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Evaluation of antihypertensive therapy in diabetic hypertensive patients: impact of ischemic heart disease
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Evaluation of antihypertensive therapy in diabetic hypertensive patients: impact of ischemic heart disease


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ABSTRACT

Macrovascular complications are common in diabetic hypertensive patients. Appropriate antihypertensive therapy and tight blood pressure control are believed to prevent or delay such complication.

Objective: To evaluate utilization patterns of antihypertensive agents and blood pressure (BP) control among diabetic hypertensive patients with and without ischemic heart disease (IHD).

Methods: Retrospective cohort study of all diabetic hypertensive patients attending Al-watani medical center from August 2006 until August 2007.

Results: 255 patients were included in the study; their mean age was 64.4 (SD=11.4) years. Sixty-one (23.9%) of the included patients was on target BP. Over 60% of the total patients were receiving angiotensin-converting enzyme inhibitors (ACEI)/angiotensin receptor blocker (ARB), followed by diuretics (40.8%), calcium channel blockers (25.1%) and beta-blockers (12.5%). The majority (>55%) of patients were either on mono or no drug therapy. More than 55% of patients with controlled BP were on ACE-I. More than half (50.8%) of the patients with controlled BP were on combination therapy while 42.3% of patients with uncontrolled BP were on combination therapy (p=0.24). More patient in the IHD achieved target BP than those in non-IHD group (p=0.019). Comparison between IHD and non-IHD groups indicated no significant difference in the utilization of any drug class with ACE-I being the most commonly utilized in both groups.

Conclusions: Patterns of antihypertensive therapy were generally but not adequately consistent with international guidelines. Areas of improvement include increasing ACE-I drug combinations, decreasing the number of untreated patients, and increasing the proportion of patients with controlled BP in this population.

Keywords: Hypertension. Diabetes Mellitus. Drug Utilization. Palestine.

EVALUACIÓN DEL TRATAMIENTO ANTIHIPERTENSO EN PACIENTES DIABÉTICOS HIPERTENSOS: IMPACTO DE LA ENFERMEDAD ISQUÉMICA CARDIACA

RESUMEN

Las complicaciones macrovasculares son frecuentes en pacientes diabéticos hipertensos. Se cree que un apropiado tratamiento antihipertensivo y un control estrecho de la presión arterial previenen o retrasan estas complicaciones.

Objetivo: Evaluar los patrones de utilización de antihipertensivos y el control de la presión arterial (PA) en pacientes diabéticos hipertensos con y sin enfermedad isquémica cardiaca (EIC).

Métodos: Estudio de cohorte retrospectivo de todos los pacientes diabéticos hipertensos que acudieron al centro médico Al-watani desde agosto 2006 a agosto 2007. Se compararon las proporciones de pacientes que recibían 1,2,3 o 4 o más medicamentos, y por separado los pacientes con y sin EIC. El control de presión arterial (menor o igual a 130/80 mmHg) se comparó en los pacientes recibiendo ningún tratamiento, monoterapia o tratamiento de combinación y por separado los que tenían o no EIC.

Resultados: Se incluyeron en el estudio 255 pacientes; su media de edad era de 64.4 (DE=11.4) años. Sesenta y uno (23.9%) de los pacientes incluidos estaban en la presión arterial deseada. Más del 60% del total recibían inhibidores de la enzima convertidora de la angiotensina (IECA)/Antagonistas del receptor de angiotensina (ARA), seguidos de diuréticos (40.8%), bloqueantes de canales de calcio (25.1%), y beta-bloqueantes (12.5%). La mayoría (más del 55%) estaban en monoterapia o sin tratamiento. Más del...
55% of the patients with the blood pressure controlled utilized IECA. More than a half (50.8%) of the patients with the blood pressure controlled were on treatment with combination, while during the study period 42.3% of the patients with blood pressure uncontrolled were on treatment combined (p = 0.24). Alcázorpera the blood pressure desired more patients of the group EIC that of the group no-EIC (p = 0.019). The comparison between the two groups EIC and no-EIC indicated that there was no significant difference significant in the utilization of any group of medications with the IECA, being these the most utilized ones in the two groups.

Conclusions: The patterns of utilization of antihypertensives were generally not consistent with the recommendations internacionales. Las posibles mejoras incluyen aumentar las combinaciones de los IECA, disminuir la proporción de pacientes no tratados, and aumentar la proporción de pacientes con PA controlada in this population.


INTRODUCTION
It is estimated that 2.7% of Palestinians living in West-Bank have hypertension and 2.1% have diabetes mellitus.1 Although, no epidemiological data are available about Palestinians who have diabetes mellitus and hypertension together, the prevalence of hypertension, in general, is few times greater in patients with diabetes mellitus than in matched non-diabetic individuals.2 The major adverse outcomes of diabetes mellitus 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).3,4 These vascular complications are augmented by the co-existence of hypertension.5 Serious cardiovascular events are more than twice as likely in patients with diabetes and hypertension as with either disease alone.6 To minimize and delay the vascular complications among diabetic hypertensive patients, a tight control of blood pressure (BP) and glucose levels is required.4,7 Although studies have indicated that tight blood glucose control can reduce microvascular end points6,8,9, no experimental studies have yet shown a causal relationship between improved glycemic blood glucose control and reduction in serious cardiovascular outcomes. In contrast, blood pressure level control is more effective than glycemic control in reducing risk for cardiovascular and microvascular events and that is why management of hypertension among patients with diabetes mellitus should be prioritized.10 However, studies consistently demonstrate that most diabetic patients do not achieve recommended levels of BP control, and the majority have a BP of $>$140/90 mmHg.11-13

There are a growing number of pharmacological treatment options for patients with hypertension. However, the choice of antihypertensive 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 much more effective when combined with thiazide-type diuretic or other antihypertensive drugs.14 The JNC 7th report recommended that BP in diabetics be controlled to levels of 130/80 mm Hg 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 ischemic heart disease (IHD), the JNC 7th report recommended the use of beta blockers (BB) unless contraindicated. If BB therapy was inadequate or contraindicated, either long acting dihydropyridine or non-dihydropyridine-type calcium channel blockers (CCB) may be used.14

The primary objectives of this project were (1) to evaluate and compare utilization of antihypertensive therapies according to JNC 7th report for diabetic patients with and without IHD, and (2) to assess BP control among diabetic hypertensive patients.

METHODS

Settings and Study Design
This is an observational retrospective study conducted at 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 were a combination of specialized and general physicians.

Participants and Data Collection
Data were collected for the period of August 1, 2006 to August 1, 2007. All inpatients as well as all outpatients from clinics were screened. We used the medical records of the patients to obtain diagnostic information, demographic information, laboratory test results, vital signs, and prescription drug use. All aspects of the study protocol, including access to and use of the patient clinical information, were authorized by the medical ethics committee and the local health authorities. All diabetic hypertensive patients seen during the study period were investigated.

History of Ischemic heart disease was obtained from patients’ medical files. Patients with history of angina pectoris or myocardial infarction or any diagnosis of coronary artery disease were considered to have IHD. Reduced renal function or renal impairment was defined as creatinine clearance (CrCl) ≤ 60 ml/min. This cut off point was used by JNC 7th report to guide therapy for patients with chronic kidney disease (CKD). Creatinine clearance was calculated using Cockcroft-Gault...
equation. To better study the use of ACE-I specifically for diabetes, patients with any record of an inpatient or outpatient diagnosis of chronic heart failure (CHF) were excluded. Furthermore, patients with End Stage Renal Disease (GFR<15 mL/min) were excluded to avoid misinterpretation of drug use.

Outcome Measure

Elevated or non-target BP was defined as greater than or equal to 130/80 mmHg, according to the JNC 7th report.14 Antihypertensive drug classes (beta-blockers, calcium channel blockers, thiazide/loop diuretics, ACE-I/ARB, and alpha-blockers) were recorded. The number of antihypertensive 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 antihypertensive 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 antihypertensive drugs among all patients 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 IHD.

Statistical Analysis

Chi square test was used to test significance between categorical variables while the independent samples t-test was used to test for significance between continuous variables. Data were expressed as mean (standard deviation) for continuous variables and as frequency for categorical variables.

RESULTS

During the study period, 340 consecutive diabetic hypertensive patients were identified. Eighty five patients were excluded because they have CHF and/or ESRD. The 255 who met the inclusion criteria were 110 (43.1%) males and 145 (56.9%) females. The mean age of the included patients was 64.58 (SD=11.40) years. The most recently recorded values of systolic, diastolic BP and random blood glucose level were 151.17 (SD=29.40); 86.22 (SD=13.06) mmHg and 257.82 (SD=131.14) mg/dL respectively. The mean CrCl of the patients was 100.24 (SD=73.1) mL/min with 79 patients had reduced renal function (CrCl<60 mL/min). The average number of chronic diseases present among the study patients was 2.83 (SD=0.7). The recommended target BP of equal or lower 130/80 mmHg was achieved in only 61 (23.9%) patients. A total of 109 (42.7%) patients (group I) were having history of IHD while 146 (57.3%) were not (group II). Table 1 shows the clinical and demographic characteristics of the study population and compares these characteristics between patients with and without IHD. No significant difference in the average number of antihypertensive medication was found between patients with and without IHD was found (1.5 SD=0.83 versus 1.4 SD=0.8, p=0.29). However, significantly (p=0.019) more patients with IHD (31.2%) were on target BP than patients without IHD (18.5%).

Table 1. Demographic and clinical characteristics of patients with and without IHD.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total N = 255</th>
<th>Group (I) IHD (+) n = 109</th>
<th>Group (II) IHD (-) n = 146</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64.4 ± 11.39</td>
<td>65.5 ± 11.4</td>
<td>63.9 ± 11.4</td>
<td>0.25</td>
</tr>
<tr>
<td>Gender: male</td>
<td>110 (43.1%)</td>
<td>53 (48.6%)</td>
<td>57 (39%)</td>
<td>0.12</td>
</tr>
<tr>
<td>CrCl (&lt;60 mL/min)</td>
<td>79 (31%)</td>
<td>29 (26.6%)</td>
<td>50 (34.2%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Number of chronic diseases</td>
<td>2.83 ± 0.7</td>
<td>3.31 ± 0.57</td>
<td>2.47 ± 0.57</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of diabetes mellitus(years)</td>
<td>11.7 ± 8.8</td>
<td>12 ± 9.0</td>
<td>11.4 ± 8</td>
<td>0.66</td>
</tr>
<tr>
<td>Duration of hypertension (years)</td>
<td>7.2 ± 7.5</td>
<td>6.6 ± 7.8</td>
<td>7.6 ± 7.2</td>
<td>0.39</td>
</tr>
<tr>
<td>Patients on target BP (&lt; 130/80 mmHg)</td>
<td>61 (23.9%)</td>
<td>34 (31.2%)</td>
<td>27 (18.5%)</td>
<td>0.019</td>
</tr>
<tr>
<td>Random blood glucose (mg/dl)</td>
<td>257.8 ± 131.1</td>
<td>249.2 ± 110.2</td>
<td>264.1 ± 144.3</td>
<td>0.35</td>
</tr>
<tr>
<td>Number of antihypertensive medications</td>
<td>1.42 ± 0.8</td>
<td>1.5 ± 0.8</td>
<td>1.4 ± 0.8</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Table 2. Overall pattern of antihypertensive therapy.

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Number of patients with target BP having the medication*</th>
<th>Total Number of drugs (%)</th>
<th>Mono therapy</th>
<th>Combination therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 255</td>
<td></td>
<td>One n = 115</td>
<td>Two n = 93</td>
</tr>
<tr>
<td>CCB</td>
<td>14 (23%)</td>
<td>64 (17.6)</td>
<td>10</td>
<td>37</td>
</tr>
<tr>
<td>ACEIs / ARB</td>
<td>34 (55.7%)</td>
<td>157 (43)</td>
<td>69</td>
<td>70</td>
</tr>
<tr>
<td>BB</td>
<td>11 (18%)</td>
<td>32 (8.8)</td>
<td>19</td>
<td>15</td>
</tr>
<tr>
<td>Diuretics</td>
<td>31 (50.8%)</td>
<td>104 (28.7)</td>
<td>27</td>
<td>61</td>
</tr>
<tr>
<td>α-blockers</td>
<td>1 (1.6%)</td>
<td>6 (1.6)</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>363 (100)</td>
<td>115</td>
<td>186</td>
<td>54</td>
</tr>
</tbody>
</table>

n= total number of patients.

ACEIs / ARB = angiotensin converting enzyme inhibitor/angiotensin receptor blocker. BB = β-blocker, CCB = calcium channel blocker.

*Total exceeds 100% because data are overlapping due to multiple use of medication.
The most commonly antihypertensive drug classes utilized by the patients were ACE-I (157, 43%) followed by diuretics (104, 28.7%) and CCB (64, 17.6%). Overall utilization of antihypertensive drug classes is shown in Table 2. Monotherapy was the most common mode of therapy among the patients (115, 45.0%). ACE-I was used as a monotherapy in 69 (60%), diuretics in 27 (23.48%), CCB in 10 (8.7%) and BB in 9 (7.8%) patients. The two-drug combination regimen was prescribed in 93 patients. The most common 2-drug combination was "ACE-I with others" which was utilized by 70 (75.26%) patients. Overall, more than half of the patients with controlled BP were on ACE-I and/or diuretics (Table 2).

Antihypertensive pattern and medications prescribed for patients with or without IHD were investigated. Patients with IHD were prescribed a total of 162 antihypertensive medications, an average of 1.49 (SD=0.83) medications per patient. A total of 11 (10.1%) patients were on non-pharmacologic therapy, 45 (41.3%) on monotherapy and 53 (48.6%) were on combination therapy. ACE-I was the most commonly (22.9%) prescribed drug class as monotherapy in this group of patients. ACE-I was the most commonly (62.5%) prescribed drug in combination therapy in group (I) patients. A total of 201 antihypertensive medications were prescribed to patients without IHD, an average of 1.41 (SD=0.78) per patient. A total of 16 (11%) patients were on non-pharmacologic therapy, 45 (41.1%) on mono therapy and 60 (41.1%) patients were on combo therapy. ACE-I (30.1%) were the most commonly prescribed monotherapy drug for patients in group (II). ACE-I was the most commonly (63.2%) prescribed drug in combination therapy in patients without IHD. There was no significant difference in the overall utilization of any drug class and patients in either group (Table 3).

**DISCUSSION**

We evaluated the patterns of antihypertensive drug therapy in diabetic hypertensive patients with and without IHD. Our study revealed that more than half (55%) of the total patients were on single or no antihypertensive therapy and that less than one third of the patients were on target BP. This study also showed that more than one third of the total patients had IHD suggesting that screening and preventive therapies for coronary artery diseases among diabetic hypertensive patients are important to decrease morbidity and mortality among this category of patients. This study also showed that the majority of patients were receiving ACE-I and/or diuretics with CCB and BB being lesser commonly used. These findings indicate that medication use was mostly consistent with JNC 7th report recommendation among diabetic hypertensive patients. However, there is still room for improvement with regard of combination therapy and better BP control. We expected that patients with IHD will be using more CCB and/or BB than patients without IHD. However, there was no significant difference in the use of CCB and BB in the groups and that ACE-I and/or diuretics were the...
ACE-I was the most commonly prescribed drug class in both mono and combination therapy. 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. The results obtained in the current study were different from those reported in a study carried out five years ago in Palestine. In the current study, there was an overall increase in the use of ACE-I compared to that reported five years ago.

In a previous study carried out on patients with diabetes and hypertension, 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. Similarly, the UKPDS Group noted that 4% of patients receiving captopril discontinued therapy due to cough. These reported adverse effects of ACE-I could partially explain the underutilization of ACE-I reported in the current study. ARBs are considered appropriate agents if patients cannot tolerate an ACE-I. However, the use of ARBs were rarely prescribed in the current study.

Diuretics ranked second when considering overall utilization of antihypertensive drugs and second when considering antihypertensive monotherapy. Combination of ACE-I with diuretic was the most commonly prescribed. This combination is pharmacologically favorable since it produces an additive antihypertensive effect and minimizes most adverse effects of either the ACE-I or the diuretics especially hypokalemia. The importance of the diuretic agent was emphasized by the "Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack Trial" ALLHAT study. Calcium channel blockers (CCB) ranked third in monotherapy and ranked third in overall antihypertensive drug utilization. The non dihydropyridine, diltiazem, was the most commonly prescribed CCB and verapamil being 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. ACE-I plus CCB combination was not very common, although it could provide synergistic antihypertensive and renoprotective activity, but their effects on proteinuria is comparable to ACE-I alone. Non-DHP (e.g. diltiazem) plus ACE-I combination has been reported to lower insulin resistance and has an additive anti-proteinuric effect.

ACE-I was most commonly prescribed as mono or combination therapy in both groups. The rationale for investigating the antihypertensive use based on the presence of IHD is that many patients with diabetes mellitus have IHD for which BB and CCB are preferred choices by JNC 7th report.

### Table 3. Patterns of use of antihypertensive drugs among patients with and without IHD

<table>
<thead>
<tr>
<th>Drug class, N (%)</th>
<th>IHD (+) Overall (%)</th>
<th>IHD (-) Overall (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=109 (100.0)</td>
<td>n=146 (100.0)</td>
</tr>
<tr>
<td>Total number of drugs</td>
<td>160 (45)</td>
<td>203 (70)</td>
</tr>
<tr>
<td>α-blockers</td>
<td>0.0 (0.0)</td>
<td>6 (4.1)</td>
</tr>
<tr>
<td>CCB</td>
<td>33 (30.3)</td>
<td>33 (22.3)</td>
</tr>
<tr>
<td>β-blockers</td>
<td>44 (40.4)</td>
<td>44 (29.3)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>25 (22.4)</td>
<td>31 (21.2)</td>
</tr>
<tr>
<td>ACEIs / ARB</td>
<td>40 (36.7)</td>
<td>44 (30.1)</td>
</tr>
</tbody>
</table>

Notes:
1. a group of 27 patients who were not on pharmacologic therapy were not included in the analysis.
2. “n” represents the number of patients.
3. IHD= ischemic heart disease, ACEIs/ ARB = angiotensin converting enzyme inhibitor/ angiotensin receptor blocker. BB = β-blocker, CCB = calcium channel blocker.
their BP control. This could be achieved through clinical pharmacist whose responsibility is to deliver continuing medical education in the field of current pharmacotherapy.

CONCLUSIONS

We concluded from this study that there was a suboptimum use of combination therapy among diabetic hypertensive patients in general. Furthermore, the majority of patients were not on target blood pressure. Patterns of antihypertensive therapy were generally but not adequately consistent with international guidelines. Areas of improvement include increasing ACE-I drug combinations, decreasing the number of untreated patients, and increasing the proportion of patients with controlled blood pressure in this population.

CONFLICT OF INTEREST

No conflict of interest. No funding was available for this project.

References


