USE OF ANGIOTENSIN CONVERTING ENZYME INHIBITORS AND RENAL FUNCTION CHECKS IN DIABETIC PATIENTS AT THE HOLY FAMILY HOSPITAL, BEREKUM.

By

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CERTIFICATION

I hereby declare that this submission is my own work towards the MSc and that, to the best of my knowledge, it contains no material previously published by another person nor material which has been accepted for the award of any other degree of the University, except where due acknowledgement has been made in the text.

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ABSTRACT

Diabetes is on the increase and with a prevalence rate of 2-8% worldwide, it is expected to affect about 366 million people by 2030. The situation is no different at the Holy Family Hospital at Berekum, where the past 3 years have recorded increased attendance from 2,112 in 2005 to 3,074 in 2008. Diabetes leads to microvascular, macrovascular, neuropathy and retinopathy complications. The most important of the microvascular complications is diabetic nephropathy leading to end-stage renal disease or failure.

Angiotensin II and proteinuria, together with several non-haemodynamic effects such as production of reactive oxygen species; up-regulation of cytokines etc. have emerged as central mediators of the glomerular haemodynamic changes associated with progressive renal injury.

The level of use of Angiotensin Converting Enzyme Inhibitors (ACEIs) and renal function checks for urine albumin in 335 diabetic patients undergoing treatment at the Holy Family Hospital at Berekum from the 24th July to 25th September, 2007 were studied. Data for the study were obtained from the patients' folders, and structured questionnaire were also given to clinicians to obtain their inputs. A minority (16.7%) of diabetic patients was on ACEI and 96.4% of such patients had hypertension as well. Also a lower proportion (31.4%) of the hypertensive diabetic population was given ACEI. 28.1% of the diabetic population ever had their renal function checked implying that 71.9% of the patients never had theirs checked. Of that number, 20.2% had urine albumin, with 26.3% of the urine albumin patients on ACEI.

In conclusion, the findings of the study have revealed that the level of use of ACEI and renal function check in the diabetic population at the Holy Family Hospital, Berekum were low.

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CHAPTER ONE: INTRODUCTION

1.1 OVERVIEW OF DIABETES MELLITUS

Diabetes mellitus is a metabolic disease characterized by hyperglycaemia and relative insulin deficiency, resistance or both. It is a rapidly growing health problem worldwide, reflected in part by improved living conditions and increasing rate of obesity. In countries where the living conditions are somewhat improving with increasing income, a corresponding increase in diabetes and chronic kidney disease is witnessed. With a global prevalence rate of 2-8% in 2003, diabetes is expected to affect about 366 million people in 2030. [1-4]

There are two types of diabetes mellitus namely Type 1 and Type 2, with the latter being the commonest accounting for over 75% of all cases of diabetes in most populations. [5] Diabetes is treated with diet, oral hypoglycaemics and insulin depending on the status of the disease, and it is important to maximize these treatments to prevent the development of complications such as nephropathy, retinopathy and cardiovascular disease. If not adequately managed, diabetes can result in a wide range of complications that have clinical, social and economic implications. [5] Diabetes was the fifth leading cause of death in 2000, and diabetic micro-vascular complications account for a significant portion of the morbidity and mortality. [4]

1.2 DIABETIC NEPHROPATHY AND ITS PROGRESSION

Diabetes mellitus leads to increased risk of developing microangiopathy, macroangiopathy, and neuropathy for both types 1 and 2 cases. [6] The most important macroangiopathic complications are diabetic nephropathy (leading to proteinuria and risk of end stage renal failure) and diabetic retinopathy. Compared with the general population the incidence of macroangiopathy is increased in patients with diabetes mellitus.

Diabetic nephropathy is a clinical condition characterized by abnormal albumin/protein excretion and gradually declining renal function. [7] Normal albumin excretion is defined as Urinary Albumin Excretion Rate (UAER) of less than 20ug/min. In 30 – 50% of all diabetics the UAER gradually increases.

The earliest functional abnormality in the diabetic kidney is renal hypertrophy associated with raised Glomerular Filtration Rate (GFR). This appears soon after diagnosis and is related to poor glycaemic control. As the kidney becomes damaged by diabetes, the afferent arteriole becomes dilated to a greater extent than the efferent arteriole. This increases the intra-glomerular filtration pressure, further damaging the glomerular capillaries. This increased pressure also leads to increased shearing forces locally which are thought to contribute to mesangial cell hypertrophy and increased secretion of extra-cellular mesangial matrix material. The process eventually leads to glomerular sclerosis. The initial structural lesion in the glomerulus is thickening of the basement membrane.

Associated changes may result in disruption of the protein cross-linkages that make the membrane an effective filter. In consequence, there is progressive leakage of large molecules (particularly protein) into the urine, a condition referred to as proteinuria or albuminuria. [8]

1.2.1 Microalbuminuria

The earliest evidence of diabetic nephropathy is microalbuminuria, in which the amount of urinary albumin is so small as to be undetectable by normal dip-sticks. Micro-albuminuria may be tested for by radioimmunoassay or by using special dip-sticks. It is a predictive marker of progression to nephropathy in type 1 diabetes, and of increased cardiovascular risk in type 2 diabetes. [8]

Microalbuminuria, defined as urinary albumin excretion rate (UAER) of between 20 – 200ug/min, predicts progression towards clinical nephropathy and End-Stage Renal Failure (ESRF) with 6 – 9% of diabetic population progressing to clinical nephropathy every year.[9] If left untreated, 80-100% of microalbuminuria patients with type 1 and 20-40% of patients with type 2 diabetes progress to overt nephropathy, a syndrome of macroalbuminuria (UEAR>200 mcg/min), declining GFR, and increased cardiovascular morbidity. [10, 11] L.M Ruilope collaborates this assertion by stating that renal damage is at first incipient only identifiable by the presence of small amounts of albumin in the urine. However without an intervention, the severity of injury to the kidney magnifies, GFR declines, and the disease becomes overt with the emergence of macro-albuminuria,

(UAER of > 300mcg/min). [12] Macro-albuminuria is a strong predictor of death, more so in type 2 (6.2% mortality per year) than in type 1 (2.3% mortality per year) patients and if left untreated it will progress to clinical nephropathy and ESRF. [9]

1.2.2 End Stage Renal Disease

End Stage Renal Disease (ESRD) is the most visible outcome of Chronic Kidney Disease (CKD). However the inter-relationship between Cardio-Vascular Disease (CVD) and CKD risk factors and the common patho-physiological role of sclerosis mediated by angiotensin II explains the fact that many renal patients will die of a cardiovascular event before ESRD develops. [13, 14] A strong and positive relationship between even low levels of kidney disease and increased risk for cardiovascular events has been demonstrated in a number of studies. The Prevention of Renal and Vascular End-stage Disease (PREVEND) study, for example, demonstrated the predictive value of albuminuria on all-cause mortality among more than 40,000 subjects in the general population. [12] It is important to note that even at very low levels of albuminuria (10-20mcg/min), which many would regard as normal; the risk of dying in the 961-day median follow-up period of the study was increased. Similarly, even mild renal impairment, defined as GFR≥ 17ml/min/1.7metre square increased significantly the risk of death or the composite end point of death from cardiovascular causes in the VALsartan In Acute myocardial iNfarction Trial (VALIANT) study. [12, 15]

When the disease finally progresses to end-stage renal disease, the management is more difficult because at that stage patients often have other complications of diabetes such as blindness, autonomic neuropathy or peripheral vascular disease. At this point, patients have to depend on dialysis or renal transplant for survival. Vascular shunts tend to calcify rapidly and hence chronic ambulatory peritoneal dialysis may be preferable to haemodialysis. [8] Continuous ambulatory peritoneal dialysis has the disadvantage of carrying the risk of peritonitis, and therefore blood glucose must be carefully monitored and controlled. Insulin may be given in the peritoneal infusate to cover high carbohydrate load administered. [16]

1.2.3 Albuminuria, Hypertension and Renal injury

Once micro-albuminuria develops, Blood Pressure (BP) increases correspondingly and in patients with clinical diabetic nephropathy, hypertension is usually present. Glomerular capillary hypertension is often maintained by angiotensin-dependent mechanisms, via increased systemic blood pressure and efferent arteriolar hypertension. [17] Although angiotensin II has emerged as a central mediator of the glomerular haemodynamic changes associated with progressive renal injury, several non-haemodynamic effects such as production of reactive oxygen species; up-regulation of cytokines; induction of TGF-beta expression; increased synthesis of ECM proteins etc may also be important in renal disease progression. [18] Angiotensin II also augments the adrenal production of aldosterone, a recognized contributor to renal injury, [19] and augments glomerular trans-capillary passage of plasma proteins, the principal cause of proteinuria.

Proteinuria has traditionally been regarded as a marker of glomerular filtration barrier integrity, and the extent of it has therefore been used as an indicator of glomerular disease severity and there is evidence that proteinuria also contributes to progressive renal injury. Growing tubule epithelial cells in the presence of a variety of plasma proteins in-vitro induces the production of pro-inflammatory cytokines and ECM proteins; responses that ultimately contribute to glomerular scarring and tubulo-interstitial fibrosis. [20] In-vivo, proteinuria is associated with the renal expression of cell adhesion molecules and chemo-attractants, the forerunners of tubulo-interstitial inflammation and fibrosis. [21] Together these facts support the hypothesis that excessive filtration of serum proteins by injured glomeruli contributes directly to progressive renal damage. [22]

1.3 TREATMENT OF PROTEINURIA/ALBUMINURIA

The prognosis of diabetes and microalbuminuria is not good, and therefore it is quite reasonable to target the treatment to modify the development of microalbuminuria at an early stage of diabetes, as well as control blood pressure in hypertensive diabetics to limit the cardiovascular and renal disease. [23] This can be achieved with good metabolic control and antihypertensive therapy.

1.3.1 Metabolic Control

Studies in experimental animals strongly suggest that improved metabolic control prevents complications and this has been confirmed in humans. The Diabetes Control and Complications Trial (DCCT) in the United States compared standard and intensive insulin therapy in a large prospective controlled trial of young patients with type 1 diabetes. Though the mean blood glucose levels were still 40% above the non-diabetic range, even at that level of control, the risk of progression to nephropathy was reduced by 30% over the seven years of the study. The United Kingdom Prospective Diabetic Study (UKPDS) also compared standard and intensive treatment in a large prospective controlled trial of type 2 diabetes patients. There was a 25% overall reduction in micro-vascular disease end points, and a 33% reduction in albuminuria. [24]

1.3.2 Antihypertensive Therapy

In patients with diabetes, progression to clinical nephropathy can at least be prevented in part with strict metabolic control, but once overt nephropathy develops, metabolic control is questionable to prevent ESRF. [25] In fact, in spite of the encouraging results of the DCCT and UKPDS, the benefits of tight BP control in patients with diabetes exceed the benefits of tight glycaemic control, and extend to the prevention of both macro-vascular and microvascular complications. [24, 26] At that point then, the most important treatment factor is antihypertensive therapy, because this treatment generally reduces/normalizes

the UAER. Indeed, BP control is known to be very important in preventing adverse cardiovascular and renal outcomes in diabetic patients. [27]

Antihypertensive therapy is the most effective treatment in patients with diabetic nephropathy, postponing the development of end-stage renal failure. And among a variety of measures that slow progression of (experimental) renal disease, alleviation of capillary hypertension was found to be the common denominator. [17] Although this effect can apparently be obtained with all anti hypertensives, some meta-analyses have indicated that the beneficial effects of Angiotensin converting enzyme inhibitors (ACEIs) on proteinuria and preserved renal function are greater than with other drugs. [28, 29]

1.3.3 The effect of ACEIs on proteinuria

Renin-Angiotensin System (RAS) antagonists for example ACEIs and Angiotensin II Receptor Blockers (ARBs) preserve kidney function not only by decreasing BP, but also by their anti-proteinuric, anti-fibrotic and anti-inflammatory properties. [30, 31] In adults with diabetic or non-diabetic kidney disease, several randomized trials demonstrate a more effective reduction of proteinuria, usually by 30-40% by ACEIs compared with placebo and/or other anti-hypertensive agents. And this is associated with a significantly reduced rate of renal failure progression in the long term. [32, 33]

ACEIs are the only drugs that have been proven in clinical trials to be effective in preventing progression from microalbuminuria to overt nephropathy. Furthermore they are more effective in diminishing albuminuria at low levels of blood pressure reduction compared with other antihypertensives; this was demonstrated by Kasiske et al in 1993. [28] Ravid et al in the same year also observed the renal protection effect with ACEIs in a multi-center, double-blind, randomized controlled trial that compared the effects of enalapril with placebo over seven years in 94 normotensive type 2 diabetics with micro-albuminuria and normal renal function. [34] Enalapril treatment was associated with stable micro-albuminuria over the seven-year follow-up; whereas micro-albuminuria increased roughly two fold in the placebo group. Subsequently, Kasiske et al again performed another meta-analysis in 1996 involving 2,494 patients and also concluded that ACEIs were uniquely renoprotective. [35]

Furthermore, a patient-based meta-analysis of 1,860 non-diabetic subjects from 11 randomized ACEI versus placebo treatment trials also concluded that ACEIs are more effective than other anti-hypertensive regimens in slowing disease progression and reducing proteinuria. [36] A similar conclusion emerged from the African-American Study of Kidney Disease (AASK) trial in hypertensive African-Americans, in which ramipril proved more renoprotective than the comparator drugs, amlodipine or metoprolol. [37] Also in the BENEDICT study, trandolapril alone or with verapamil combination delayed the onset of micro-albuminuria in more than 40% of patients compared with placebo in hypertensive diabetic patients. The effect of verapamil alone was similar to placebo. This indicates that the apparent advantage of ACE inhibitors over

other antihypertensive agents includes also a protective effect on the kidney against the development of micro-albuminuria. [38]

In comparison with beta-blockers, ACEIs have the advantage that they do not mask the subjective symptoms of hypoglycaemia, nor do they affect the serum lipid profile. [39]
Also in non-diabetics, treatment with ACEIs may delay or prevent the development of congestive heart failure following acute myocardial infarction. It is possible then that diabetics with hypertension stand to receive this additional benefit from ACEIs use. [40, 41]
So with the increase in diabetes cases, it would be important to manage them well with ACEIs to increase their life expectancy and also to reduce expensive health costs to clients, families and the state as a result of the development of end-stage renal failure.

1.4 SCREENING FOR ALBUMINURIA

Because of the deleterious consequences of hypertension on the progression of renal disease and cardiovascular outcomes, an active screening approach should be adopted in patients with all stages of CKD. [42] And as a way to detect this problem early and take the necessary action, there is a recommendation that all patients with diabetes mellitus should be screened regularly for an elevated UAER and should have their blood pressure measured periodically under standardized conditions. [43] This makes it possible to identify patients who are developing microalbuminuria. The American Heart Association also emphasizes the importance of recognizing CKD as one of the major risk factors for

CVD and recommends that measurement of urinary albumin excretion and estimation of GFR be included in the evaluation of patients with or at high risk for CVD. [44]

Furthermore J. E. Siegel et al (1992) in their work about cost effectiveness of screening and early treatment quoted WHO's advice that patients with microalbuminuria should be screened for UAER and hypertension more often and should also be screened for other late diabetic complications. And if blood pressure is found to be increasing over time, then anti-hypertensive treatment should be given. This WHO approach then seems to recommend a programme that would increase cost for the healthcare system. But clinical studies to analyze the cost/benefit effectiveness of this approach shows that the treatment costs of ESRF by dialysis or renal transplantation are very high compared with screening and treatment costs to prevent the development of ESRF. [45] Furthermore with a treatment effect of 33 to 67%, median life expectancy increases by 4 to 11 years, and the need for renal transplants or dialysis decreases by 25 to 70%. [46, 47]

1.5 AIM AND OBJECTIVES

1.5.1 Aim

The aim for this study was to determine the level of use of Angiotensin Converting Enzyme Inhibitors (ACEIs) and renal function checks in diabetic patients undergoing treatment at the Holy Family Hospital at Berekum.

1.5.2 Objectives

- To determine the percentage of diabetic patients on ACEIs
- To find out whether ACEIs are used for their antihypertensive and/or nephroprotective properties in such diabetic patients
- To determine the level of renal function checks in diabetic patients

CHAPTER TWO

METHODOLOGY AND RESULTS

2.1 METHODOLOGY

2.1.1 Study Population

This comprised diabetic patients attending clinic on Tuesdays at the Holy Family Hospital, Berekum from 24th July to 25th September, 2007.

2.1.2 Data collection

Data for the study were obtained from:

(a) Information from patients' folders

(b) Questionnaire for clinicians

(a) Data from Patients' Folders

The folders of all diabetic clients who visited the diabetic clinic at the hospital on Tuesdays from 24th July to 25th September, 2007 were collected for this study. In all 335 folders of diabetic clients were studied. A retrospective study was then carried out for each patient from the time he/she was diagnosed as diabetic.

Information gathered from each patient's folder included;

- Patient personal data e.g. name, sex, age etc.
- Diagnosis date
- Type of diabetes
- Presence of hypertension
- Use of ACEI
- Period of ACEI use
- Urine albumin check and frequency
- Level of urine albumin

(b) Questionnaire for clinicians

A questionnaire to know the acceptability or otherwise of ACEI use among clinicians in diabetics was developed and distributed to the clinicians at post at the hospital. The format of the questionnaire is set out in the Appendix.

2.1.3. Inclusion Criteria

- All diabetic patients, both normotensives and hypertensives.
- Both type 1 and 2 diabetics.

2.1.4. Exclusion Criteria

- Diabetic patients on diet management only

2.1.5 Data Analysis

The data was analyzed by means of Microsoft Excel Templates and SPSS 16.0 windows.

2.2 RESULTS

2.2.1 INFORMATION FROM PATIENTS' FOLDERS

2.2.1.1 Sex Distribution

Of the 335 clients, 110 (32.8%) were male and 225 (67.2%) were female. (Fig 2.1)

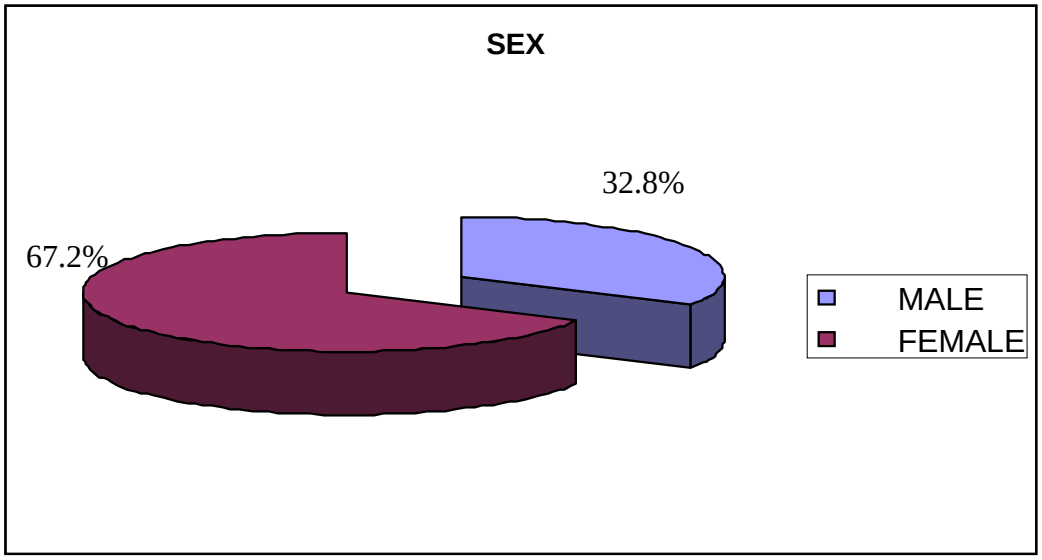

Fig 2.1 Sex distribution

2.2.1.2 Age Distribution

Only one person was below 20 years, with 11 people (3.3%) ranging from 20 to 30 years. 26 patients (7.8%) aged between 31 and 40 years, and 71 people (21.2%) fell between 41 and 50 years. The age group with the highest number was in the 51 – 60 brackets, with 88 people making up 26.3% of the study population. Those between 61 and 70 years were 71 (21.2%), with 67 people (20%) being older than 70 years. (Fig. 2.2)

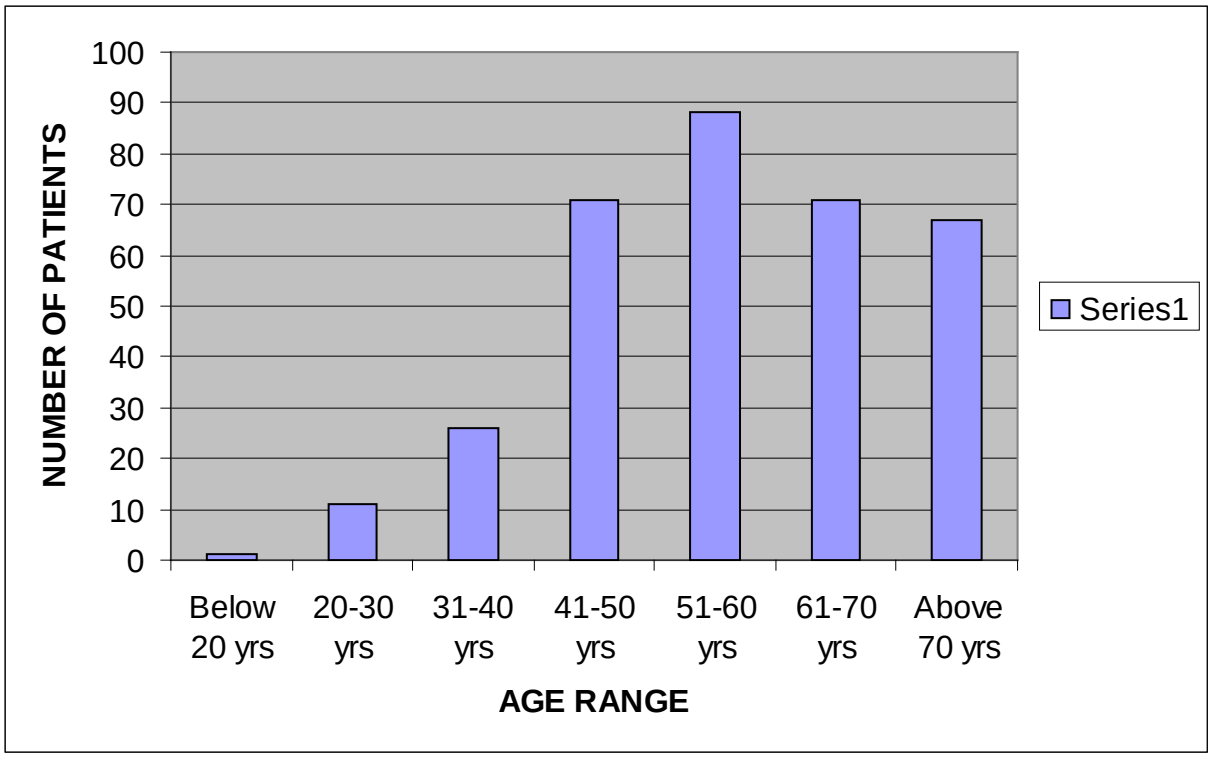

Fig 2.2 Age distribution

2.2.1.3 Sex and Type of diabetes

Type 2 diabetes cases were 273 (81.5%), and Type 1 cases were 62 (18.5%) of the study population. (Fig. 2.3)

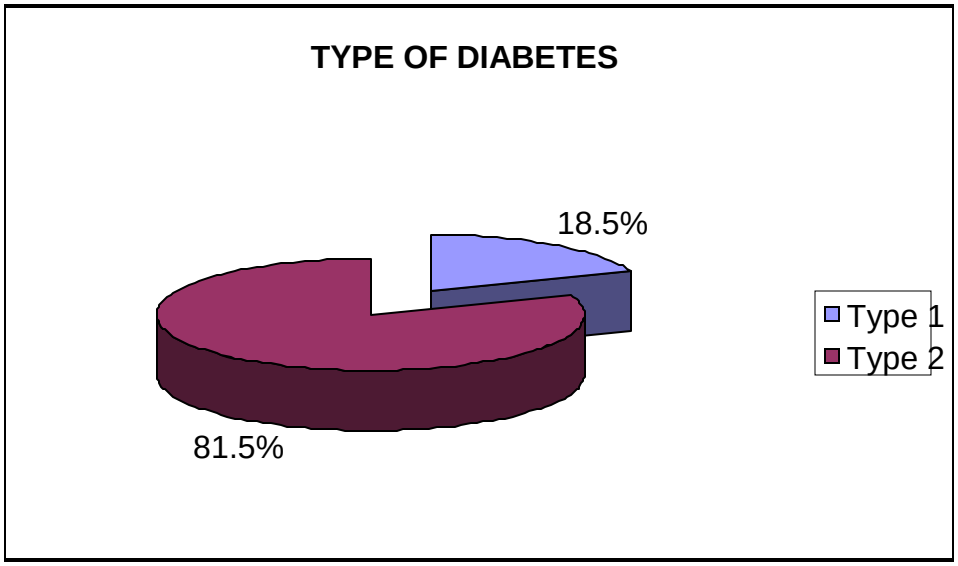

Fig 2.3 Type of diabetes

For the type 1, females constituted 56.5% whilst males constituted 43.5%. Also more females (69.2%) had type 2 than their male counterparts (30.4%).

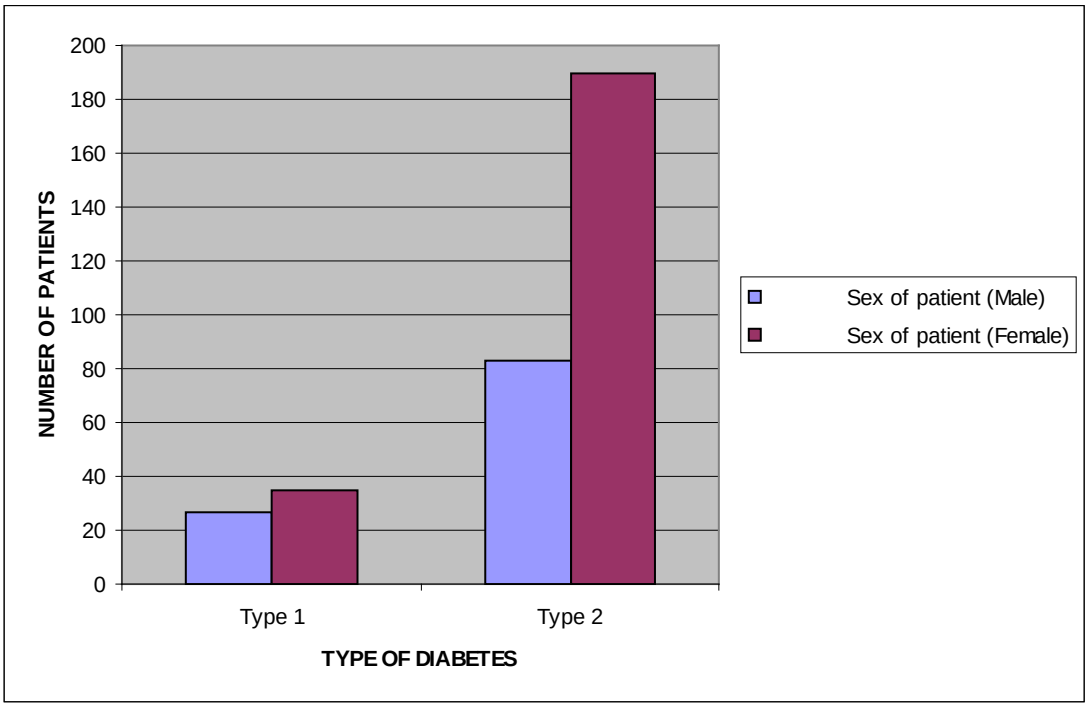

Fig. 2.4 Sex and type of diabetes

2.2.1.4 Duration of condition

62 (18.5%) patients had lived with the condition for less than a year and those who had lived with it for between 1 and 2 years were 98 (29.3%). 96 people (28.7%) have lived with the condition for 3 to 5 years, 50 people (14.9%) for 6 to 10 years, and 28 people (8.4%) for 11 to 15 years. Only one person has had the condition between 16 and 20 years, and none among the study population has lived with the condition for more than 20 years. (Fig 2.5)

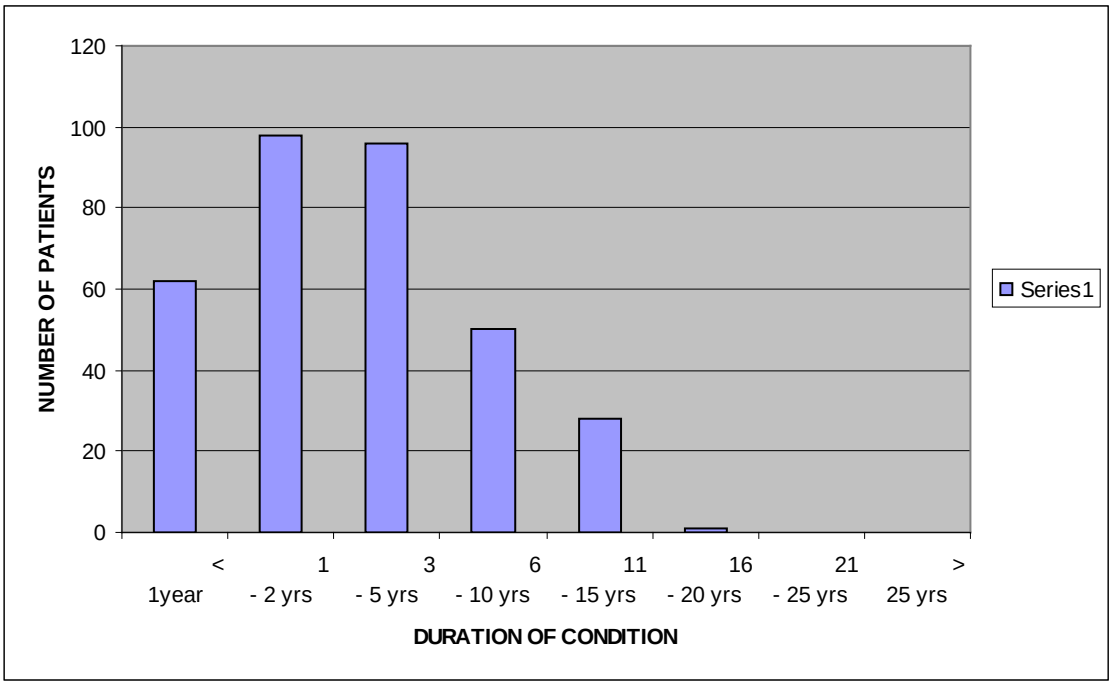

Fig 2.5 Duration of condition

2.2.1.5 Type of diabetes and the age groups

The one person under 20 years old with diabetes had type 1, so also did 8 out of the 11 in the 20-30 years group. The numbers however increased for the type 2 and decreased for type 1 from age 31 upwards, with those above 70 having more (89.6%) type 2 cases than type 1. (Fig 2.6)

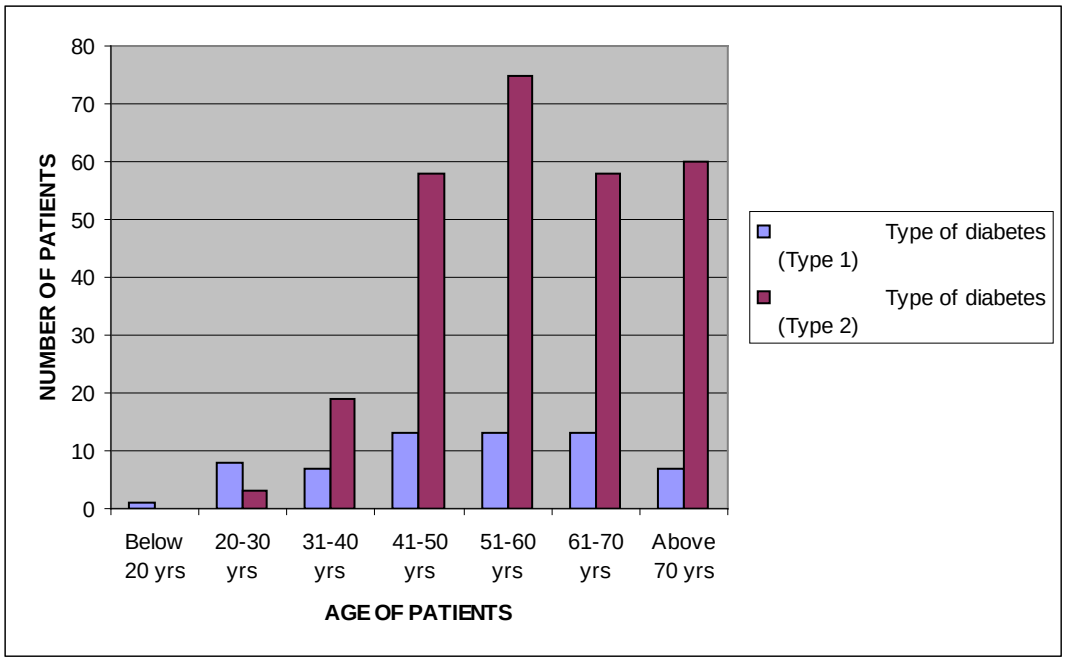

Fig 2.6 Diabetes and Age groups

2.2.1.6 Hypertensive Status of patients

Of the 335 diabetic patients in the study, 172 (51.3%) of the study population were hypertensive and 163 (48.7%) were normotensive. (Fig 2.7)

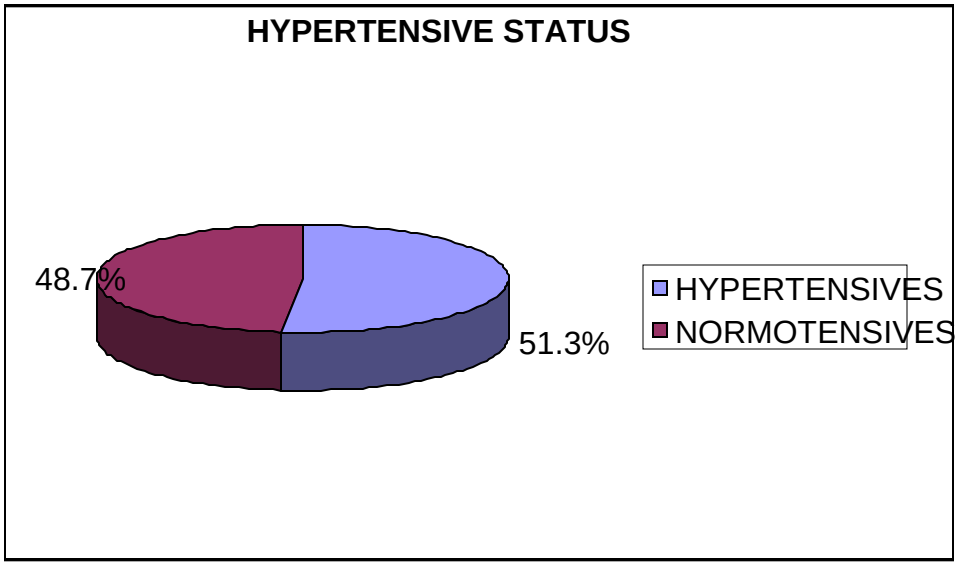

Fig 2.7 Hypertensive status of patients

2.2.1.7 Distribution of hypertension among the ages

No patient below 20 years had hypertension, with only 5 people (out of the 172) below 40 years having hypertension. Hypertension increased from the 41-50 year group, with a marked increment from age 51. (Fig 2.8)

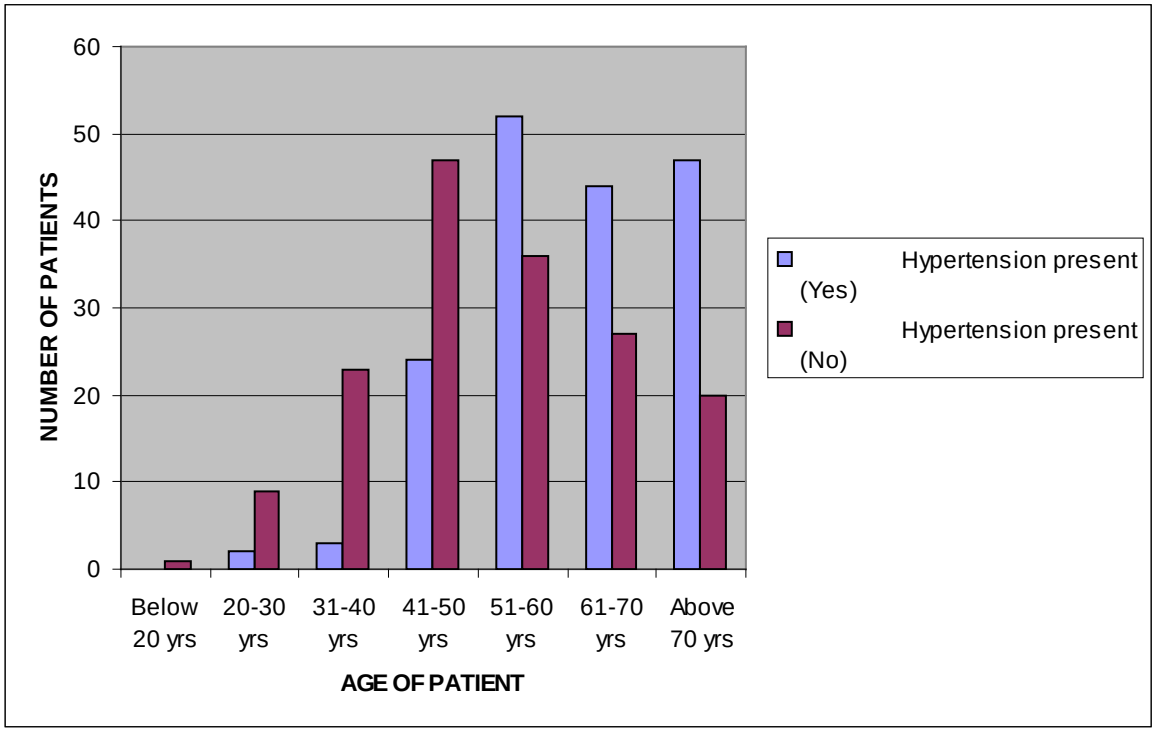

Fig 2.8 Distribution of hypertension among the ages

2.2.1.8 Sex and Hypertension

121 female patients (70.3%) and 51 (29.7%) male patients respectively had hypertension. Among the sexes however, 53.8% of females and 46.4% of males were hypertensive. (Fig 2.9)

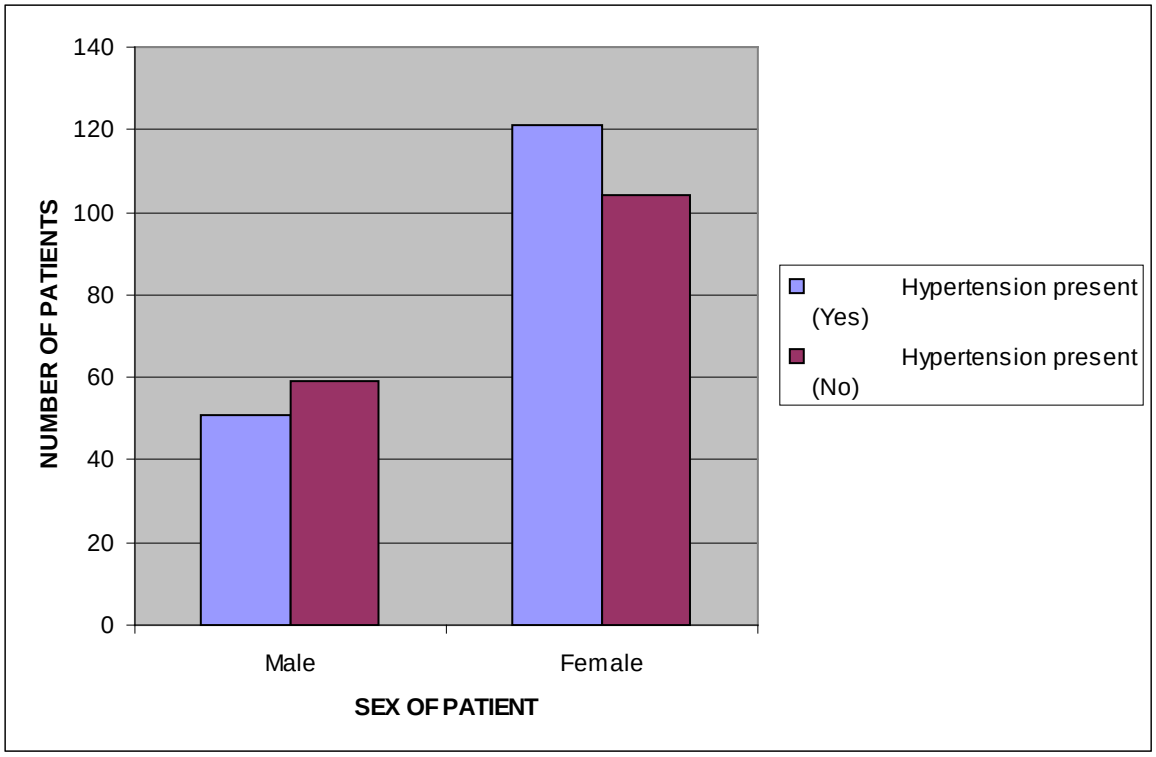

Fig 2.9 Sex and hypertension

2.2.1.9 Patients receiving ACEI and the treatment period

Of the 335 patients, only 56 (16.7%) were given that treatment, whilst 279 people (83.3%) did not receive it. (Fig 2.10) Also only 2 out of the 56 patients given the ACEI were normotensive, with the remaining 54 being hypertensive. (Fig 2.11)

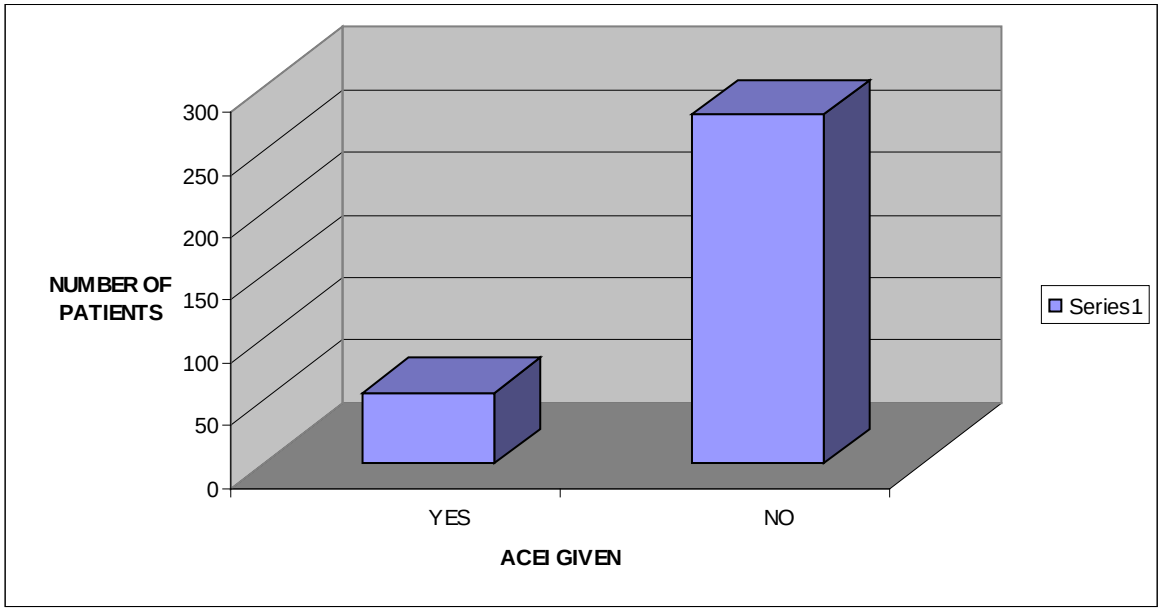

Fig 2.10 Patients receiving ACEI

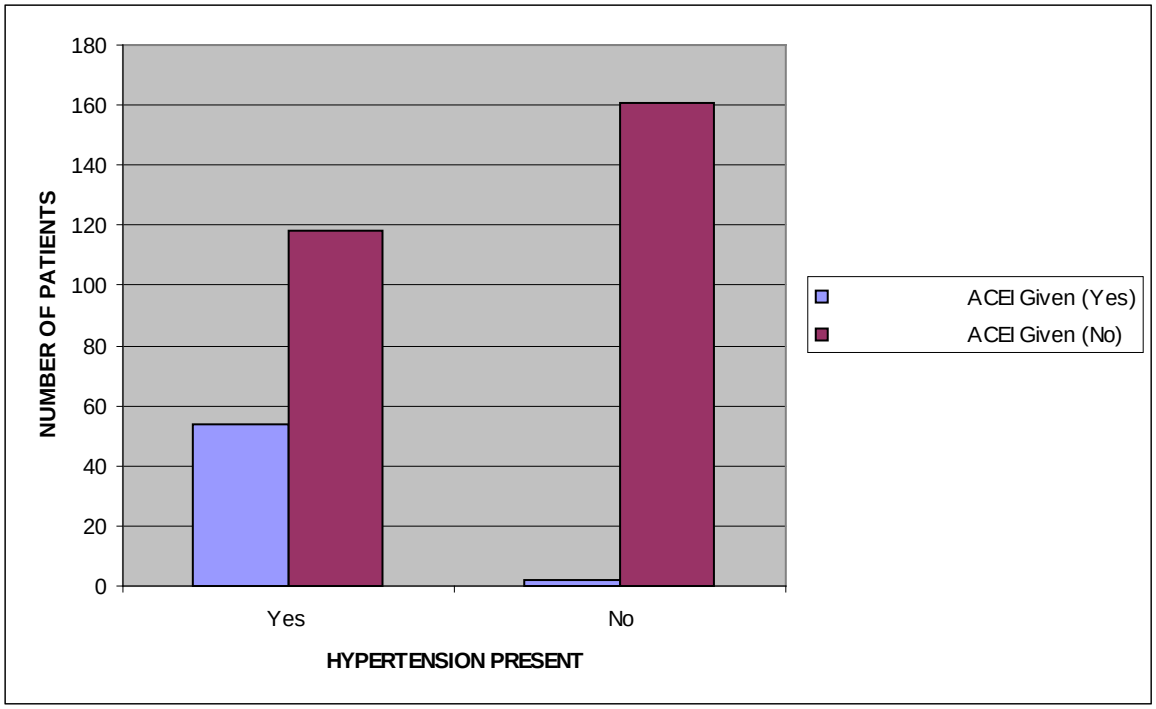

Fig 2.11 Hypertensives and Normotensives on ACEI

For those on ACEI, only 3 patients (0.9%) were on the medicine for 1 to 3 years. It was prescribed for 7 to 12 months for 5 patients, 4 to 6 months for 7 patients, 2 to 3 months for 28 patients and a month for 12 patients. (Fig 2.12)

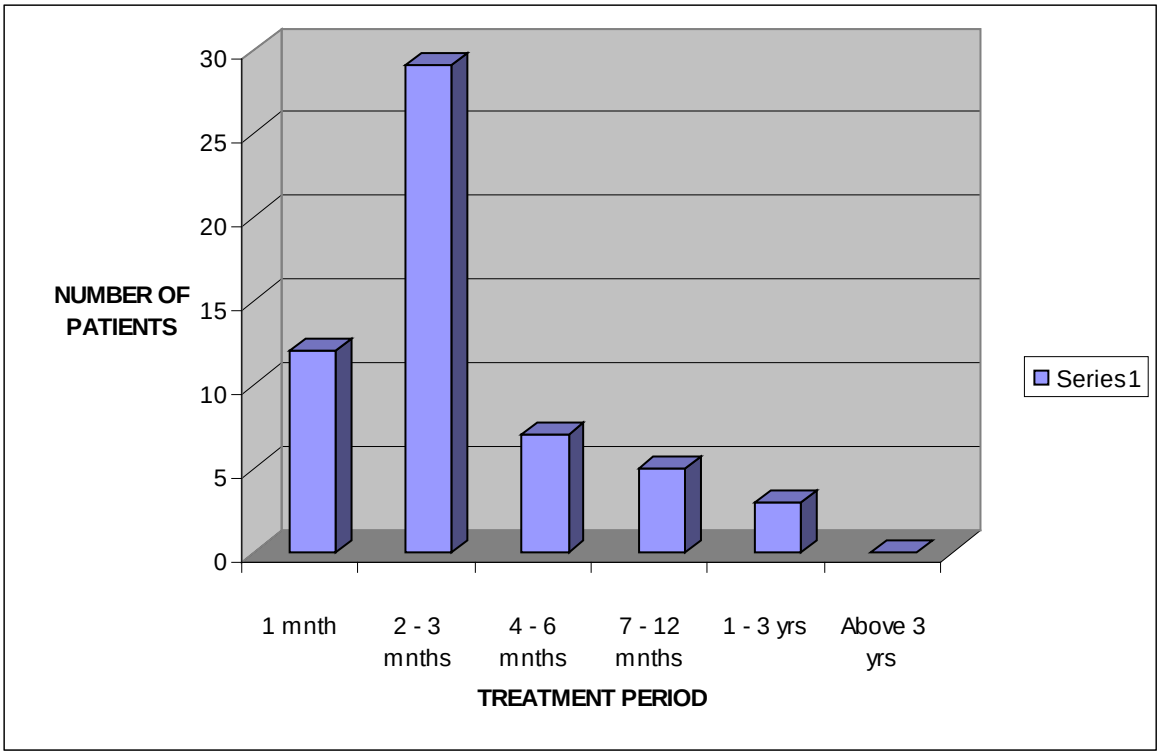

Fig 2.12 Treatment period on ACEI

2.2.1.10 Frequency of Renal Function Tests

94 patients (28.1%) out of the 335 had their renal function checked, with the remaining 241 patients (71.9%) not having theirs done. (Fig 2.13) And of the 94 patients, 80 (85.1%) had it checked once, 11 (11.7%) twice, 2 (2.1%) three times. Only one person had his checked four times. (Fig 2.14)

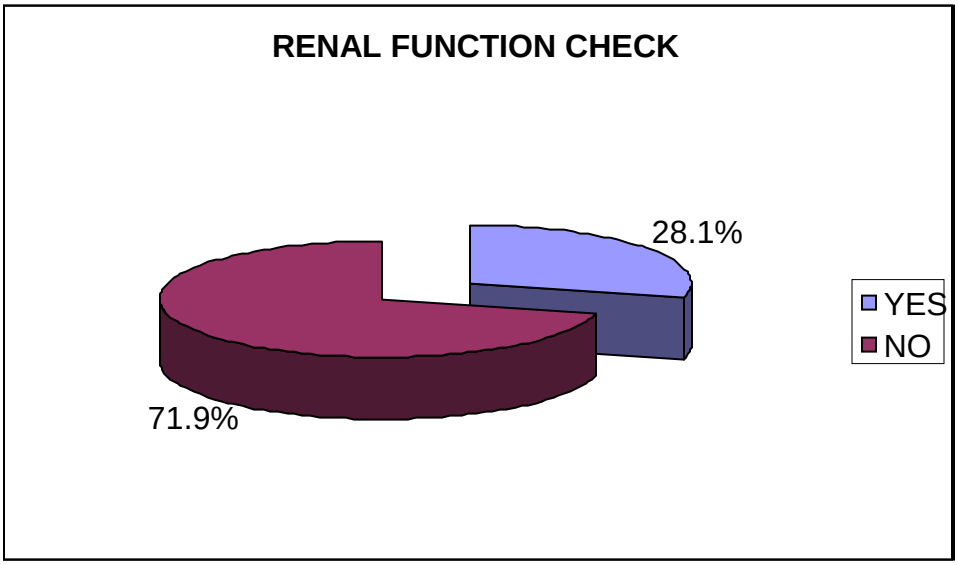

Fig 2.13 Renal function tests in patients

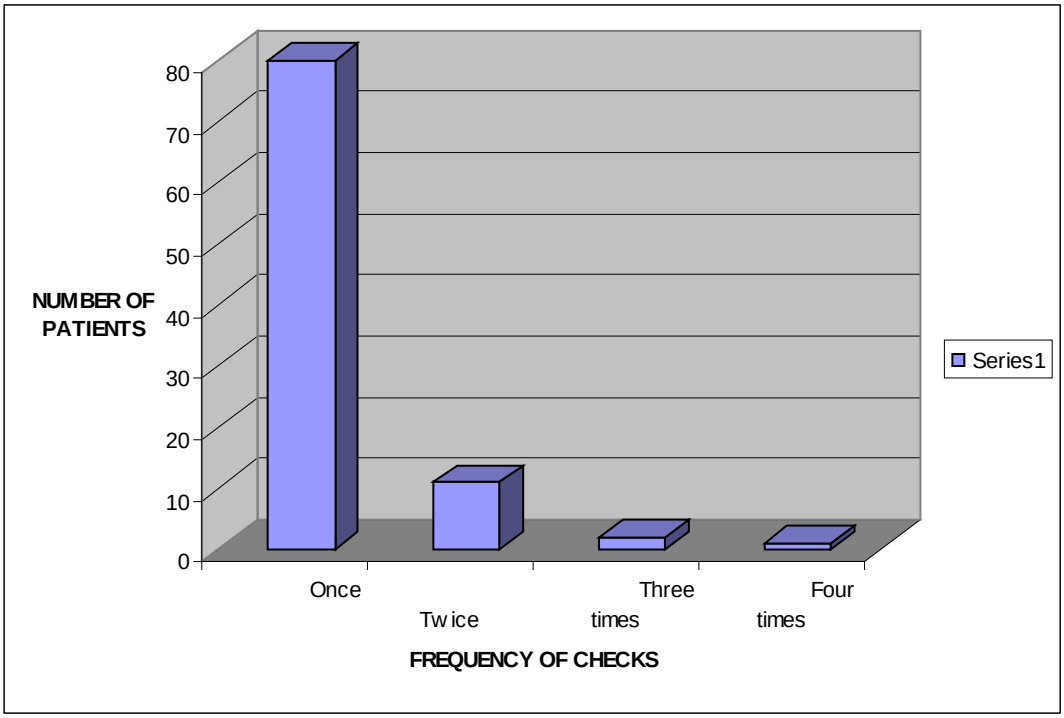

Fig 2.14 Frequency of renal function tests

2.2.1.11 Urine albumin check and hypertension

Out of the 172 patients who had hypertension, urine albumin was checked in 41 (23.8%) of them leaving the remaining131 patients. However in the 163 patients without hypertension, urine albumin was checked in 53 (32.5%) of them. (Fig 2.15)

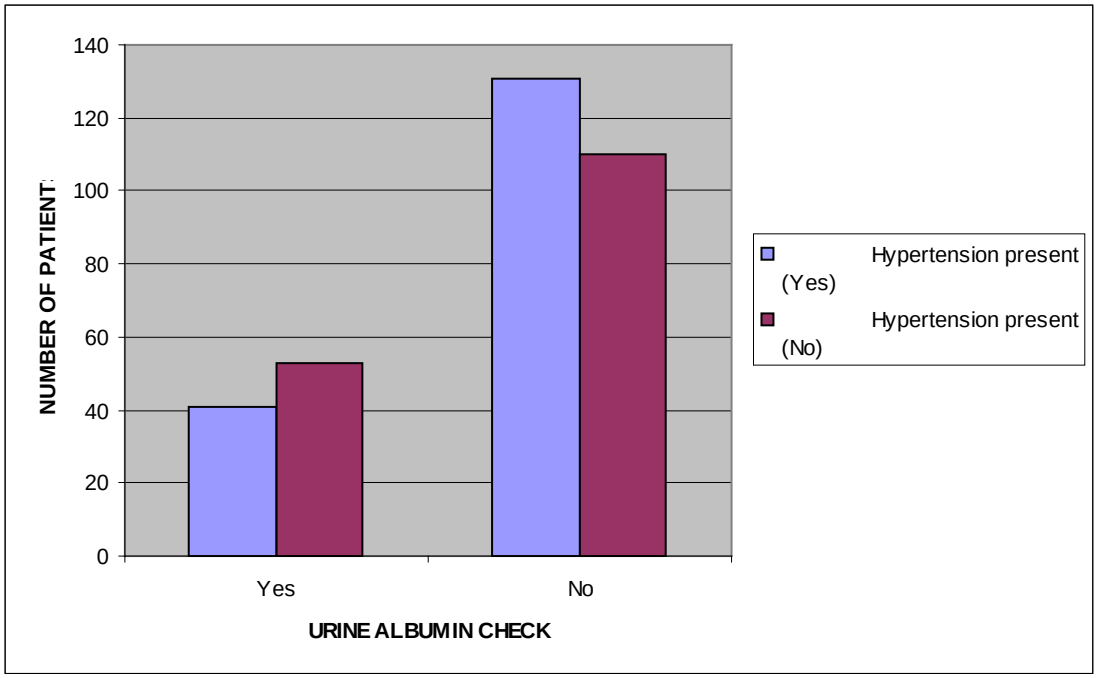

Fig 2.15 Urine albumin check and hypertension

2.2.1.12 Presence of Urine Albumin and Albumin concentration

Out of the 94 patients screened, 19 (20.2%) of them had urine albumin and 75 people (79.8%) had no albumin in their urine. (Fig 2.16) 7 out of the 19 patients had trace level of albumin; 8 had 1+ urinary albumin, 2 had 2+, with 2 patients having 3+ albumin level. (Fig 2.17)

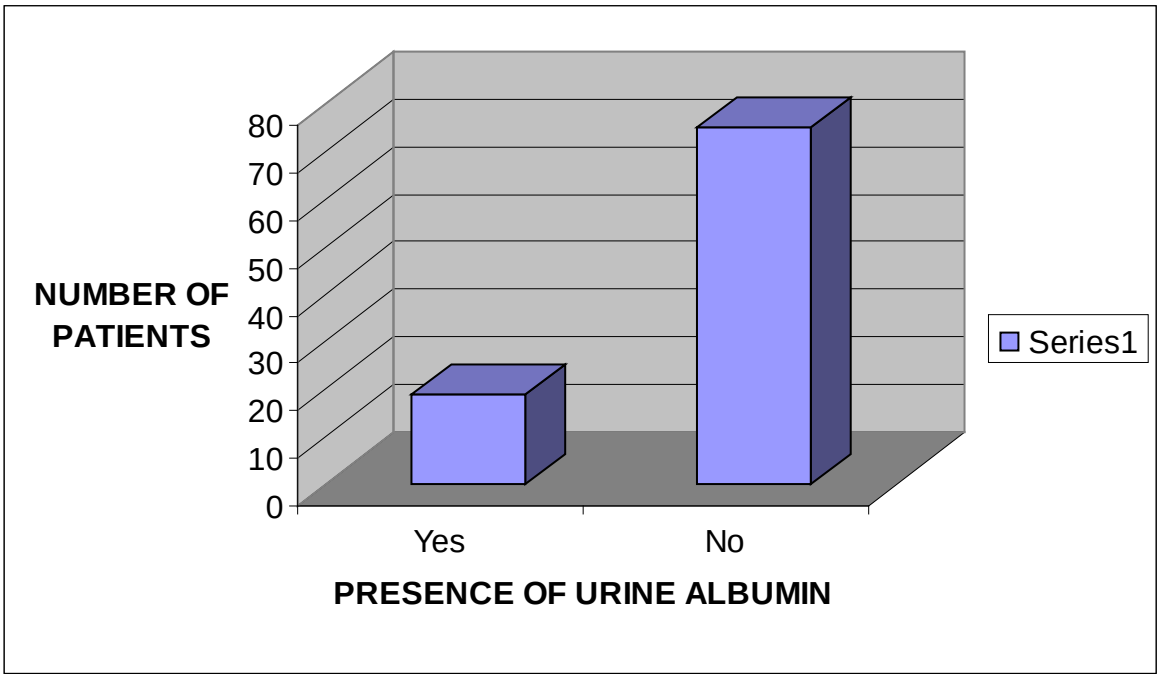

Fig 2.16 Presence of Urine albumin in patients

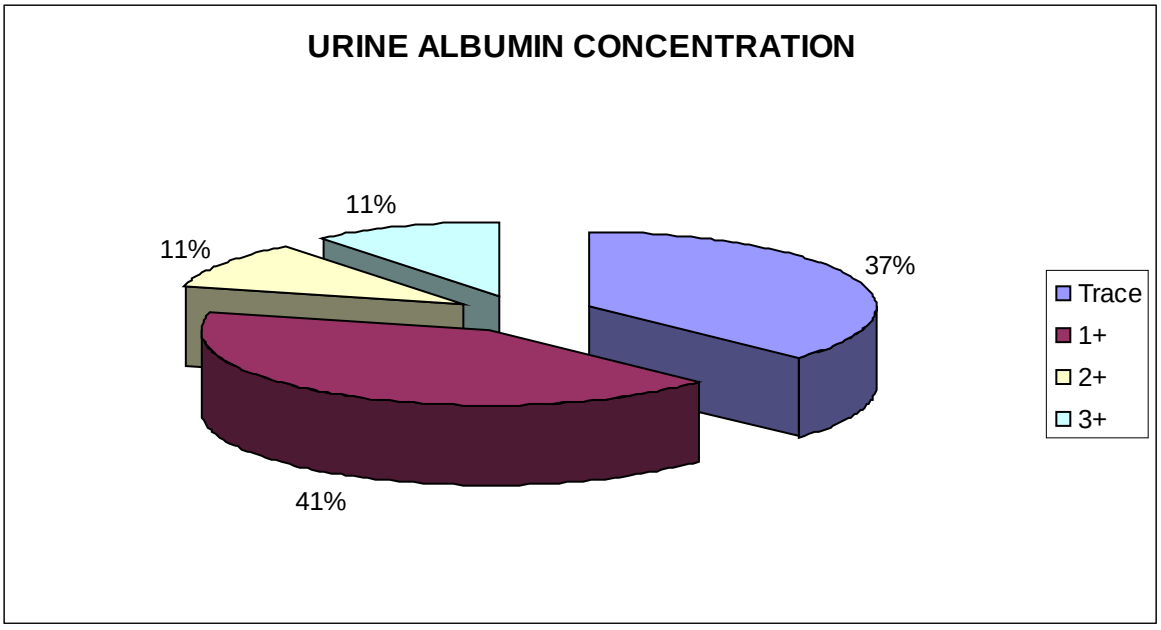

Fig 2.17 Urine albumin concentration

2.2.1.13 Urine Albumin, Hypertension and ACEI Use

It was observed that 9 patients out of the 19 with urine albumin had hypertension and 10 had no hypertension. Also those without urine albumin but who had hypertension were 33, and those without hypertension were 43. (Fig 2.18)

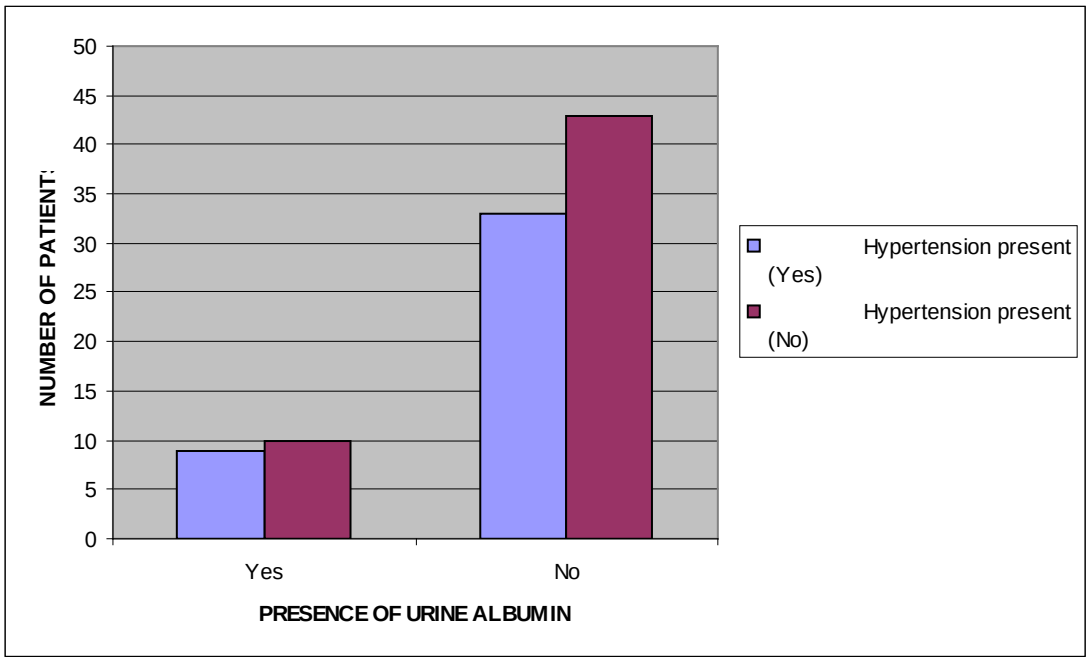

Fig 2.18 Urine albumin and hypertension

Out of the 19 patients with urine albumin, ACEI was prescribed for 5 (26.3%) of them excluding the remaining 14. And for the patients without urine albumin, 14 of them were prescribed with the ACEI, whilst 62 of them were not given the ACEI. (Fig 2.19)

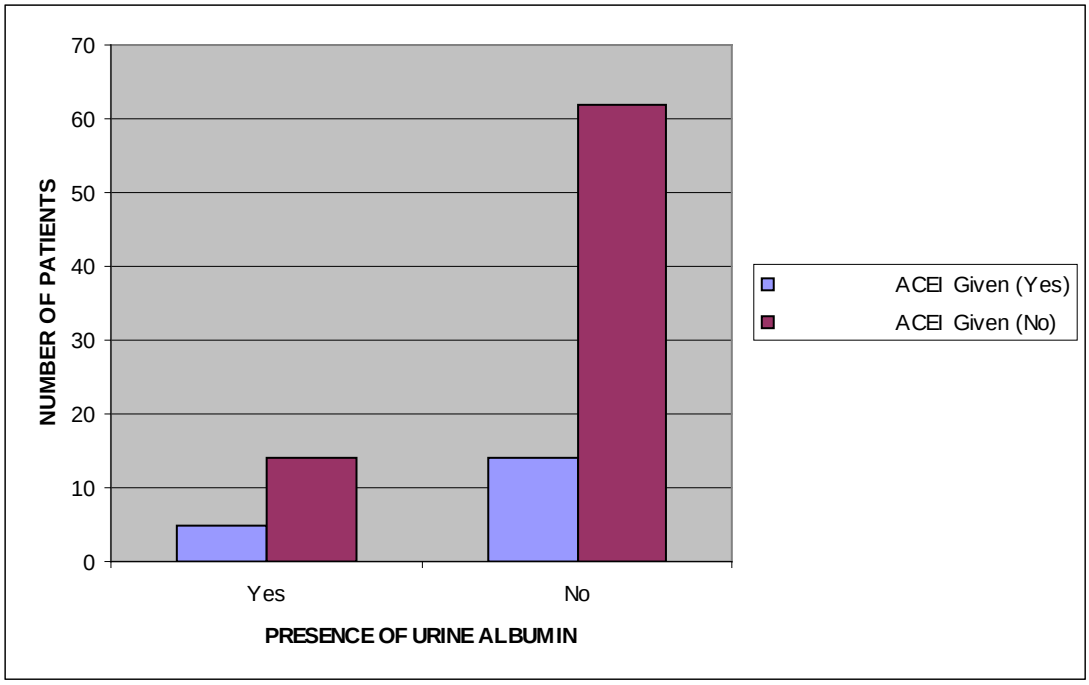

Fig 2.19 Urine albumin and ACEI use

2.2.2 RESPONSE TO QUESTIONNAIRE FROM CLINICIANS

In all nine clinicians at the Hospital responded to the questionnaire. One was a senior Medical Assistant, three were House officers, two were Medical Officers and three were Senior Medical Officers.

Five of them had been in the clinical practice for 1 to 5 years, two had practiced between 11 and 20 years and two had practiced for more than 20 years. As to the number of years of practice at the Holy Family Hospital, Berekum, aside the three house officers and one medical officer, the rest had been practicing at the hospital for three to twenty years.

2.2.2.1 Diabetic Complications

Nephropathy, neuropathy, hypoglycaemia and retinopathy were the common diabetic complications encountered in their clinical practice. Other complications observed were hyperglycaemia, diabetic ketoacidosis (DKA), necrotic toes, infected wounds and hypertension.

2.2.2.2 Antihypertensives used in diabetic hypertensives

Concerning the antihypertensives used to manage increased blood pressure in diabetic patients, 7 of the clinicians used ACEIs in combination with other antihypertensives, and 7 used Calcium channel blockers with others. One clinician used beta-blocker, and one used diuretic in combination with other antihypertensive drugs.

2.2.2.3 Use of ACEIs in diabetic patients

All the 9 respondents said they used ACEIs in managing their diabetic clients, and the following were the reasons for using them:

- to reduce the risk of nephropathy
- as a nephroprotective with some cardiac modeling effect
- to offer protection to the kidneys
- to decrease the incidence of coronary events
- reduction in the frequency of stroke
- in elderly patients
- for those not responding to Nifedipine and Esidrex
- as renal protective in clients with normal renal function test
- delays the onset of renal complication/nephropathy
- decreases the progression of renal dysfunction and retinopathy
- for those not responding to Nifedipine and Propranolol

2.2.2.4 **ACEI Use in Hypertensive and Normotensive patients**

As to the use of ACEIs in hypertensive diabetics only, 5 clinicians responded positively to it whilst 4 of them said they did not use them only in such patients. The reasons given by those who prescribed them for hypertensive diabetics only were the same as in sub-section 2.2.2.3. (Fig 2.20) For their use in normotensive patients, 3 prescribed them and 3 did not. One clinician said he prescribed them sometimes but two did not respond to it. (Fig 2.21)

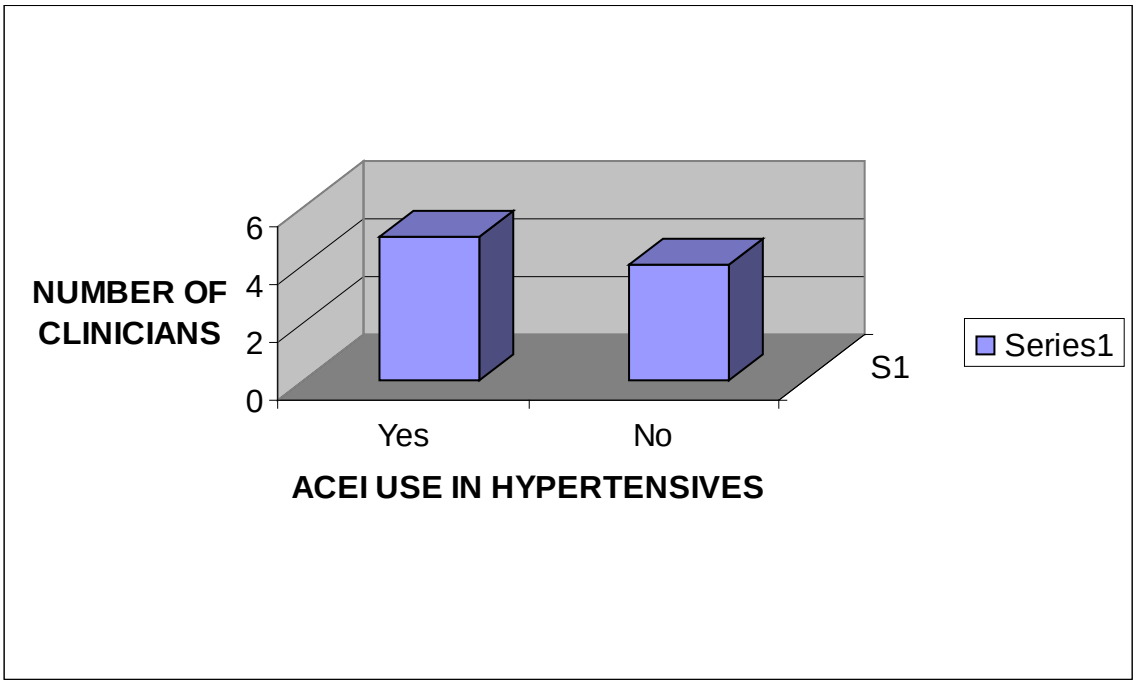

Fig 2.20 Use of ACEIs in hypertensive diabetics by clinicians

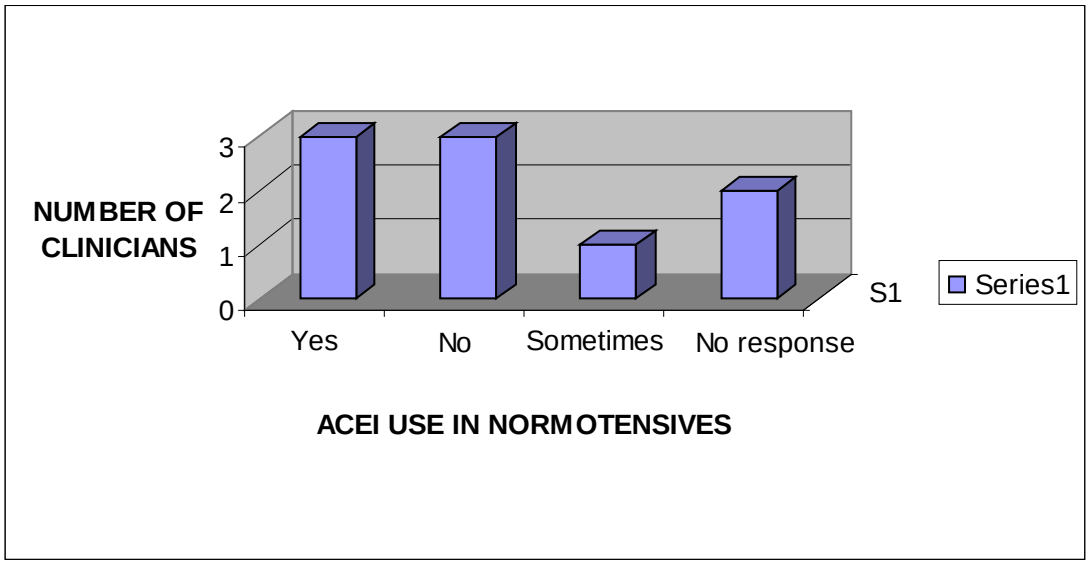

Fig 2.21 Use of ACEIs in normotensive diabetics by clinicians

And for those who prescribed them, their reasons were;

- normotensives with evidence of renal dysfunction or visual impairment
- for renal protection
- ACEIs protect kidneys generally; diabetes mellitus patients would develop renal complication and hence the use of ACEI

Out of the three who did not prescribe them, only one person gave a reason as not seeing any protocol for ACEI use in normotensives; the others did not give any reasons.

2.2.2.5 Screening for Albuminuria

Eight out of the nine clinicians said they screened their patients with only one not doing it. And for him his reason for not checking for the urine albumin was due to lack of logistics. (Fig 22)

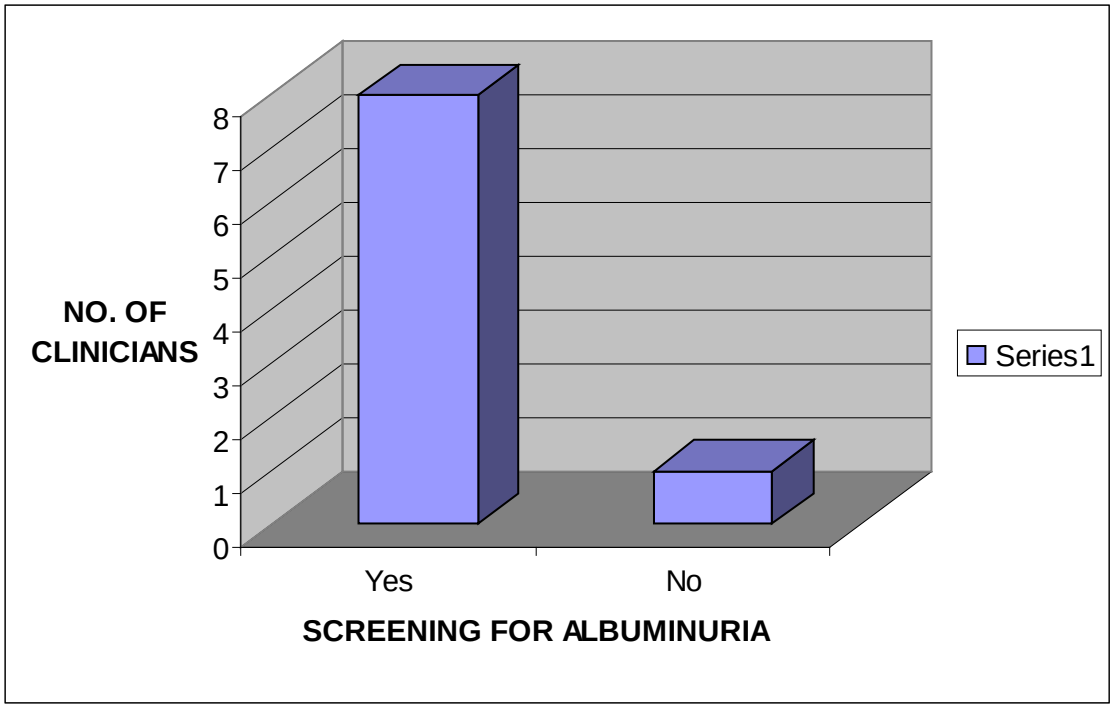

Fig 2.22 Screening for albuminuria by clinicians

For those that checked it, the following were the reasons they gave;

- to rule out kidney involvement and problems
- to detect any onset of nephropathy
- albuminuria is a well known complication in long standing disease
- to assess renal function

- albuminuria is early presentation of renal complication
- to protect renal function and to evaluate kidney state to rule out renal complications

CHAPTER THREE

DISCUSSION, CONCLUSION AND RECOMMENDATIONS

3.1 DISCUSSION

From the results, 67.2% of the study population was female as compared to the 32.8% male (Fig.2.1) indicating that the incidence of diabetes at Holy Family Hospital, Berekum was about twice in female as in the male population. Patients older than 51 years constituted the majority (67.5%) of the study population, and that supports the fact that the incidence of the disease, particularly type 2, increases with age. [5]

3.1.1 Sex and type of diabetes

Considering the type of diabetes, 81.5% had type 2 implying that it is more common than type 1 with 18.5% incidence. (Fig 2.3) The prevalence rate of the type 2 diabetes thus compares well with the prevalence rate of over 75% of type 2 cases quoted by J.A. Cantril et al, [5] and that by P. Zimmet in his study. [54] Relating type of diabetes to the sex of patients, more males (43.5%) had type 1 than type 2 (30.4%), and more females on the other hand had more type 2 cases (69.6%) than type 1 cases (56.5%). (Fig 2.4) But in general more females, 225 (67.2%) had diabetes than males with 110 (32.5%) cases. The current rise in diabetic cases has been accompanied by a similarly drastic increase in obesity, [48] and with women being more prone to obesity than men in the general population; it may be the reason for this. In fact compelling scientific evidence indicates that lifestyle modification effectively prevents or delays the occurrence of type 2 diabetes

and clinical trials have also demonstrated that success in the treatment of obesity leads to the prevention of type 2 diabetes. [48]

3.1.2 Duration of condition

It was observed from the results that only one person had lived with the condition for between 16 and 20 years, with nobody having the condition more than 20 years. (Fig 2.5) The majority of the people (76.4%) had been diagnosed as diabetic for the past five years, and that could be due to increased awareness about the disease over the period and/or change in lifestyle of Ghanaians leading to increased rate of the condition. The 2008 Annual Report of the Holy Family Hospital, Berekum testifies to this increased trend, [49] and it is well collaborated by the World Health Report 2003. [1]

Another interesting observation made was about the number of people who had been diagnosed for the past two years; they formed about 50% (47.8%) of the study population. The advent of the National Health Insurance Scheme in 2005 brought about an increase in many cases seen at the hospital. And those with diabetes who could not probably afford the cost of management before that time had to take advantage of the scheme to attend clinic.

3.1.3 Hypertension and ACEI use

The use of ACEI in diabetic patients was very low – 16.7% as compared to 83.3% of patients in whom it was not used. Considering the fact that ACEIs are very useful in the management of such patients, it means their use is not being well explored to the benefit of the patients and this is not encouraging.

Of the 56 patients (16.7%) given the ACEI, 54 of them had hypertension with 2 being normotensive. (Fig 2.11) The use of these drugs in the hypertensive diabetics is in the right direction since at this point of increased blood pressure, antihypertensive therapy with ACEI is the most effective treatment to delay the onset and/or progression to nephropathy [28, 29] and offers much benefit to the patients.

This approach is commendable but the number of patients offered was small. In all, there were 172 diabetic patients with hypertension and if only 54 (31.4%) of them received ACEI (as mono-therapy and in combination with other anti-hypertensives) then it means the majority of them (68.6%) did not get the treatment and were therefore not benefiting from its advantages. That was in sharp contrast with the 62.2% of ACEI mono-therapy and 83.5% combination therapy usage among diabetic patients in the "Patterns of Antihypertensive Therapy" study conducted by Johnson and Singh in 2005. [50] This situation placed the patients who were not prescribed with the ACEI at risk of developing nephropathy earlier. Hypertensive diabetic individuals have a 7-fold greater risk of progression to ESRD, and a 2 to 4-fold vascular complications. Reduction of high blood pressure reduces cardiovascular morbidity and mortality, and delays the progression to

ESRD, [51] and this effect is better achieved with ACEIs and ARBs. Though those who did not receive the ACEI had other antihypertensives like Nifedipine, Propranolol, and Hydrochlorothiazide, some meta-analyses have indicated that the beneficial effects of ACEIs on proteinuria and preserved renal function are greater than with other antihypertensive drugs. [29, 52, 53] Evidence from the HOPE trial also suggested their cardiovascular protection benefit. [54]

In spite of the advantages for prescribing ACEIs for diabetic patients with or without hypertension, 118 out of the 172 hypertensive diabetics however were not given any ACEI. In the questionnaire administered however, all the nine clinicians said they used ACEI in managing their diabetic patients, but this did not reflect from the information obtained in the patients' folders. So why then was the prescribing percentage so low?

One Senior Medical Officer commented that though they appreciated the benefits of ACEIs, they did not use them because of the information in literature of poor response of ACEIs in controlling blood pressure in blacks. It is true that black people have reduced plasma renin activity and as a result ACE inhibitors and angiotensin antagonists are less effective in reducing blood pressure in this population. [55] But these drugs are effective in diminishing albuminuria at low levels of blood pressure reduction compared with other antihypertensives, [28] and so at that low level of BP control in that population, their nephroprotective property could still be achieved. Furthermore ACEIs preserve kidney function not only by decreasing BP but also by their anti-proteinuric and anti-fibrotic properties. [31]

3.1.4 The need to use ACEIs

The reason of poor response of ACEIs in black people with hypertension should not deter clinicians from prescribing these drugs for the diabetic patients since there can be good results when the ACE inhibitors are used in combination with diuretics because of synergism. [56] An extensive review by Townsend and Holland and other researchers has reinforced the usefulness of these two drugs together. [57, 58] In addition to the ACEI/diuretic combination, the combination of ACEI with calcium channel blockers also has antihypertensive synergistic activity and able to bring about good reduction in blood pressure. Clinical trials have been carried out extensively with this combination, and results have been shown by Frishman et al that the combination is superior to either agent in reducing blood pressure remarkably with no greater incidence of side effects. [59] Cappucio and MacGregor also demonstrated this combination's ability to markedly reduce blood pressure with different drugs from these two classes. [60]

In fact the use of two or more (multiple) antihypertensive drugs in combination is being increasingly recognized in patients with diabetes. Several well conducted clinical trials indicate that aggressive treatment of hypertension in individuals with diabetes reduces the cardiovascular and renal complications. And combinations of two or more antihypertensive drugs are frequently required to reach the target blood pressure and to improve the cardiovascular and renal outcomes in these patients. Trandolapril/Verapamil SR is an example of this combination required in patients who require more than one drug to reach target BP. [23] Sharma et al in their study in 2007, found that over four

years of follow-up, trandolapril/verapamil SR delayed the onset of microalbuminuria by a factor of 2.1 while verapamil alone had no significant effect. [23] Also Johnson and Singh observed that a majority of pharmacologically treated patients (about 80%) were on two or more antihypertensive agents including ACEI/ARB. [50] Evidence also supports the need for using multiple ant-hypertensive agents rather than mono-therapy to achieve target BP control and greater reno-protection. [61] In addition more data from The Antihypertensive & Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) highlights the frequent need to use multi-drug regimens to treat BP to target levels especially in the diabetic population. [62] It is therefore of necessity to use ACEI as mono-therapy or in combination therapy in this population to offer them greater benefit.

Another issue of much concern was the period the patients were given the ACEI. Only 5.4% (0.9% of the study population) was given the drug for one to three years, with none of them taking it for more than three years. (Fig 2.12) It was prescribed for only a month for 21.4% of the patients, 2-3 months for 51.8% of the patients, 4-6 months for 12.5%, and 7-12 months for 8.9%. The reason for discontinuation after a few weeks and months of treatment was due to the cough and angiodema side effects of the drugs. The benefit of ACEI in nephro-protection is more evident when it is taken for a longer period, and if it was prescribed for one to three years for only 5.4% of the patients, with the rest getting prescriptions for a few months, then it was not encouraging. And in case the side effects of the ACEIs were the reason for stopping treatment, then Angiotensin II antagonists, which do not have these two worrying side effects of the ACEIs should have been substituted to offer uninterrupted benefit for the clients. [63]

3.1.5 Importance of Urine Albumin Tests in Renal Disease

On the issue of urine albumin tests to detect the onset of micro-albuminuria and subsequently nephropathy, the results showed that it was done only in 28.1% of the study population and that was incredibly low. And even for this low figure, as much as 85.1% had it checked only once. 71.9% of the patients never had theirs ever checked, so in case nephropathy was developing, it could not have been identified and treated. The responses from the clinicians in the questionnaire however showed that almost all of them did regularly/periodically check for urine albumin of their clients. And since this did not reflect from the patients' data, it implies that though they were much aware of the usefulness of this test, they were yet to put it into practice. The WHO recommends that all patients with diabetes mellitus should be screened regularly for an elevated urine albumin excretion rate (UAER) to make it possible to identify patients who are developing microalbuminuria. Furthermore those found to have microalbuminuria should be screened for UAER and hypertension more often; and in case blood pressure is found to be increasing over time, then antihypertensive treatment should be given. [(43)] In particular, if there is microalbuminuria in patients with the condition for 5 or more years, UAER should be performed twice a year and BP in such patients should also be checked 2 – 4 times in a year. Those without microalbuminuria should however have theirs checked annually. [(43)]

Though the percentage of patients with positive urine albumin in those tested was low (20.2%), it was quite significant. And if in case a similar trend were to be found in the 240 patients whose urine albumin were not checked, then it meant about 49 patients with albuminuria would not have theirs detected and could go on to develop microalbuminuria, nephropathy and end-stage renal failure without any intervention. And for the patients who had positive urine albumin, only 5 (26.3%) of them were given the ACEI treatment and that was quite low. There is convincing evidence from studies of adults that all proteinuric patients should receive rennin-angiotensin system blockade drugs even if they do not have hypertension. [64] In addition The ACE Inhibition in Progressive Renal Disease (AIPRD) meta-analysis confirmed that proteinuria is a strong risk factor for progression of chronic renal disease and those patients with more severe renal disease benefit most from ACE inhibitor treatment. [65] It is therefore important for clinicians to adopt this guideline to prevent or slow down the development of kidney disease.

Kidney or renal failure is a serious long-term medical condition with the main treatment being dialysis or transplantation and the condition is increasing. Diabetes is the most common cause of ESRD in the United States and many other countries. Patients that have diabetes and are on renal replacement therapy (RRT) have a worse outcome and their management costs a great deal compared with those with other diseases on dialysis. [66] Forecast analysis based on the US Renal Data System and Medicare predicts that by the year 2010, the total number of patients on RRT will double and is expected to increase public expenditure for dialysis to $ 28m/year. [67]

Approximately 1.8m people are treated with RRT which consists primarily of kidney transplantation, haemodialysis and peritoneal dialysis. More than 90% of these individuals that benefit from this therapy live in industrialized countries, while available RRT in developing countries is scarce and null in under-developed areas. [68, 69] Kidney transplantation is not very common in Ghana as dialysis, and these two procedures are very expensive. So if screening and intervention can reduce or prevent this burden, then it is worthwhile to rigorously pursue it for the benefit of the diabetic patients. Wenzel et al in their study "Is screening and intervention for microalbuminuria worthwhile in patients with type 1 diabetes?" established that though it costs to perform UAER and treat with ACEI, the cost/benefit effectiveness of this approach shows that it costs far more to treat ESRF by dialysis/renal transplantation than screening and treatment costs to prevent ESRF from developing. [70] It is therefore important for our clinicians to take advantage of the importance of screening for albuminuria and the effectiveness of the treatment with ACEIs in the diabetic population to prevent or slow down the development of nephropathy and end stage renal failure.

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3.2 CONCLUSION

The results from this study has brought to the fore that only 16.7% of the diabetic population at the Holy Family Hospital, Berekum received ACEI and this was very low. Even among the hypertensive diabetic sub-group, as low as 31.4% was given the ACEI, with only 5.4% of them taking it for between one and three years. Moreover renal function test was performed for only 28.1% of the study population implying that 71.9% of the patients never had theirs checked. Of that number, 20.2% had urine albumin, with 26.3% of the urine albumin patients on ACEI. Clinicians however appreciated the benefits of ACEI use and urine albumin check in diabetic patients, only that they were not applying them much in practice.

3.3 RECOMMENDATIONS

Diabetes continues to be a public health problem and many people are being affected by it these days. It is important therefore to adopt strategies that would bring greater benefits to the diabetic patients so that they would live longer and contribute to the good of the community. And on the basis of observations and inferences, the following are recommended:

(1) The Clinical and Social Pharmacy Department of the Faculty of Pharmacy and Pharmaceutical Sciences, KNUST should assign this topic to some of its research students and the study should be undertaken at other hospitals in the country so as to have a broader look at the issue.

(2) The Holy Family Hospital management should organize an orientation for the clinicians at the hospital on the WHO recommendations in the management of diabetic nephropathy so as to offer greater benefit to the diabetic clients. At that forum, the research findings made in this study should be disseminated for them to appreciate the issue very well. This recommendation states that;

(i) All patients with diabetes mellitus should be screened regularly for an elevated UAER and should have their blood pressure measured periodically under standardized conditions. This makes it possible to

identify patients who are developing microalbuminuria and/or increasing blood.

(ii) Patients with microalbuminuria should be screened for UAER and hypertension more often, and should also be screened for other late complications. And if blood pressure is found to be increasing over time, antihypertensive treatment should be given.

(3) A physician specialist with special interest in managing diabetes should be invited by the Hospital Management or Medical Director as a visiting consultant to interact with the clinicians from time to time to enable them acquire and apply the skills in managing the diabetic clients more effectively.

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APPENDIX

QUESTIONNAIRE TO DETERMINE THE USE OF ACEIs IN DIABETICS AMONG CLINICIANS

1. Professional background

☐ Nursing Officer ☐ Medical Assistant

☐ House Officer ☐ Medical Officer

☐ Senior Medical Officer ☐ Specialist

2. How long have you been in clinical practice?

☐ Less than 1 year ☐ 1-5 years ☐ 6-10 years

☐ 11 – 20 years ☐ Above 20 years

3. Which of the complications of diabetes do you often encounter in your practice? …….

4. What are the antihypertensives of your choice for managing hypertension in diabetics? …….

5. Do you use ACE inhibitors in the management of your diabetic clients?

☐ Yes ☐ No

6. If Yes, What are your reasons?

……
……

7. If No, what are your reasons?

……
……

8. If yes to (5), do you use them in;

(a) Hypertensive diabetics only? ☐ Yes ☐ No

or

(b) In normotensive diabetics as well? ☐ Yes ☐ No

9. If Yes to (8a), what are your reasons?

……
……

10. If No to (8a), what are your reasons?

……
……

11. Do you regularly/periodically screen your diabetic clients for micro-albuminuria/macroalbuminuria? ☐ Yes ☐ No

12. If Yes, why?

……...
……...
……...

13 If No, why?

……..
……..
……..