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Original Article

Patterns of Anti-hypertensive Therapy in Diabetic Patients with and without Reduced Renal Function

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ABSTRACT Renal function deterioration is a common complication in patients with diabetes mellitus and hypertension. Appropriate use of anti-hypertensive agents and tight control of Blood Pressure (BP) can minimize and delay such complications. This study was performed in order to investigate the utilization patterns of anti-hypertensive agents and to evaluate BP control among diabetic-hypertensive patients with and without reduced renal function. In a retrospective cohort study, all diabetic-hypertensive patients attending The Al-Watani Medical Governmental Center from August 01, 2006 until August 01, 2007 were enrolled in the study. Patients with congestive heart failure and/or end-stage renal disease were excluded from the study. The proportion of use of five different anti-hypertensive drug classes were compared for all patients receiving 1, 2, 3, or 4 drugs, and separately among patients with and without reduced renal function. Over 60% of patients were receiving angiotensin-converting enzyme inhibitors (ACEI)/angiotensin receptor blocker (ARB), followed by diuretics (40.8%), calcium channel blockers (25.1%) and β-blockers (12.5%). The majority of patients (> 55%) were either on mono or no drug therapy. Patients on monotherapy were mostly receiving ACEI/ARB (60%). In patients with reduced renal function, use of diuretics, but not ACEI/ARB or CCB, was higher and 41.8% of the patients were on monotherapy compared to 46.6% in patients with normal renal function. The proportion of patients achieving good BP control was 20% with mono-therapy and 28% with combination therapy. Our study suggests that the pattern of anti-hypertensive therapy was generally consistent with inter-national guidelines. Areas of improvement include in-creasing use of ACEI/ARB and diuretics, decreasing the number of untreated patients, and increasing the proportion of patients with well controlled BP in this population.

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Introduction

It is estimated that 2.7% of Palestinians living in the West-Bank have hypertension (HTN) and 2.1% have diabetes mellitus (DM).[1] Although, no epidemiological data are available about Palestinians who have combined DM and HTN, the prevalence of HTN, in general, is

few times greater in patients with DM than in matched non-diabetic individuals.[2,3] The major adverse outcomes of DM are a result of vascular complications, both, at the microvascular (retinopathy, nephropathy or neuropathy) and macrovascular levels (coronary artery disease, cerebrovascular and peripheral vascular disease).[4] These vascular complications are augmented by the co-existence of HTN.[5] To minimize and delay the vascular complications among diabetic-hypertensive patients, a tight control of Blood Pressure (BP) and glucose levels is required.[4,6] Although studies have indicated that tight blood glucose control can reduce microvascular end-points,[7-9] no experimental studies have yet shown a causal relationship between improved blood glucose control and reduction in serious cardiovascular outcomes. In contrast, the level of control of HTN is more effective than glycemic control in reducing risk for cardiovascular and microvascular events and that is why, management of HTN among patients with DM should be prioritized.[10]

There are a growing number of pharmacological treatment options for patients with HTN. However, the choice of anti-hypertensive drug class is influenced by many factors such as the presence of co-morbid conditions. The seventh report of the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC) stated that angiotensin converting enzyme inhibitors (ACE-I) is an important component of most regimens to control BP in diabetic patients. In those patients, ACE-I may be used alone, but are much more effective when combined with thiazide-type diuretic or other anti-hypertensive drugs.[11] The JNC seventh report recommended that the BP in diabetics should be controlled to levels of 130/80 mmHg or lower. Rigorous control of BP is paramount for reducing the progression of diabetic nephropathy to end-stage renal disease (ESRD). In hypertensive patients with chronic kidney disease (CKD), defined as a glomerular filtration rate (GFR) < 60 mL/min, the JNC seventh report recommended a goal BP of < 130/80 mmHg and a need for using more than one anti-hypertensive drug to achieve this goal. The guidelines indicate that most patients with CKD should receive an ACE-I or an angiotensin receptor blocker (ARB) in combination with a diuretic and that many will require a loop diuretic rather than a thiazide.[11]

The primary objectives of this study were:

a) to evaluate the utilization of ACE-I/ARBs and other anti-hypertensive therapies recommended by the JNC seventh report,
b) to compare utilization of anti-hypertensive therapies for diabetic patients with, and without, reduced renal function,
c) to investigate whether diabetic-hypertensive patients with renal dysfunction receive more intensive anti-hypertensive therapy than those with normal renal function and,
d) to assess BP control in this population.

Methodology

We conducted this study at the Al-Watani Governmental Hospital and Medical Center, the largest non-surgical medical center in North Palestine with in and out-patient community medical services. Practitioners at this center include a combination of specialized and general physicians. We used the medical records of the patients to obtain diagnostic information, demographic information, laboratory test results, vital signs, and prescription drug use. Data were collected retrospectively for the period August 1, 2006 to August 1, 2007. Records of all inpatients and outpatients from various clinics were screened. All aspects of the study protocol, including access to and use of the patients' clinical information, were authorized by the medical ethics committee and the local health authorities. All patients with DM and HTN seen during the study period were analyzed. Elevated or non-target BP was defined as greater than or equal to 130/80 mmHg, according to the JNC seventh report.[11] Reduced renal function or renal impairment was defined as creatinine clearance (Cr Cl) ≤ 60 mL/min. This cut off point was used by JNC seventh report to guide therapy for patients with CKD. Creatinine clearance was calculated using Cockcroft-Gault equation. To better study the use of ACE-I specifically for diabetes, patients

Table 1. Demographic and clinical characteristics of the study sample.

Variable	Result*
Age (years)	64.4 ± 11.39
Gender (male)	110 (43.1)
Ischemic heart disease	109 (42.7%)
Creatinine clearance	100.24 ± 73.1
Number of chronic diseases	2.83 ± 0.7
Random blood glucose (mg/dL)	257.82 ±131.14
Number of anti-hypertensive medications	1.42 ± 0.8
Systolic blood pressure	151.17 ± 29.4
Diastolic blood pressure	86.22 ± 13.06

Results were expressed as mean +/- SD except for gender and IHD which were expressed as frequency and percentage

with any record of inpatient or outpatient diagnosis of chronic heart failure (CHF) were excluded. Furthermore, patients with ESRD (GFR < 15 mL/min) were excluded to avoid misinterpretation of drug use.

Antihypertensive drug classes (β-blockers, calcium channel blockers, thiazide/loop diuretics, ACE-I/ARB, and α-blockers) were recorded. The number of anti-hypertensive drugs being prescribed was tabulated. We classified patients with any prescriptions for ACEI or ARB as ACEI users and classified patients with any prescriptions for thiazide or loop diuretics as diuretic users. The proportion of use of these anti-hypertensive drug classes, among patients with 1, 2, 3, or 4 or more drugs, was tabulated for all patients. We present the patterns of use of anti-hypertensive drugs among all patients overall, and in sub-groups of patients on 1, 2, 3, or 4 or more drugs. We compared the proportions of drug class use among patients with and without renal impairment.

Statistical Analysis

Chi square or Fischer's exact test, whatever appropriate, were used to test significance between categorical variables. Data were expressed as mean ± SD for continuous variables and as frequency for categorical variables.

Results

During the study period, 340 diabetic-hypertensive patients were identified of whom, 255 met the inclusion criteria (110 males and 145 females) and were included in the analysis. The mean age of the included patients was 64.58 ± 11.40 years. The average number of chronic diseases present among the study patients was 2.83 ± 0.7 with ischemic heart disease (42.7%) being the most prevalent (Table 1). The median duration of history of HTN was five years while that for DM was ten years. The most recently recorded value of systolic, diastolic BP and random blood glucose level indicated that the mean systolic BP of the patients was 151.17 ± 29.40 mmHg; diastolic BP was 86.22 ± 13.06 mmHg and the mean random blood glucose level was 257.82 ± 131.14 mg/dL. The recommended target BP of ≤ 130/≤ 80 mmHg was achieved in only 61 patients (23.9%).

A total of 363 anti-hypertensive medication episodes were prescribed for the 255 patients. The average number of anti-hypertensive medications prescribed for the patients was 1.42 ± 0.8 (range: 0-4) and was positively correlated with the duration of DM ($P< 0.001$), duration of HTN ($P= 0.049$), and number of chronic diseases ($P< 0.0001$) but not with age ($P= 0.16$). Of the study patients, 228 (89.4%) were treated with anti-hypertensive drugs, whereas 27 (10.6%) were solely on non-pharmacological interventions. Monotherapy was prescribed for 115 (45.09%), and combination for 113 patients (44.31%); of these, two-drug regimen was used in 93 (82.30%), three-drug regimen in 18 (15.92%), and four-drug regimen was used in two patients (1.76%) (Table 2). Patients with controlled BP tended to use combination therapy more often than patients in the

Table 2. Overall pattern of anti-hypertensive therapy in the study subjects.

Drug class	Total Number of drug episodes	1 Drug N=115	2 Drugs N=93	3 Drugs N=18	4 Drugs N=2
ACEIs /angiotensin II inhibitors	157	69	70	16	2
Calcium channel blockers	64	10	37	15	2
B-blockers	32	9	15	6	2
Thiazide or loop diuretics	104	27	61	14	2
A-blockers	6	0	3	3	0
Total Number of drug episodes	363	115	186	54	8

uncontrolled BP group (50% *versus* 42%), although this difference was not significant (P= 0.3). Furthermore, there was no significant difference in the overall utilization of anti-hypertensive drug classes among patients with con-trolled or uncontrolled BP. Approximately 28% of the patients on ≥ two anti-hypertensive drugs achieved control of BP while approximately 20% of the patients on ≤ 1 anti-hypertensive drug achieved good control of BP.

The most commonly prescribed anti-hypertensive drug classes were ACE-I (61.5%) followed by diuretics (40.78%) and CCB (25.1%). The overall utilization of anti-hypertensive drug classes is shown in Table 2. Captopril (28.66%) and enalapril (66.24%) were the main types of ACE-I used. Few patients (5%) were prescribed ARB. The only two diuretics prescribed were furosemide (89.42%) and thiazides (10.57%). Calcium channel blockers used were mainly diltiazem (54.68%) and amlodipine (31.25%). Monotherapy was the most common mode of therapy among the patients the patients (115, 45.09%). ACE-I was used as monotherapy in 69 (60%), diuretics in 27 (23.48%), CCB in 10 (8.7%) and BB in nine patients (7.8%). The two-drug combination regimen was prescribed in 93 patients with the most common combination being ACE-I with others, which were prescribed in 70 patients (75.26%).

The mean Cr Cl of the patients was 100.24 ± 73.1 mL/min; 79 patients had Cr Cl < 60 mL/min (Group-I) and 176 patients had Cr Cl ≥ 60 mL/min (Group-II). Clinical differences between patients in Group-I and those in Group-II are shown in Table 3. Patients in Group-I were significantly older (67.57 ± 13.90 *versus* 63.24 ± 9.76 years, P= 0.014), had significantly longer duration of DM (P< 0.0001) as well as higher number of chronic diseases (P< 0.017) compared to those in Group-II (Table 3). The average number of anti-hypertensive medications prescribed for patients in Groups-I and –II was not significantly different (1.44 *versus* 1.41, P = 0.8).

The pattern of anti-hypertensive medications

Table 3. Demographic and clinical characteristics of patients with and without renal dysfunction.

Variables	Total = 255		*P* value
	Group-I Cr Cl=15-59 mL/min	Group-II Cr Cl ≥ 60 mL/min	
Number of patients	79	176	
Age (years)	67.57 ± 13.9	63.24 ± 9.76	0.014
Gender (male)	36 (45.6)	74 (42)	0.6
Ischemic heart disease	29 (36.7%)	80 (45.5%)	0.19
Creatinine clearance	39.03 ± 12.87	127.72 ± 72.46	< 0.001
Number of chronic diseases	2.99 ± 0.69	2.76 ± 0.7	0.017
Duration of diabetes mellitus	15.07 ± 8.54	10.27 ± 8.5	0.001
Duration of hypertension	8.88 ± 8.93	6.52 ± 6.6	0.14
Systolic blood pressure	146.76 ± 28.40	153.16 ± 29.71	0.103
Diastolic blood pressure	84.16 ± 12.46	87.15 ± 13.25	0.084
Random blood glucose	265.06 ± 166.6	254.12 ± 112.07	0.61
Number of anti-hypertensive medications	1.44 ± 0.81	1.42 ± 0.8	0.8

Table 4. Pattern of anti-hypertensive therapy in group-I and group-II patients.

Drug Class	Total	Group-I N=79 (30.98%)	Group-II N=176 (69.01%)	*P* value
Non-Pharmacologic Therapy [n (%)]				
	27 (10.6)	9 (11.4)	18 (10.2)	0.32
Monotherapy (n (%)				
A	69 (60)	18 (22.8)	51 (28.9)	0.31
B	9 (7.8)	0 (0.0)	9 (5.1)	0.014
C	10 (8.7)	3 (3.8)	7 (3.9)	0.5
D	27 (23.5)	12 (15.2)	15 (8.5)	0.016
Total	**115 (45.1)**	**33 (28.7)**	**82 (71.3)**	
Combination therapy [n (%)]				
A+D	40 (35.3)	14 (17.7)	26 (14.7)	Combination *versus* monotherapy *P* = 0.56
C+D	18 (15.8)	9 (11.4)	9 (5.1)	
A+B	11 (9.7)	2 (2.5)	9 (5.1)	
A+C	17 (15)	4 (5)	13 (7.4)	
B+D	3 (2.7)	0 (0.0)	3 (1.7)	
A+E	2 (1.8)	1 (1.3)	1 (0.6)	
C + E	1 (0.9)	0 (0.0)	1 (0.6)	
B + C	1 (0.9)	0 (0.0)	1 (0.6)	
A+C+D	9 (8)	4 (5)	5 (2.8)	
A+B+D	2 (1.8)	0 (0.0)	2 (1.2)	
B+C+D	2 (1.8)	1 (1.3)	1 (0.6)	
A+D+E	1 (0.9)	1 (1.3)	0 (0.0)	
B + A + C	2 (1.8)	1 (1.3)	1 (0.6)	
A + C + E	2 (1.8)	0 (0.0)	2 (1.2)	
A+B+C+D	2 (1.8)	0 (0.0)	2 (1.2)	
Total	**113 (44.3)**	**37 (32.7)**	**76 (67.3)**	

A: ACE-I, B: Beta Blockers, D: Diuretics, C: Calcium Channel Blockers, E: α-blockers

prescribed for Groups-I and -II were studied. Patients in Group-I were prescribed a total of 114 anti-hypertensive medications, an average of 1.44 ± 0.81 medication per patient. A total of nine patients (11.4%) were on non-pharmacologic therapy, 33 (28.7%) on monotherapy and 37 (32.7%) were on combo therapy. ACE-I was the most commonly (22.8%) prescribed drug class as monotherapy in this group of patients. ACE-I with diuretics (14/79) followed by CCB with diuretic (9/79) were the most commonly prescribed 2-drug combination therapy in Group-I patients.

In Group-II, a total of 249 anti-hypertensive medications were prescribed, an average of 1.41 ± 0.8 per patient. A total of 18/176 (10.22%) patients were on non-pharmacological therapy, 82 (46.6%) on monotherapy and 76 patients (43.18%) were on combo therapy. ACE-I (51, 28.97%) were the most commonly prescribed monotherapy drug for patients in Group-II. ACE-I with diuretics (26, 14.77%) followed by ACE-I with CCB (13, 7.4%) were the most commonly utilized 2-drug combination therapy in Group-II patients.

No significant association was seen between prescribing CCB or ACE-I and patients in either Group. However, beta blockers (*P*= 0.011) were significantly more prescribed to patients in Group-II, while diuretics (*P*= 0.016) were significantly more prescribed to patients in Group-I.

There was no significant association between patients in either Group and the use of combination therapy.

Discussion

We investigated the patterns of anti-hypertensive drug therapy in diabetic-hypertensive pa-

tients with and without renal impairment. Our study revealed that more than half (55%) of the total patients was on single or no anti-hypertensive therapy. This study also showed that one-third of the total patients had reduced renal function (< 60 mL/min) suggesting that screening for renal function among diabetic-hypertensive patients and implementing rigorous therapy is important to delay progression to ESRD.

ACE-I was the most commonly prescribed drug class both in mono and combination therapy. The use of ACE-I was not significantly associated with age (≥ 65 years) or renal function. The use of ACE-I among diabetic-hypertensive patients is in accordance with the JNC recommendations for the management of hypertension among diabetic-hypertensive patients. The reported mono and combination use of ACE-I was 43.3% which is closer to that reported from Bahrain but less than that reported from USA in treating diabetic-hypertensive patients.[12,13] The results obtained in this study were different than those reported five years ago in Palestine.[14] In this study, we observed that there was an increase in the use of ACE-I and CCB and a decrease in the use of BB. The overall under-utilization of ACE-I could be attributed to the intolerance or adverse effects of ACE-I. In a study of patients with DM and HTN, the reported prevalence of cough associated with the use of ACE-I was 14.9%, with 4.7% of patients interrupting treatment as a result.[15] Similarly, the UKPDS Group noted that 4% of patients receiving captopril discontinued therapy due to cough. ARBs are considered appropriate agents if patients cannot tolerate an ACE-I. However, ARBs were rarely prescribed in this study.[16]

Diuretics ranked second when considering overall utilization of anti-hypertensive drugs and second when considering anti-hypertensive monotherapy. Combination of ACE-I with diuretic was the most commonly prescribed. This combination is pharmacologically favorable since it produces an additive anti-hypertensive effect and minimizes most adverse effects of either the ACE-I or the diuretics, especially hypokalemia.[17] Calcium channel blockers ranked third both in monotherapy and overall anti-hypertensive drug utilization. The non-dihydropyridine, diltiazem, was the most commonly prescribed CCB and verapamil was the least commonly prescribed. The dihydropyridine, nifedipine and amlodipine, were in between. The popularity of the non-DHP diltiazem may be due to its reported positive effects on diabetic proteinuria.[18] ACE-I plus CCB combination was not very common, although it could provide synergistic anti-hypertensive and reno-protective activity, but their effects on proteinuria is comparable to ACE-I alone.[19] Non-DHP (e.g. diltiazem) plus ACE-I combination has been reported to lower insulin resistance and has an additive anti-proteinuric effect.[20]

In this study, patients with reduced renal function were significantly more commonly prescribed diuretics than patients in Group-II. This is understandable given the fact that diabetic patients with reduced renal function are volume-expanded necessitating sodium restriction and diuretic treatment. Ideally, diabetic-hypertensive patients are to be treated with ACE-I plus diuretic. The importance of the diuretic agent was emphasized by the "Anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial", ALLHAT study.[21] In these patients, loop diuretics are preferred. Patients with reduced renal function were prescribed combination anti-hypertensive agents less frequently than patients with normal renal function. This is not in agreement with the JNC recommendation which emphasizes the role of combination therapy in this particular category of patients to delay progression to ESRD.

Similar studies conducted by a research group in Bahrain on patients with type-2 DM and HTN showed that the prescribing patterns of anti-hypertensive medications differ in many instances from the World Health Organization guidelines especially, regarding the choices and drug combinations of anti-hypertensive drugs; also, the appropriateness of anti-diabetic drug choice is questionable in relation to the anti-hypertensive drug used.[22]

A second study carried out in Bahrain by the same group mentioned above compared family physicians' and general practitioners' approa-

ches to drug management of diabetic hypertension.[12] In this study, the authors carried out a retrospective prescription-based study on 1266 diabetic-hypertensive patients. The authors concluded that there are substantial differences between family physicians and general practitioners in terms of preference of different drug classes for the management of diabetic-hypertension and that there was sub-optimal compliance among both family physicians and general practitioners to international recommenddations.

We concluded from this study that there was a suboptimum use of combination therapy among diabetic-hypertensive patients in general. Furthermore, diabetic-hypertensive patients with renal impairment were not given intensive anti-hypertensive therapy compared to patients with normal renal function. We recommend better drug education for health-care providers regarding appropriate and international guidelines for this category of patients. This monitoring can be achieved through the clinical pharmacist, whose responsibility is to deliver continuing medical education in the field of current pharmacotherapy.

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