sodium (mmol/l) *Normal range (135 –150) mmol/l*	138.40±5.48	140.55±2.18
Potassium (mmol/l) *Normal range (3.5 –5) mmol/l*	4.48±0.48	3.72±0.21
Macroalbuminuria *Normal range (0)* *+1 > 200 micro gm*	2±0.44	2.33±0.33

All values are given as mean ± standard error (S.E).

Table 12

Lipid profile in type II diabetic male and female subjects of groupIII (62 – 75) Years.

Parameters	Male (n-5)	Female (n-9)
Cholesterol (mg/dl) *Normal range <200 mg/dl*	223.20±15.15	227.22±10.90
Triglycerides (mg/dl) *Normal range <200 mg/dl*	250.40±44.49	245±22.98

All values are given as mean ± standard error (S.E).

Fig. 9 Percentage of smoking, stress and exercise in subjects with Type II diabetes mellitus in Group III (62 – 75).

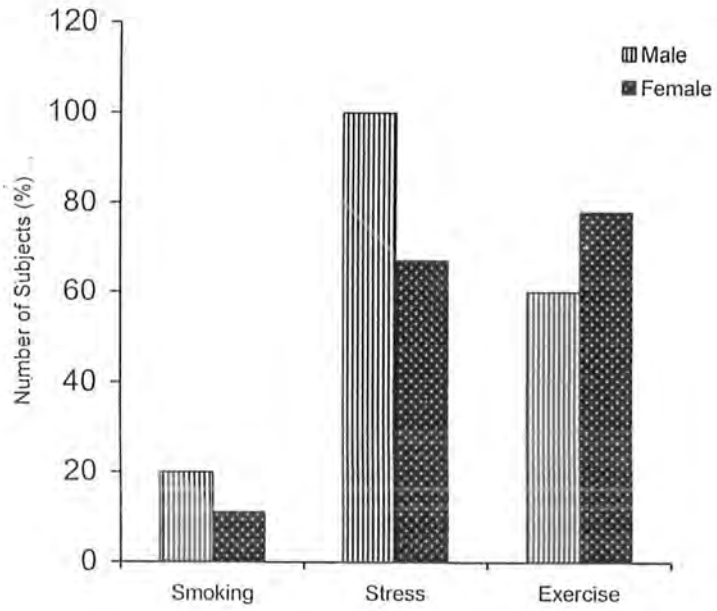
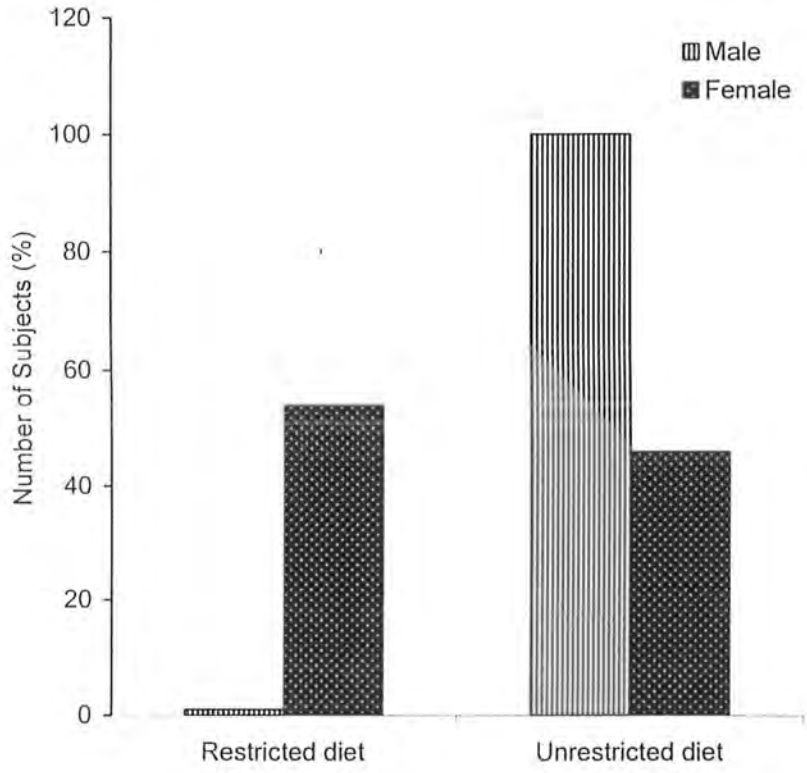


Fig. 10 Percentage of taking restricted and unrestricted diet in Type II diabetes mellitus in Group II (62 – 75) years.



Antihypertensive drugs

Majority of Subjects were taking ACE inhibitors, out of which 40% were males and 22 % were females the numbers of male subjects taking Capotin was 20% while those females were 23%. Males and females taking norvasc were 20% and 23% respectively. Males and females using ACE inhibitors + ARB's were 20% and 23% respectively. Tenormin was not being used by any of the subjects (Fig.11)

Hypoglyceamic Drugs

In this group of aged Males and Females, all subjects exclusive of gender were taking a combination of diaonin and glucophage (Fig.12)

Fig. 11 Percentage of male and female subjects taking antihypertensive drugs in Type II Diabetes in group III (62 – 75 years).

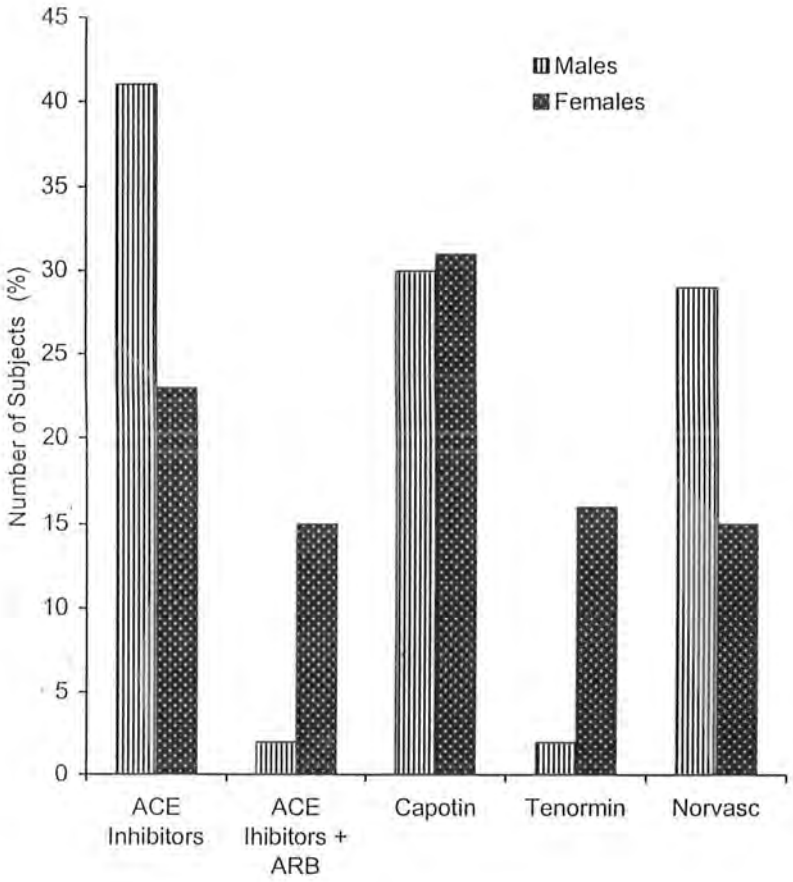
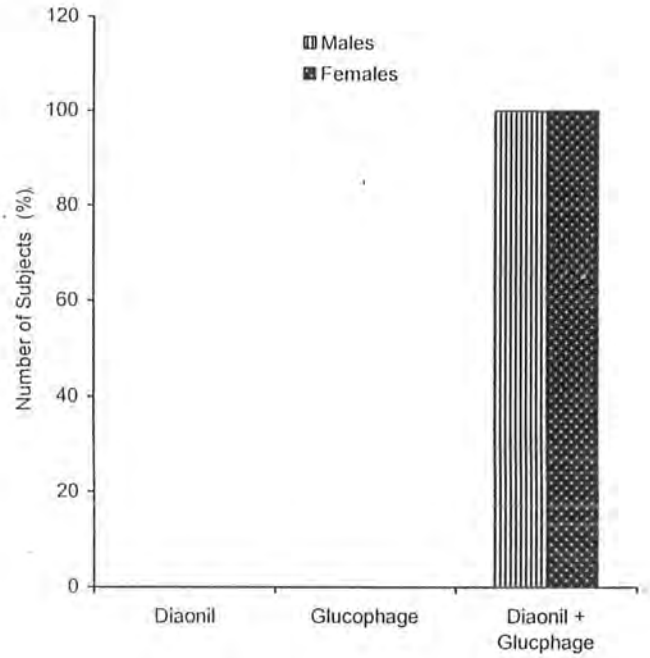


Fig. 12 Percentage of male and females subjects taking hypoglycemic drugs in Type II diabetes mellitus in Group II (62 – 75) years.



COMPARISON OF DRUGS

Males and females subjects were combined while doing the comparison of the effects of different antihypertensive drugs and hypoglyceamic drugs. Comparisons were made using one-way Anova, Dunn's test, Tukey's test. For antihypertensive drugs ACE inhibitors were kept as control while for hypoglyceamic drugs diaonil was considered as control.

ANTIHYPERTENSIVE DRUGS

Five different antihypertensive drugs were included. ACE inhibitor was taken as control and compared with subjects on combination of ACE inhibitors and ARB's, capotin, tenormin and norvasc.

BMI

None of the treatment drugs effected BMI. All five drugs behave in a similar manner.

BLOOD PRESSURE

ACE inhibitors significantly ($P<0.003$) reduced systolic blood pressure while norvasc was the second best drug in lowering significantly ($P<0.05$) the systolic blood pressure. Capotin, Tenormin and combination of ACE inhibitors + ARB's on the other hand failed to bring the systolic blood pressure closer to target blood pressure. None of the antihypertensive drugs showed significant difference in lowering the diastolic blood pressure among them as regard their action showed no difference.

BLOOD SUGAR RANDOM

BSR was significantly lowered ($P<0.029$) in subjects on ACE inhibitors while the rest of the drugs failed to bring any change in BSR or bringing it closer to normal levels.

HEAMOGLOBIN

Heamoglobin concentration was not affected by any of the antihypersentive agents.

RENAL FUNCTION TESTS

None of the treatment drugs affected albuminuria while serum urea highly significantly ($P<0.001$) affected. ACE inhibitors reduced serum urea while capotin and tenormin reduced it significantly ($P<0.05$) Norvasc and a combination of ACE inhibitors and ARB's remained ineffective in reducing serum urea. Serum creatinine was significantly lowered ($P<0.005$) with ACE inhibitors while the second effective drug in lowering the serum creatinine was the combination of ACE inhibitors + ARB's with significantly ($P<0.05$) decreased the creatinine. Serum sodium showed no response to drugs while serum potassium was significantly ($P<0.006$) lowered the ACE inhibitors, and norvasc was the second drug in lowering the potassium levels significantly ($P<0.05$). Other three drugs however show no such effect.

LIPID PROFILE

None of the treatment drugs control serum cholesterol and triglycerides level.

Table 13

Comparison among antihypertensive drugs Using one-way ANOVA keeping ACE inhibitor as control in subjects with Type II diabetes mellitus.

Parameter	ACE Inhibitor + ARB`s	Capotin	Tenormin	Norvasc	ACE inhibitor
Number					
BMI (kg/m^2)	N.S	N.S	N.S	N.S	N.S
Systolic B.P(mm Hg)	N.S	N.S	N.S	<0.05	<0.001*
Diastolic B.P(mm Hg)	N.S	N.S	N.S	N.S	N.S
BSR (mg/dl)	N.S	N.S	N.S	N.S	<0.029**
Hb (mg/dl)	N.S	N.S	N.S	N.S	N.S
Albumin	N.S	N.S	N.S	N.S	N.S
Urea (mg/dl)	N.S	<0.05	<0.05	N.S	<0.001***
Creatinine (mg/dl)	<0.05	N.S	N.S	N.S	<0.005****
Sodium (mmol/l)	N.S	N.S	N.S	N.S	N.S
Potassium (mmol/l)	N.S	N.S	N.S	<0.05	<0.006*****
Cholesterol (mg/dl)	N.S	N.S	N.S	N.S	N.S
Triglyceride (mg/dl)	N.S	N.S	N.S	N.S	N.S

N.S Non significant

*P<0.001 shows highly significant difference in controlling systolic blood pressure > norvasc (P<0.05)>tenormin, capotin ACE inhibitors + ARB's

**P<0.029 shows highly significant difference in controlling BSR then other four antihypertensive drugs.

***P<0.001 shows highly significant difference in controlling serum urea > tenormin and capotin (P<0.05) > norvasc and ACE inhibitors + ARB's.

****P<0.005 shows highly significant difference in controlling serum creatinine > ACE inhibitors + ARB's (P<0.05) > other three drugs.

*****P<0.006 shows highly significant difference in controlling serum potassium > norvasc (P<0.05) > other three drugs.

HYPOGLYCEAMIC DRUGS

BMI

None of the treatment affected BSR and behave in the same mannger.

BLOOD PRESSURE

Diaonil helped in significantly ($P<0.003$) reducing the systolic blood pressure while glucophage also reduced the systolic blood pressure ($P<0.05$). Similarly diastolic blood pressure was also significantly ($P<0.008$) reduced with diaonil while glucophage alone or in combination with diaonil had no effect.

BLOOD SUGAR RANDOM

None of the treatment affected BSR.

HEAMOGLOBIN

All hypoglyceamic agents behaved similarly and did not effect heamoglobin concentration.

RENAL FUNCTION TESTS

No marked difference was observed In case of albuminuria. Serum urea was significantly lowered ($P<0.004$) with diaonil while the other two did not bring any change. Serum creatinine remained the same. Serum electrolytes viz. sodium and potassium remain unaffected.

LIPID PROFILE

In comparison serum cholesterol and triglycerides remain the same.

Table 14

Comparison among Hypoglycemic drugs using one way ANOVA keeping Diaonil as control in subjects with type II diabetes mellitus.

Parameter	Glucophage	Diaonil + Glucophage	Daonil
Number			
BMI (kg/m^2)	N.S	N.S	N.S
Systolic B.P(mm Hg)	<0.05	N.S	<0.003*
Diastolic B.P(mm Hg)	N.S	N.S	<0.008**
BSR (mg/dl)	N.S	N.S	N.S
Hb (mg/dl)	N.S	N.S	N.S
Albumin	N.S	N.S	N.S
Urea (mg/dl)	N.S	N.S	<0.004***
Creatinine (mg/dl)	N.S	N.S	N.S
Sodium (mmol/)	N.S	N.S	N.S
Potassium (mmol/l)	N.S	N.S	N.S
Cholesterol (mg/dl)	N.S	N.S	N.S
Triglyceride (mg/dl)	N.S	N.S	N.S

N.S non significant.
*P<0.003 shows significant difference in controlling systolic blood pressure > glucophage (P<0.05) > glucophage + Diaonil
**P<0.008) shows significant difference in controlling diastolic blood pressure than other two drugs.
***P<0.004) shows significant difference in controlling urea than the other two drugs.

DISCUSSION

DISCUSSION

The present prospective study was carried out on subjects afflicted with type II diabetes mellitus, known hypertension and macroalbuminuric. The study was designed to determine the role of agents that inhibit the rennin angiotensin system (ACE inhibitor) in both preventing the development of diabetic nephropathy and limiting its progression. These agents can provide a greater cardiac and renal protection than that can be achieved through lowering of the blood pressure alone and hence they are an essential part of modern diabetes management (Barnett, 2005). The study was carried out on n=95 subjects with Type II diabetes mellitus along with hypertension and macroalbuminuria.

BLOOD SUGAR

Plasma glucose showed no variation when compared age wise or gender wise in our study. Raised levels of glucose are responsible for various complications of diabetes (Ruderman and Haudenschild, 1984). Hyperglycemia is a risk factor for diabetic nephropathy (DCCT group, 1993) and in patients with overt nephropathy it is related with the loss of renal function (Mulec et al., 1998). The United Kingdom Prospective Diabetes Study (UKPDS; 1998) has shown conclusively that intensive control of blood glucose reduces the risk of diabetic nephropathy in patients with Type II diabetes, while in the present study the patients presented with high levels of glucose and were nephropathic. The reason for raised glucose levels were quite possibly unawareness, lack of education and less understanding of the disease. Elevation of blood sugar levels as observed here may have been due to there lesser percentage of subjects on restricted diet. Moreover these subjects had the history of taking unrestricted diet, lack of exercise and a greater stress. In the present study there was statistically no difference gender wise while Laasko (1987) showed elevated levels of blood sugar in females. This increase of blood sugar in females implicate marked metabolic disturbances in them which may predispose them to various complications of diabetes than their male counter parts (Ahmad, 1981). Recent studies suggest that dietary modification and increase physical activity can reduce the risk of Type II diabetes. (Tuomilethoi et al.,2001; DPPRG.,2002)

Prior to the publication of the UKPDS results in 1998, all the evidence for the benefits of blood pressure lowering in patients with diabetes had been extrapolated from data taken from the general population. UKPDS in 1998 studied hypertensive subjects with diabetes Type II that showed a dramatic risk reduction in vascular endpoints and mortality. There was significant reduction in the incidence of nephropathy with strict glyceamic control.

Obesity has a strong relationship with hyperglycemia. Increased blood sugar levels tend to predispose to complications like nephropathy and cardiovascular problems unless there is mitigation of obesity (WHO,1980).In present study, in the age Group II (49-61 yrs) BMI was significantly ($P<0.004$) greater with increased levels of blood sugar as compared to the Group I and Group III. These patients were taking sulfonylureas and metformin as oral hypoglyceamic drugs. The effect of metformin in reducing the risk of renal failure was similar to other hypoglyceamics but it reduces the risk of myocardial infarction than other hypoglyceamic agents. It was recommended that metformin should not be used in subjects with impaired renal functions as it increases the risk of lactic acidosis (UKPDS, 1998)

Type II diabetic subjects have a risk of fatal and non-fatal cardiovascular events and nephropathy. This poor outcome is related to hyperglycemia and hypertension (Gall et al., 1995; Dinneen et al., 1997; Gerstein et al., 2001). Hyperglycemia is a risk factor for diabetic nephropathy and the glucose levels are correlated with a loss of renal functions (Mulec et al., 1998). Intensive control of blood glucose reduces the risk of diabetic nephropathy and other microvascular complications (UKPDS, 1998).

RENAL FUNCTION TESTS

Increased urinary excretion of albumin is known to predict clinical nephropathy in diabetes (Viberti et al., 1982). One quarter and one third of subjects with Type II diabetes show evidence of renal disease, defined as persistent proteinuria along with hypertension (Remuzzi et al., 2002). About one half of subjects are hypertensive at the time of diagnosis out of which 80% later develop proteinuria (Ramsay et al., 1999; Barnett et al., 2000,). Proteinuria predicts progression and renal outcome in diabetic subjects (Risdom et al., 1968, Remuzzi et al., 2002). Cases with low-grade proteinuria have good prognosis while patients with heavy proteinuria progress to renal

insufficiency (Cameron et al., 1983). More than 80% of these patients still retain normal renal function 10 years after the diagnosis of nephropathy (Rydel, 1995). When disease reaches the malignant stage around 50% of patients reach end stage renal disease within 6-8 years.

And randomized trial involving patients with diabetes and nephropathy showed that as compared with high intake of protein, restriction of protein reduced the decline in the glomerular filtration rate, lowered blood pressure and stabilized renal function in some patient and reduced the rate of progression to end stage renal disease (Zeller et al., 1991, Hensen et al., 2001). In the present study majority of the subjects were not on restricted diet and it could be one of the reason for macroalbuminuria.

Microalbuminuria progresses to macroalbuminuria, which will result in the rise of serum creatinine levels and serum urea that eventually leads to end stage renal disease (Gall et al., 1997; Ritz et al., 2003). When serum creatinine is elevated beyond certain level, progression to end stage renal disease becomes inevitable (Mitch et al., 1976). All subjects were known macroalbuminuric but a comparison between males and females of Group II was significant for serum urea, serum creatinine and serum potassium, while all the three groups had higher levels of renal function test. Type II diabetic patients studied presently showed marked renal impairment that predisposed them to nephropathy. This tendency towards nephropathy might be due to the presence of certain risk factors like hyperglycemia and hypertension and therefore renal impairment is the hall mark of increased mortality in Type II diabetics (Mogensen et al., 1984, Remuzzi et al., 2002, Remuzzi et al., 2006).

LIPID PROFILE

High levels of cholesterol and triglycerides were encountered in all the three age groups and in both males and females. This increase in the level of total cholesterol and triglycerides in Type II diabetics make them prone to coronary heart disease and is one of the risk factor, which is the major cause of ischemic heart disease (Jarret et al., 1984; Laasko et al., 1987). And round 80% subjects die of cardiovascular diseases (Kannel et al., 1979, Haffner et al., 1998, Fisher et al., 2001).

This association of increased levels of cholesterol and triglycerides with coronary heart disease in Type II diabetes has been shown in a large number of previous studies (Miller et al., 1975, Pooling Project Research Group 1978, UKPDS Group 1998, Remuzzi et al., 2002, Remuzzi et al., 2006). All these studies showed that along with dyslipidemia other risk factors like obesity, physical inactivity are important. A positive relationship between body weight and hyperlipedemia has already been observed (Nikkila and Horvila 1978; Sjoberg et al., 1987 ; UKPDS 1998 ; Remuzzi et al., 2002) .

It has been shown that decreasing the levels of cholesterol and triglycerides decreases , the incidence of coronary heart disease . (Remuzzi et al., 2002). Hyperlipedemia is frequently associated with diabetes and is often considered as a major factor of its atherosclerotic complications as shown by (Castelli et al., 1977; kannel and MCGee , 1979)

In the present study the BMI was above border line and majority of subjects were smokers. Smoking besides increases the risk of cardiovascular events, is an important risk factor for the development of nephropathy in patients with Type II diabetes and is associated with an accelerated loss of renal functions. Smoking cessation alone may reduce the risk of disease progression by thirty percent. (Ritz et al., 2000). Dyslipidemia is common in patients with diabetes, especially with overt nephropathy. Proteinuria decreases as the levels of lipids are lowered and this preserves the renal functions. (Fried et al., 2001).

ROLE OF ANTIHYPERTENSIVE AGENTS

ACE inhibitors were found to have a greater renoprotective effect than other antihypertensive drug in patients with diabetes and nephropathy (Anderson et al., 1986, Zatz et al., 1986; Anderson et al., 1983) and a similar out come was observed presently in some cases, ACE inhibitors failed to reduce proteinuria or protect kidneys from injury (Marinides et al., 1987, Fogo et al., 1988), II.

In patients with diabetic nephropathy, lowering blood pressure with an ACE inhibitor decreases urinary protein excretion and slows the decline in the GFR more than does lowering blood pressure to similar levels with beta blockers (Bjorck et al., 1992). It was observed by Lewis (1993) that ACE inhibitors preserve renal function better than beta-blockers or other antihypertensive drugs and lower the rate of dialysis. Urinary

proteins decrease in patients treated with ACE inhibitors as compared to other drugs (Breyer et al., 1995). Drug wise comparison of ACE inhibitors with other antihypertensive drugs in the present study showed better blood pressure control with ACE inhibitors along with better response of renal functions even though the subjects were on antihypertensive and hypoglycemic drugs, BSR, renal function and blood sugar did not achieve target levels. The optimal range of blood pressure in patients with Type II diabetes is unclear. In recent trials involving patients with Type II diabetes it has been shown that there were no cardiovascular events when diastolic blood pressure was 70-84 mm Hg than when it was 85 mm Hg or higher (Bakris et al., 2000). Conversely if diastolic blood pressure was less then 70 mm Hg, the rates of cardiovascular event increase by eleven percent for each additional reduction of 5mm Hg with an increasing mortality (Hansson et al., 1998)

Calcium channel blockers (norvasc) may worsen proteinuria and accerelate the progression of disease in patients with nephropathy (Bakris et al., 1991, Ruggenenti et al., 1998, Agodoa et al., 2001). While according to Smith et al. (1998) calcium channel blockers may reduce overt proteinuria in patients with nephropathy in Type II diabetes. According to meta analysis, at any level of blood pressure control, patients with diabetes who were treated with calcium channel blockers (norvasc) had more severe proteinuria and a more rapid decline in the GFR than those treated with other antihypertensive agents (Weidmann et al ., 1995).ARB's in reducing the risk of renal events was not diminished by concomitant use of calcium channel blockers (Brenner et al., 2001).In the present study the calcium channel blockers were the drugs which were in least use, the reason could have been due to their least efficacy and that they increase the progression of the disease.

Beta-blockers (tenormin) may be beneficial in the treatment of diabetic nephropathy. In UKPDS group (1998), beta-blockers and ACE inhibitors were equally effective in lowering the incidence of macroalbuminuria. In patients with overt nephropathy beta-blockers and ACE inhibitors had similar protective effects on renal functions (Nielsen et al ., 1997). While ARB's did not offer additional renal protection in patients who were already receiving treatment with beta-blockers (Brenner et al., 2001)

Ruggenenti (2004) concluded in his study that ACE inhibition as a renoprotective effect, reduces the risk of development of nephropathy in subjects with type II diabetes. This benefit appears to be over and above than that achieved by reduction in blood pressure alone, given that the group taking only calcium channel blockers or other antihypertensive drugs achieve similar blood pressures, but with much more rapid progression to nephropathy. This supports the view that inhibition of renin angiotensin system protect the already damaged kidney in Type II diabetes and also reduces the risk of complication. .

Progression to irreversible renal damage and end stage renal disease is the final common pathway of chronic proteinuric nephropathies and is relatively independent of the type of initial insult. The increase in urinary protein excretion correlated with the tendency of the renal disease to progress more than with the underlying disease. Whenever urinary protein excretion is reduced, the decline in the GFR decreases or stops. ACE inhibitor and other antihypertensive drugs, which lower the rate of urinary protein excretion effectively limit the progressive decline in the GFR.

Quantification of urinary protein helps predict the risk of disease progression and the need for dialysis. These findings leaves the question whether the renoprotective effect of the ACE inhibitor was related to its antiproteinuric effect or to its antihypertensive effect unanswered.

APPENDIX

APPENDIX

DATA SHEET

Name

Age

Sex

Address

Permanent Address

Family H/O Diabeties mother father brother / sister uncle / aunty

Period of Illness

History of Smoking

Dietary History

Exercise

Stress

Treatment History

B.P

Weight

Height

SYSTEMIC EXAMINATION

Cardiovascular System

Gastrointestinal System

Respiratory System

INVESTIGATIONS

Blood sugar random (mg/dl)

Hb %

Urine Proteinuria

Creatinine (mg/dl)

Urea (mg/dl)

Serum Electrolytes (mmol/l)

Na

K

Total Cholesterol (mg/dl)

Triglycerides (mg/dl)

Renal U/S

TREATMENT HISTORY

Diabetes

Oral Hypoglycemics

Hypertension

ACE inhibitors

ACE +ARB

Beta Blockers

Others

REFERENCES

REFERENCES

Adler, A.L., Stevens, R.J., Manley, S.E., et al (2003). Development and progression of nephropathy in type 2 diabetes: the United Kingdom prospective Diabetes Study (UKPDS 64). Kidney. Int.; 63: 225-32.

Agodoa, L.Y, Apple, L, et al,. (2001) Effects of ramipril vs amlodipine on renal outcome in hypertensive nephrosclerosis; a randomized control trial. JAMA; 285:2719-28

Ahmed, N. (1991) Glycation and diabetic complications. J. Pak. Med. Assoc.; 41:171-4.

American Diabetic Association (1999). Consensus development conference on the diagnosis and management of nephropathy in patients with diabetes mellitus (Editorial). Diabetes Digest; 9(2): 5-11.

Anderson, A.R., Christiansen, J.S., Anderson, J.K. et al (1983). Diabetic nephropathy in type I (insulin dependent) diabetes: an epidemiological study. Diabetologia; 25:496-501.

Anderson, S, Rennke H.G., Brenner, B.M.(1986) therapeutic advantage of converting enzyme inhibitors in arresting progressive renal disease associated with systemic hypertension in the rat. Journal Clinical Invest.; 76:1993-2000.

Anthony, P.F, Turnner, Beining. Chem and Sergey. A. Pileksky. (1999). In vitro diagnostics in diabetes meeting the challenge. Clinical Chemistry.; 45 (9) :1596-1601.

Bakris, G.L, William, M et al,. (2000) Preserving renal function in adults with hypertension and diabetes; a consensus approach. Am J Kidney Dis; 36:646-61

Bakris, G.L (1991) Renal effects of calcium and antagonist in diabetes mellitus; an overview of studies in animal models and humans. Am J Hypertens ; 4:suppl:487-493

Barnett, A.H. (2000) Hypertension as a risk factor for diabetic vascular disease. In: Barnett, A.H., Dodson, P.M. (eds). Hypertension and diabetes (3rd edn). London:Science press: 11-20.

Barnett, A.H. (2005) Hypertension as a risk factor for diabetic vascular disease. In: Barnett, A.H., Dodson, P.M. (eds). Hypertension and diabetes (3rd edn). London:Science press; 11-20.

Bell, G.L., Xiang, K., Horita, S., Sanz, N., Karam, J.H. (1987). The molecular genetics of diabetes mellitus. In: Siba Foundation Symposium 130: Molecular approaches to human polygenic disease. John Wiley and Sons; New York.; 167-183.

Bjorck,S,Mulec, H et al., (1992) Renal protective effect of enalapril in diabetic nephropathy. BMJ; 304:339-43

Borch-Johnsen, K., Andersen, P.K., Deckert, T. (1985). The effect of pronteinuria on relative mortality in type I (insulin dependent) diabetes mellitus. Diabetologia.; 28: 590-96.

Bohrer, M.P., Deen, W.M., Robertson, C.R., et al. (1977). Mechanism of angiotensin II-induced proteinuria in the rats. Am. J. Physiol.; 233: F13-F21.

Breyer, J.A. (1995) Medical Management of nephropathy in Type I diabetes mellitus : Current recommendations. J Am Soc nephrol; 6:1523-9

Brenner, B.M., Meyer, T.W., Hostetter, T.H. (1982). Dietary protein intake and the progressive nature of kidney disease: the role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. N. Engl. J. Med.; 307: 652-9.

Brenner, B.M, Copper, M.E et al, (2001). Effect of Losartan on renal and cardiovascular outcomes in patients with Type II diabetes and nephropathy. N Engl J Med ; 345:8619

Castelli, W.P., Doyle, J. T., et.al. (1997) HDL cholesterol and other lipids in coronary hear disease. The cooperative lipoprotein phenotyping study. Circulation.; 55: 767-772.

Cameron,J.S.et al., (1983). Idiopathic mesengiocapillary glumerulonephritus. Comparison of types I and II in children and adults and long term prognosis. Am. J. Med. 74:175-192.

Colditz, G.A., Willet, W.C., Rotnitzky, A.,et al (1995). Weight gain, as a risk factor for clinical diabetes mellitus in women. Ann. Intern. Med.; 122: 481-86.

Colditz, G.A., Willet, W.C., Rotnitzky, A.,et al (1997). Increasing prevelance rate of mainly Type II diabetes in the UK-Projected to the year 2010. Diabet Med.; 14 (suppl 5) :57-85.

DCCT (diabetes control and complications trial research group). (1993). The effect of intensive treatment of diabetes on the development and progression of long term complications of insulin dependant diabetes mellitus. N. Engl. J. Med.; 329:977-9

Diabetic care and research in Europe: the Saint Vincent Declaration (1990). Diabet. Med.; 7: 360.

Diabetes prevention program research Group (2002) Reduction in the incidence of Type II diabetes with life style invention or metformin. N Engl J Med ; 346:393-403

Dinneen, S.F, Gerstein, H.C. (1997) The association of Microalbuminuria and mortality in NIDDM. Arch Intern Med; 157:1413-1418.

Edward, C.R.W., Baird, G.D., Toft, A.D. (1991). Endocrine and metabolic diseases. Christopher, R.W., Edwards, Ian, A.D., Bouchies. (eds). In: Davidsons. Principles and practice of medicine. Chuchill Livingstone. 16th edition. 607-698.

Fisher, M., Shaw, K.M. (2001). Diabetes – a state of premature cardiovascular death. Pract. Diabet. Int.; 18: 183-84.

Fried, L. F., Orchard, T. J., L et, al. (2001). Effect of lipid reduction on the progression of renal disease; a meta analysis. Kidney. Int; 59: 260-9.

Fogo, A., Yoshida, Y et al., (1988) Serial micro puncture analysis of glomerular function in two rat models of glomerular sclerosis. J Clin Invest. 82:322-30.

Gall, M.A., Hougaard, P., Borch-Johnsen, K., et al (1995). Albuminuria and poor glycemic control predicts mortality in NIDDM. Diab; 44:1303-1309

Gall, M.A., Hougaard, P., Borch-Johnsen, K., et al (1997). Risk factors for development of incipient diabetic nephropathy in patients with non insulin dependent diabetes mellitus: prospective, observational study. Br. Med. J.; 314:783-88.

Gerstein, H.C, Mann, J.F et al,. (2001) Albuminuria and the risk of cardiovascular events, death and heart failure in diabetic and non diabetic individuals. JAMA; 286:421-426

Haak, T., Haak, E., Jungmann, E., et al (1997). Therapy of diabetic nephropathy. Effect of ACE inhibition on microcirculation. Fortschr. Med.; 115(15): 26-9.

Habib,R., kleinknecht, C., et al (1973) Idiopathic membranoprolifirative glumerulonephritus in children. Report of 105 cases. Clin Nephrol. 1: 194-214

Haffner, S.M., Lehto, S., Ronnemaa, T. et al. (1998). Mortality from the coronary heart disease in subjects with type II diabetes and in non diabetic subjects with and without prior myocardial infarction. N. Engl. J. Med ; 339: 229-34.

Hansen, H.P, Tauver-Lassen, E, et al,. (2001) Effect of dietary protein restriction on prognosis in Type I diabetic patients the diabetic nephropathy. Presented at the European diabetic nephropathy study Group 14th Annual meeting, county Durham, United Kingdom. Abstract.

Hansson,L,Zanchetti, A et al,. (1998) Effect of intensive Blood pressure lowering and low dose aspirin in patients with hypertension; principals results of the hypertension optimal treatment randomized trial. Lancet ; 351:1755-62

International diabetes federation. The kidney issue. Diabetes Voice (2003). 18:Special issue.

Jarrett, R.J., Alberti, G.C., Argyropoulos, A.,et al (1984). Microalbuminuria predicts mortality in non-insulin-dependent diabetics. Diabet. Med.; 1: 17-19.

Kannel, W.B., McGee, D.L., (1979). Diabetes and cardiovascular risk factors: The Framingham study. Circulation; 59: 8-13.

King, H., Albert, K.E., Herman, W.H. (1998). Global burden of diabetes, 1995-2025. Prevalence numerical estimates and projection. Diabetes Care.; 21: 1414-1431.

Korbet, S.M., Schwartz.M.M., and Lewis, E.J. (1994). Primary focal segmental glomerulosclerosis: clinical course and response to therapy. Am. J. Kidney. Dis. 23:773-783.

Koren, W., Koldanov, R., Pronin, V. S., Postnov, E., et al. (1998). Enhanced erythrocyte Na/H ion exchange predicts diabetic nephropathy in patients with IDDM. Hypertension unit. Diabetologie; 41 (2): 201-5.

Krolewski, A.S., Canessa, m., Warram, J.H., Laffel, L.M.B., et al. (1988) Predisposition to hypertention and susceptibility to renal disease in insulin-dependent diabetes mellitus. N. Ehgl. J. Med; 318: 140-145.

Kuczmarski, R. J., Flegal, K.M., Campbell, S.M., et al (1960 to 1991). Increasing prevalence of overweight among US adults. The National Health and Nutrition Examination surveys. JAMA.; 272: 205-11.

Lacourciere, Y., Belanger, A., Godin, C. et al (2000). Long term comparison of losartan and enalapril on kidney function in hypertensive type 2 diabetics with early nephropathy. Kidney Int; 58:762-69.

Laasko, M., Pyorala, K., et.al (1987) Plasma insulin and serum lipids and lipoprotein in middle aged non insulin dependant diabetic and non diabetic subjects. Am. J. Epidemiol; 125: 611-621.

Lapinski, R., Perico, N., Remuzzi, A., Sangalli, F., Benigni, A., Remuzzi, G. (1996). Angiotensin II modulates glomerular capillary perselectivity in rat isolatesd perfused kidney. J. Am. Soc. Nephrol.; 7: 653-60.

Lee, G.S. (2005). Retarding the progression of diabetic nephropathy in type 2 diabetes mellitus: focus on hypertension and proteinuria. Ann. Acad. Med. Singap.; 34: 24-30.

Lewis, E.J, Hunsicker, L.G et al,. (1993). The effect of angiotensin converting enzymes inhibition on diabetic nephropathy. N Engl J Med; 329:1456-62

Lovell, H. G. (2000). Angiotensin converting enzyme inhibitors in normotensive diabetic patients with microalbuminuria. Cochrane Review. In; The Cochrane Library; 2: 1-13.

Marinides G.N, Groggel, G.C et al,. (1987) Failure of angiotensin converting enzyme inhibition of affect the course of chronic puromycin aminonucleoside nephropathy. Am J Pathol; 129:394-401.

MacLeod, J.M., Lautale, J., Marshall, S.M. (1995). Albumin excretion and vascular death in NIDDM. Diabetologia.; 38: 610-16.j

Mayfield, J. (1998). Diagnosis and classification of diabetes mellitus; new criteria. Am. Fam. Physicians. ; 58 (6) : 1355-62, 1369-70.

Miller, G. J., and miller, N. E. (1975) Plasma high density lipoprotein concentration and development of ischemic heart disease. Lancet.; 1: 16-19.

Mitch, W.E., Walser, M., Buffington, G.A., et.al (1976). A simple method of estimating progression of chronic renal failure. Lancet. 2:1226-1328.

Mogensen, C.E. (1984) Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. N. Engl. J. Med.; 310:356-60.

Mulec,H,Blohme,G, et al,. (1998) The effect of metabolic control on rate of decline in renal function in insulin dependent diabetes with overt diabetic nephropathy. Nephrol Dial Transplant; 13:651-5

Nelson, R.G., Knowler, W.C., Pettitt, D.J. et al (1991). Assessing risk of overt nephropathy in diabetic patients from albumin excreation in untimed urine specimens. Arch. Intern. Med; 151: 1761-65.

Nielsen, P.S, Rossing, P et al,. (1997) Long term effect of lisinnopril and atenolol on kidney function in hypotensive NIDDM subjects with diabetic nephropathy. Diabetes; 46:1182-8

Nikkila, E.A. (1984) Plasma Lipid and lipoprotein abnormalities in diabetes. In (Jarrett RJ. Ed) Diabetes and heart disease. New York. Elsevier Science Pub. P. 133-167.

O'Donnell, M.J., Chowdhury, T.A. (2000). Hypertension and nephropathy in diabetes. In:Barnett AH, Dodson PM (eds). Hypertension and diabetes (3rd edn). London: Science press; 21-31.

Office for Population Censuses and Surveys (1991). Health Survey for England. London: HMSO.

Parving, H. H., Tarnow, L., and Rossing, P., (1996). Genetics of diabetic nephropathy (Editorial). J. Am. Soc. Nephrol; 7(2): 2509-17.

Pooling Project research group: (1978) relationship or blood pressure, serum cholestrol, smoking habit, relative weight and E.C.G. abnormalities to incidence of major coronary events. Final report of the pooling project. J. Chronic. Dis.; 31: 201-306.

Ramsay, L., Williams, B., Johnston, G. et al (1999). Guidelines for management of hypertension; report of the third working party of the british hypertention society. J. Hman. Hypertens.; 13:569-92.

Remuzzi, G. Ruggenenti, P., et al,. (2002) Chronic Renal disease; Renoprotactive benefits of reninangiotensin system inhibition. Ann. Intern. Med 136:604-615

Remuzzi, G., Bertani, T. (1990). Is glomerular sclerosis aconsequence of altered glomerular permeability to macromolecule? Kidney. Int. 38: 384-94.

Remuzzi, G., and Weening, J. (2005). Albuminuria as early test for vascular disease. Lancet.; 365: 556-557.

Remuzzi, G., Schieppati, A., Ruggenenti, P. (2002). Clinical practice. Nephropathy in patients with type 2 diabetes. N. Engl. J. Med.; 346: 1145-1151.

Remuzzi, G., Schieppati, A., Ruggenenti, P. (2002). Nephropathy in patients with type 2 diabetes. N. Engl. J. Med; 346:1145-51.

Remuzzi, A., et al. (2006). Ace inhibition reduces glomerulosclerosis and regenerates glomerular tissue in a model of progressive renal disease. Kidney. Int.; In press.

Risdon, R.K, Sloper, J.C et al,. (1968) Relationship between renal function and histological changes found in renal biopsy specimens from patients with persistent glomerular nephritis. Lancet 2;363-366.

Ritz, E. (2003). Albuminuria and vascular damage-the vicious twins. N. Engl. Med.; 348:2349-52

Ritz, E , Ogata, H et al,. (2000). Smoking; a factor promoting onset and progression of diabetic nephropathy. Diabetes Metab; 26:Suppl 4:54-63

Ruderman, N.B., & Haudens, child C: (1984) Diabetes as an atherogenic factor. Prog. Cardio Vasc Disease.; 26: 373-412.

Ruggenenti, P., et al. (2004). Preventing microalbuminuria in type 2 diabetes. N. Engl. J. Med.; 351: 1941-1951.

Ruggenenti, P., et al. (1998). Effects of dihydropyrodine calcium channel blocker, angiotencin converting enzyme inhibition and blood pressure control on chronic non diabetic nephropathies. J.Am Soc Nephrol; 9:2096-101.

Rydel, J.J, Korbet, S.M, et al (1995) Focal segmental glomerular sclerosis in adults; presentation , course, and response to treatment. Am. J. Kidney. Dis. 25: 534-542

Sjoberg, S., Gunnarsson, R., Rossner, S., et. Al (1987) Serum lipid and lipoprotein levels in long term insulin dependant diabetes mellitus. Acta. Med. Scand.; 222: 445-451.

Smith, A.C, Toto, R, Bakris, G.L. (1998). Differential effects of calcium channel blockers on size selectivity of proteinuri in diabetic glomerulopathy. Kidney Int; 54:889-96.

Stammler, J., Vaccaro, O., Neaton, J.D., et al (1993). Diabetes, other risk factors and 12-year for men as screened in the multiple risk factors intervention trial. Diabetes Care; 16:434-44

Shera, A.S., Rafique, G., Khawaja, I.A., Ara, J., Baqai, S., King, H. (1991). Pakistan national diabetes survey; prevalence of glucose intolerance an associated factors in Shikarpur Sind Province. Diabet. Med.; 16th ed.; 607-698.

Thomas, S.M., and Viberti, G.C. (2005). Cardiovascular risk in diabetic kidney disease: a model of chronic renal disease. Kidney. Int.; 68(suppl.98): S18-S20.

The diabetes Control and Complication trial research Group. (1993) The effect of intensive treatment of diabetes on the development and progression on long term complication in IDDM. N Engl J Med ; 329:977-86

Tuomilehto, J. Lindstorm, J et al,. (2001) Prevention of Type II diabetes mellitus by changes in life style among subjects will impaired glucose tolerance. N. Engl J Med; 344:1343-50

United Kingdom Prospective Diabetes Study (UKPDS) group (1998). Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancent ; 352: 837-53.

United Kingdom Prospective Diabetes Study (UKPDS) group (1998). Effect of intensive blood glucose control with metformin on complications in overweight patients with Type II diabetics (UKPDS34) Lancet; 352:854-65

UKPDS Group (1998) afficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complication in Type II diabetes (UKPDS39) BMJ; 317:713-20

United states Renal Data System. (2005). Annual data report atlas. usrds.org/atlas.htm.

Valmadrid, C.T., Kleine, R., Moss, S.E., et al (2000). The risk of cardiovascular disease mortality associated with microalbuminuria and gross proteinuria in persons with older onset diabetes mellitus. Arch. Intern. Med. ; 160:1093-100.

Viberti, J. C., Jarrett, R. J., Mahmud, U., et.al (1982) microalbuminuria as a predictor of clinical nephropathy in insulin dependant diabetes mellitus. Lancet.; 1: 1430-1432.

Viberti, G.C., Keen, H., and Wiseman, M.J., (1987). Raised arterial pressure of proteinuric insulin-dependent diabetics. Br. Med. J; 295:515-17.

Waugh, N.R., and Robertson, A.M., (2000). Protein restriction for diabetic renal disease. Cochrane Review In; The Cochrane Library Issue; 2:1-11.

Weidmann, P, Schneider, M, Bohlen, L. (1995) Therapeutic efficacy of different antihypotensive drugs in human diabetic nephropathy. ; and updated meta analysis. Nephrol Dial Transplant ; 10:Suppl 9:39-45.

Williams, G., and Pickup, J.C., (1999). Handbook of diabetes (second edition) WCIN 2BL.: 1-206.

World Health Organization: (1980). Expert committee on diabetes mellitus. Technical report series No. 646.

World Health Organization. The Diabetes Programme 2004. who.int/diabetes/ent.

Wolfe, R.A., et al. (1999). Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. N. Engl. J. Med.; 341: 1725-1730.

Wild S,Roglic G, Green A et al. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004; 27: 1047-53.

Xue, J.L., Ma, J.Z., Louis, T.A., and Collins, A.J. (2001). Forecast of the number of patients with end stage renal disease in the United States to the year 2010. J. Am. Soc. Nephol.; 12: 2753-2758.

Zimmet, P., Macathy, D. (1995). The NIDDM epidemic, global estimates and projections : a look into the crystal ball. IDF Bull.; 40 (30): 8-16.

Zeller, K, Whittaker, E, et al,. (1991) Effect of restricting dietary protein on the progression of renal failure in patients with IDDM. Engl J Med; 324:78-84

Zatz R; Dunn, B.R., et al., (1986) prevention of diabetic glomerulopathy by pharmacological amelioration of glomerular capillary hypertension J Clin Invest; 77:1925-30.