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THE USE OF ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITORS AND ANGIOTENSIN-II RECEPTOR BLOCKERS (ARB) AS MONOTHERAPY ANTIHYPERTENSIVE AGENTS IN SUDANESE PATIENTS: A PRELIMINARY STUDY ON EFFECTIVENESS AND PRESCRIBING PATTERNS

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ABSTRACT

Introduction: It is increasingly apparent that black hypertensive individuals differ substantially from their white counterparts in several important aspects. Both the prevalence and severity of hypertension are greater in blacks compared with whites, leading to risks for blacks of the secondary complications of hypertension. Patients of African ancestry as a group respond better to calcium blockers and diuretics, while the response to β-adrenergic blockade and inhibition of the angiotensin converting enzyme is attenuated. A number of studies has demonstrated that black hypertensive patients may respond differently to antihypertensive drugs especially ACE inhibitors than white hypertensive patients; therefore this study was conducted to assess the use of angiotensin converting enzyme inhibitors and angiotensin-II receptor blockers as antihypertensive agents in Sudanese population and to identify the degree of blood pressure control among patients using ACEIs and ARBs. **Methodology:** A case finding study was done by using pre-tested, pre-validated questionnaire. **Results:** Angiotensin Converting Enzyme inhibitors (ACEIs) and Angiotensin-II Receptor Blockers (ARBs) were found to be associated with controlling the diastolic blood pressure (DBP) of the patients enrolled in this study. It was found that the total number of patients controlled

was 75 (79%) patients out of 95. Out of 55 of the patients who were using ARBs 39 (71%) patients were controlled and 16 (29%) patients were uncontrolled; whereas those who were using ACEIs (n=40) 36 (90%) were controlled and 4 (10%) patients were uncontrolled. Therefore ACEIs seems to be more likely to control DBP than ARBs. P-value = 0.024. **Conclusion:** In spite of the small sample size in this study, the study could be taken as a nucleus for the effectiveness of ACEI/ARBs as a mono therapy in controlling high blood pressure among Sudanese patients, since 79% of the population involved in the study has a controlled blood pressure.

KEY WORDS: ACE inhibitors, ARBs, Hypertension, Black hypertensive patients.

INTRODUCTION

Hypertension is defined as either a sustained systolic blood pressure equal to or greater than 140 mm Hg or a sustained diastolic blood pressure equal to or greater than 90 mm Hg.[1, 2] Elevated blood pressure is an extremely common disorder. Globally, the overall prevalence of raised blood pressure in adults aged 25 and over was around 40% in 2008.[3] Although many of these individuals have no symptoms, chronic hypertension (either systolic or diastolic) can lead to cerebrovascular accidents (strokes), congestive heart failure, myocardial infarction, and renal damage.[1, 3]

The World Health Organization (WHO) estimates that in Sudan hypertension affects 1 in 4 people suffering from non-communicable diseases (NCDs) such as heart disease and stroke, cancers, diabetes, and chronic respiratory diseases.[4] Hypertension has the highest prevalence among the major NCDs in Sudan (prevalence of 23.6 in Khartoum state). Hypertension accounts for 1.3% of the out patients visits; it is represented as one of the 10 leading diseases treated in health facilities (outpatients) and also one of the 10 leading causes of death in Sudan.[5]

Most patients with hypertension have primary hypertension (also known as essential hypertension), in which there is no identifiable cause for their chronically elevated BP.[2, 6, 7]

Genetic factors may play a role, and when hypertension develops in people below the age of 40 years it is important to exclude a secondary cause (secondary hypertension) such as kidney disease, endocrine disease and malformations of blood vessels.[1, 2, 6]

Patients with secondary hypertension have a specific identified cause for elevated BP; although only 5% to 10% of those among the hypertensive population have causes that are purely secondary.[2, 7, 8]

The goal of antihypertensive therapy is to reduce cardiovascular and renal morbidity and mortality. The relationship between blood pressure and the risk of a cardiovascular event is continuous, and, thus, lowering of even moderately elevated blood pressure significantly reduces cardiovascular disease.[9, 10]

According to the Joint National Committee (JNC 8) guideline, there is a strong evidence to support treating hypertensive persons aged 60 years or older to a BP goal of less than 150/90mmHg and hypertensive persons 30 through 59 years of age to a diastolic goal of less than 90mmHg; however, there is insufficient evidence in hypertensive persons younger than 60 years for a systolic goal, or in those younger than 30 years for a diastolic goal, so the panel recommends a BP of less than 140/90mmHg for those groups based on expert opinion. The same thresholds and goals are recommended for hypertensive adults with diabetes or non-diabetic chronic kidney disease (CKD) as for the general hypertensive population younger than 60 years.[11, 12]

Many drugs are used in the management of hypertension, this include: (1) *Drugs that alter sodium and water balance*(Diuretics), (2) *Drugs that alter sympathetic nervous system function,* (3) *Direct vasodilators and* (4)*Agents that block production or action of angiotensin.*[13, 14]

ACE inhibitors lower blood pressure by reducing peripheral vascular resistance without reflexively increasing cardiac output, rate, or contractility. These drugs block the ACE that cleaves angiotensin-I to form the potent vasoconstrictor angiotensin-II. The converting enzyme is also responsible for the breakdown of bradykinin. ACE inhibitors decrease angiotensin-II and increase bradykinin levels. Vasodilation occurs as a result of the combined effects of lower vasoconstriction caused by diminished levels of angiotensin-II and the potent vasodilating effect of increased bradykinin. By reducing circulating angiotensin-II levels, ACE inhibitors also decrease the secretion of aldosterone, resulting in decreased sodium and water retention.[9, 15]

The angiotensin-II receptor blockers (ARBs) are alternatives to the ACE inhibitors. These drugs block the AT1 receptors. Their pharmacologic effects are similar to those of ACE inhibitors in that they produce an attractive therapy in hypertensive diabetics. Their adverse effects are similar to those of ACE inhibitors, although the risks of cough and angioedema are significantly decreased.[9, 15]

American guideline (2014)

The JNC 8 guidelines recommend the use of either dihydropyridines calcium channel blockers or thiazide diuretics as first line agents in the management of hypertension in black patients. ACEI or ARBs are recommended to be used as a combination with other agents only.[11]

British guideline (2011)

Similar to the JNC recommendation, the National Institute for Health and Care Excellence (NICE) guidelines recommend the use of either dihydropyridines calcium channel blockers or thiazide diuretics as first line agents in the management of hypertension in black patients. ACEI or ARBs are recommended to be used as a combination with other agents only.[16]

Sudanese guideline (2012)

Following the JNC and NICE recommendations, the Sudanese national guideline for hypertension recommend the use of either dihydropyridines calcium channel blockers or thiazide diuretics as first line agents in the management of hypertension. ACEI or ARBs are recommended to be used as a combination with other agents only.[5]

As more data concerning the prevalence, etiology, and treatment of essential hypertension become available, it is increasingly apparent that black hypertensive individuals differ substantially from their white counterparts in several important aspects. Both the prevalence and severity of hypertension are greater in blacks compared with whites, leading to high risks for blacks for the secondary complications of hypertension, including stroke, renal failure, left ventricular hypertrophy, and congestive heart failure. The relative contribution of environmental factors, such as diet and access to health care, and a genetic predisposition are uncertain.[17, 18, 19]

In general, blacks have a higher sodium intake and, in certain cases, a diminished ability to excrete sodium.[17, 20] Plasma volume may also be greater in blacks than in whites and more

black than white hypertensive patients have low plasma rennin levels. Blacks also may show deficiencies in Kallikrein and Bradykinin systems that play a role in the regulation of vascular reactivity.[17]

Hypertension in the black population has been termed 'type 2 hypertension'. This terminology focuses on the role of renin in raising blood pressure levels through its action promoting sodium retention. In type 1 hypertension, renin secretion is inappropriately high for the level of blood pressure, resulting in high sodium excretion. Type 2 hypertension is characterized by low renin levels, resulting in low sodium excretion. The distinction may be related to nephron mass, since black people have lower nephron mass (hence less sodium excretion and lower renin levels). Similarly, nephron numbers decline with age, resulting in an age related fall in renin levels. On theoretical grounds, drugs that block the renin–angiotensin system would be expected to be more effective in type 1 hypertension. This is reflected in National Institute for Health and Clinical Excellence (NICE) guidelines for the management of hypertension (NICE CG34 and CG127), which specifically recommend angiotensin-converting enzyme (ACE) inhibitors for younger white patients, in contrast to thiazide-like diuretics or calcium antagonists recommended for black patients; beta blockers are no longer recommended as first line treatment.[21, 22]

Certain subsets of the hypertensive population respond better to one class of drug than they do to another. For example, black patients respond well to diuretics and calcium-channel blockers, but monotherapy with β-blockers or ACE inhibitors is often less effective. Similarly, calcium-channel blockers, ACE inhibitors, and diuretics are favored for treatment of hypertension in elderly patients, whereas β-blockers and α-antagonists are less well tolerated.[9, 22]

There is moderate evidence to support initiating drug treatment with an angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, calcium channel blocker, or thiazide-type diuretic in the non-black hypertensive population, including those with diabetes. In the black hypertensive population, including those with diabetes, a calcium channel blocker or thiazide-type diuretic is recommended as initial therapy.[11]

There is a great need for individual treatment options in hypertensive patients of African ethno-geographical ancestry. Compared with hypertension in other population subgroups, the disorder in these patients is often more severe, more resistant to treatment, and leads to earlier

end organ damage and premature death. Thus, hypertension seems to be a more aggressive disease in patients of African ancestry. This has important implications for the choice of an antihypertensive agent.[18, 19, 23]

Antihypertensive drugs were the first cardiovascular therapy for which there was wide recognition of differences in clinical efficacy related to ethno-geographical ancestry.[23] Patients of African ancestry as a group respond better to calcium blockers and diuretics, while the response to β-adrenergic blockade and inhibition of the angiotensin converting enzyme is attenuated. However, there is considerable inter-individual variation in this response. ACEI monotherapy is generally more effective at lowering BP in white patients than in black or elderly patients. Elderly and black patients are more likely to have low renin hypertension, which may partially explain some of the differences in response.[22, 23]

Subsequent studies with angiotensin converting enzyme (ACE) inhibitors as mono therapy in black patients reported a statistically significant decrease in diastolic, but not in systolic, BP when compared with placebo. Comparative data in white patients showed a statistically significant decrease in systolic as well as diastolic BP compared with placebo; ACE inhibitors reduce BP in black patients to a considerably lesser degree than in whites. Although some studies suggest a dose response curve with increased BP lowering in black patients on higher doses of ACE inhibitors, studies with dosages as high as 450 mg/day of captopril do not confirm this.[24]

Data with other ACE inhibitors, ie, lisinopril, have shown that as monotherapy, sitting diastolic pressure is reduced by only about 7 mm Hg, but when HCTZ is added, there is a further significant decrease in BP. In non-blacks, a similar dosage of lisinopril reduced sitting diastolic BP by 14 mm Hg with a further increase in response when HCTZ was added.[24]

A number of studies has demonstrated that black hypertensive patients may respond differently to antihypertensive drugs especially ACE inhibitors than white hypertensive patients; therefore this study was conducted to assess the use of angiotensin converting enzyme inhibitors and angiotensin-II receptor blockers as antihypertensive agents in Sudanese population and to identify the degree of blood pressure control among patients using ACEIs and ARBs.

METHODOLOGY

Study Design

The design of the study was a case finding observational health facility based Study.

Study area and population

The study was conducted in Khartoum State, targeted patients diagnosed with hypertension at two centers belonging to Khartoum medical insurance services company.

Inclusion criteria

Hypertensive patients to whom ACEI or ARBs were prescribed as mono-therapy.

Exclusio criteria

Patients taking more than one antihypertensive medication, and patients with chronic renal failure.

Study duration

The study was carried out during 1 month period from September to October 2014.

Sampling

Direct interview of patients diagnosed with hypertension and prescribed ACEI or ARBs as mono-therapy was conducted.

Sample size

The total number of patients interviewed was 95 patients.

Study variables

Gender, age, daily salt use, duration of use**,** medical history, drug history and family history of the parents.

Data collection

After obtaining the consent from the health insurance center administration, data was collected using a pre-tested, pre-validated questionnaire, this process was performed by the researcher himself and by some *general* practitioner*s (*GPs) who are working at the health insurance centers after they were trained on the data collecting strategy.

Data analysis

The data obtained was compared to those found in the literature regarding the effectiveness of ACEI as mono-therapy in Africans hypertensive patients. SPSS version 19 was used for data entry, cleaning, categorization of variables and eventually analysis.

RESULTS

This research was approached through an observational case finding study, where a number of 95 hypertensive patients, who were using ACEI or ARBs as a mono therapy for the management of hypertension, were enrolled. The patients (n = 95) were selected according to a specific eligibility criteria from all hypertensive patients who are present during the study data collection period.

Patients socio-demographic factors

Gender distribution

Classification of the participants according to the gender showed that 63 (66.3%) of them were females.

Age distribution

Age distribution of the responders showed that 42 (44%) of them were within the age group (44 - 55) years, whereas 31 (32.6%) were fallen within the age group (56 – 66) years, as shown in figure 1 below.

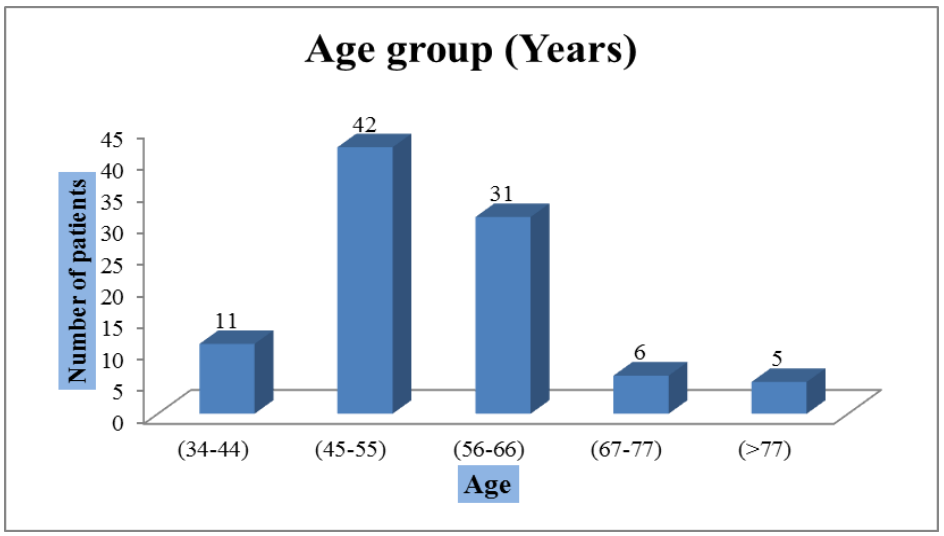

Fig. 1: Distribution of study sample according to age.

Family history

When the participants were classified according to the presence of history of chronic diseases among their families, it was observed that 51 (53.7%) of them were found to have family history of hypertension among their families, whereas 42 (44.2%) of them were found to have family history of diabetes, as shown in figure 2 below.

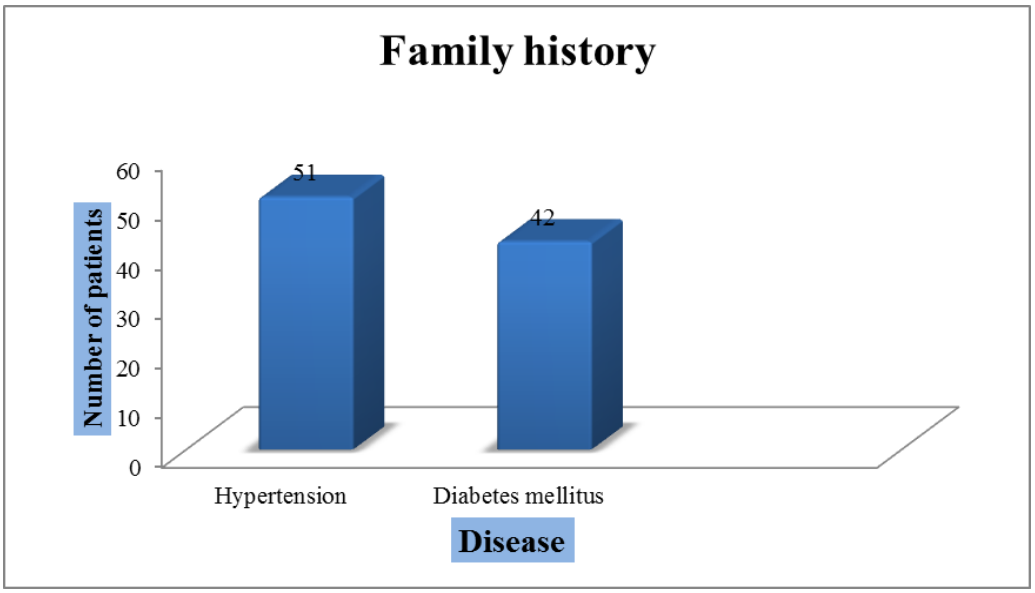

Fig. 2: Family history among study population.

Medical history

As shown in table (1); Investigation of medical history among the study population (n = 95), showed that 60 (63.1%) of them were also diabetics, whereas 20 (21%) were found to have hyperlipidemia. Gout and asthma constituted 8 (8.4%) and 5 (5.3%) respectively.

Table 1: Medical history of patients among study population.

Medical history of patients	Number of patients	Percent
Diabetes mellitus	60	63.1%
Hyperlipidemia	20	21%
Gout	8	8.4%
Asthma	5	5.3%
Ulcer	2	2.1%
Benign prostatic hypertrophy	2	2.1%
Glaucoma	1	1.1%
Osteoarthritis	1	1.1%
Hypothyroidism	1	1.1%
Hyperthyroidism	1	1.1%
Deep vein thrombosis	1	1.1%
Study population = 95		

Drug history

Table 2 below classify the participants according to the medications they use for conditions other than hypertension, where anti-platelets, metformin, statins and sulfonylurea were found to be used by 48 (50.5%), 36 (37.9%), 33 (34.7%) and 27 (28.4%) of the patients, respectively.

Table 2: Drug history among study population.

Drug history	Number of patients	Percent of yes
Anti-platelets	48	50.5%
Metformin	36	37.9%
Statins	33	34.7%
Sulfonylurea	27	28.4%
Vitamin b12	17	17.9%
Insulin	8	8.4%
Salbutamol inhaler	6	6.3%
Allopurinol	6	6.3%
Omerprazole	1	1.1%
Glucosamine	1	1.1%
Diclofenac sodium	1	1.1%
Thyroxin	1	1.1%
Carbimazole	1	1.1%
Vitamin b complex,	1	1.1%
Vildagliptin	1	1.1%
Pioglitazone	1	1.1%
Study population = 95		

Daily salt intake

Classification of the patients according to the daily salt intake showed that 49 (57.6%) of them showed moderate daily intake, whereas 34 (35.8%) of them showed low intake, and 12 (12.7%) of them were found to have high salt intake in their diet.

Current medication for hypertension

About 55 (57.9%) of the patients were using ARBs, whereas 40 (42.1%) of them were using ACEIs. Figure 3 below gives quick visual impression.

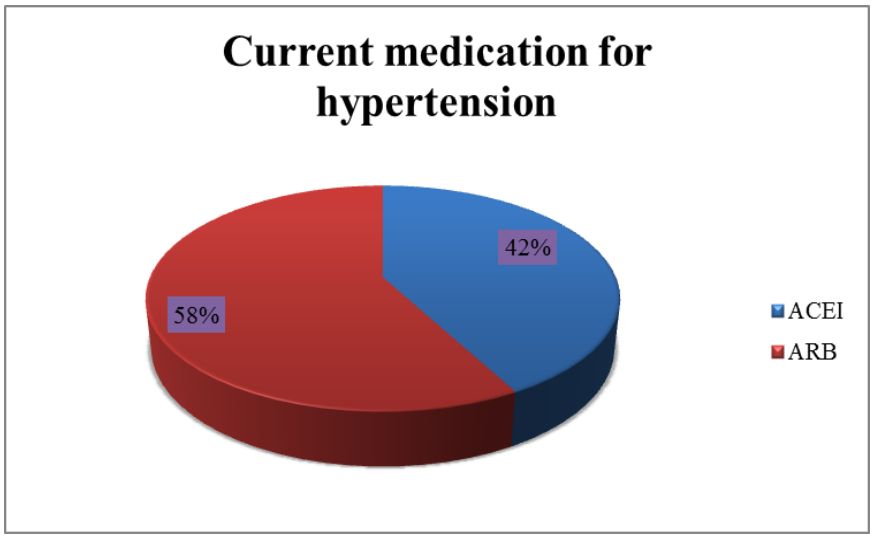

Fig. 3: Distribution of study sample according to current medication used for hypertension.

Duration of ACEIs/ARBs use

About 82 (86.3%) of the patients were taking them from 1 to 5 years, whereas 9 (9.5%) were taking them from 6 to 10 years, with a standard deviation of 3 years. Figure 4 below clarify more.

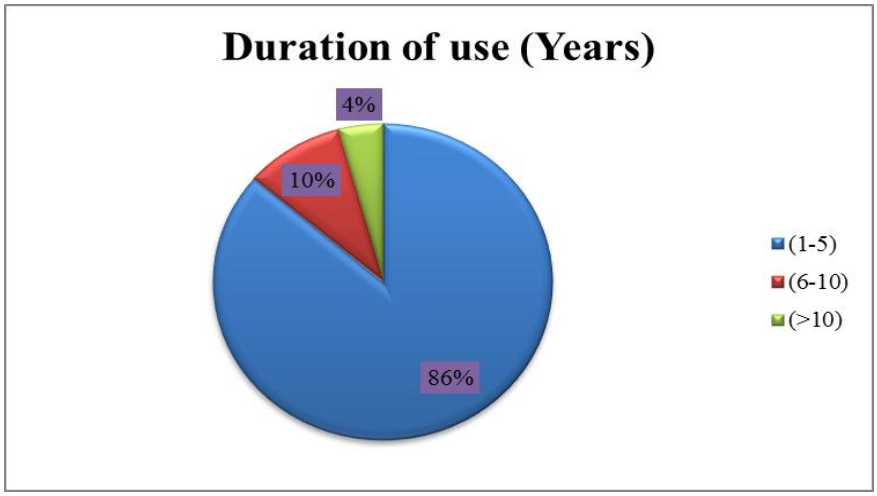

Fig. 4: Distribution of study sample according to Duration of ACEI & ARB use (Years).

Associations

Application of statistical tests of association, cha square (X^2) in particular between some of the variables dealt with in this study, showed the following significant association.

Association of current hypertension medications with B.P

Type of the current medications used for hypertension was found to be associated with controlling the diastolic blood pressure (DBP) of the patients.

It was found that the total number of patients controlled was 75 (79%) patients out of 95. Out of 55 of the patients who were using ARBs 39 (71%) patients were controlled and 16 (29%) patients were uncontrolled; whereas those who were using ACEIs (n=40) 36 (90%) were controlled and 4 (10%) patients were uncontrolled. Therefore ACEIs seems to be more likely to control DBP than ARBs. P-value = 0.024.

Association of ACEI/ARBs duration of use with B.P

Duration of ACEIs and ARBs use (years) was not found to be associated with controlling the DBP. P-value = 0.615.

Association of daily salt intake with B.P

Low daily salt intake, as independent variable, was found to be associated with controlling the systolic blood pressure (SBP) of the patients. The lower daily salt intake the greater the probability of controlling blood pressure. P-value = 0.039.

DISCUSSION

There were neither studies evaluating the use of ACEIs/ARBs as mono-therapy in Sudanese population, nor studies to measures the renin activity among them, since they could have a unique genetic composition.

Nevertheless, a large number of medical practitioners among Sudan prescribe ACEIs/ARBs for newly diagnosed hypertensive patients, despite the fact that most of the literature studies that was the base for constructing the guidelines globally are against that. Still, there is no documentation of this practice until now. For that reason, performing researches to evaluate the degree of effectiveness of these drugs and to determine the genetic variation in rennin level among Sudanese population is considered as a major demand for developing more suitable practical strategies that fit our needs. Therefore, this research could be a good starting point to investigate this variation in clinical response.As mentioned previously, the ultimate objectives of this study was to assess the use of angiotensin converting enzyme inhibitors and angiotensin-II receptors blockers as mono-therapy in the management of hypertension in Sudanese population. 75 (79%) Patient out of 95 were found to have their

DBP controlled at the time of measurement (P-value = 0.024).This high percentage of control rate may indicate a higher effectiveness value for ACEIs and ARBs when they are used in Sudanese patients as mono-therapies. About 12 (12.7%) patients out of 95were found to have high salt intake in their diet, suggesting that they had poor knowledge about the importance of reducing the salt intake and about its role in the reduction of their blood pressure, since existing evidence suggests that a high dietary intake of salt may contribute to the rise in blood pressure, and can promote the development of hypertension, or aggravate hypertension already present. Drug dosages can be reduced, and medications sometimes ceased altogether, in individuals who adopt a healthy lifestyle by increased physical activity, reduced salt intake, weight loss, moderate alcohol intake, increased potassium intake and an overall healthy eating pattern. In fact, there are data to suggest that these measures might even prevent development of hypertension in the first place.

Most of the participants (93 patients), as shown in figure 2, were found to have a family history of either hypertension (51 patients) or diabetes (42 patients), this may indicate a strong genetic etiology of hypertension among them, which may play a role in the degree of its severity and its resistance to ACEIs or ARBs. Diabetes on the other hand is a well-known risk factor for hypertension and it is also known to has a genetic etiology for its own. This will increase the chance of these patients to be diabetics in the future, and therefore increasing their risk to develop hypertension later on.

As illustrated in table 1, most of the hypertensive patients enrolled in this study were either diabetics or hyperlipidemics or a combination of both. Diabetes and hyperlipidemia are known to have a negative impact on the progression of hypertension and this may play a role in the hypertension resistance to ACEIs or ARBs that had seen in the uncontrolled patients who reported high blood pressure measurements.

Many drugs are known to counteract the effect of antihypertensive medications; fortunately, patients included in this study were not using such medications. This is cleared in Table 2.

CONCLUSION

In spite of the small sample size in this study, the study could be taken as a nucleus for the effectiveness of ACEI/ARBs as a mono therapy in controlling high blood pressure among Sudanese patients, since 79% of the population involved in the study has a controlled blood pressure.

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