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PHARMACOLOGICAL AND THERAPEUTIC ANALYSIS OF ANTI-DIABETIC AND ANTI-HYPERTENSIVE DRUGS AMONG DIABETIC HYPERTENSIVE PATIENTS IN PALESTINE

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التحليل الدوائي والعلاجي لأدوية السكري والضغط عند المرضى الذين يعانون من مرض السكري والضغط معا في فلسطين

ملخص: الهدف من هذه الدراسة هو تحديد كيفية وصف أدوية الضغط والسكري للمرضى الذين يعانون من الضغط والسكري معا". لدراسة ذلك، تم دراسة وتحليل 342 ملف دوائي لمرضى يعانون من السكري النوع الثاني والضغط. بين هذه العينة من المرضى، كان حوالي 74.3% يتناولون دواء واحد للسكري وكان هنالك استعمال قليل للأنسلين مع أدوية سكري أخرى وكذلك لوحظ استعمال غير مبرر لدواء الميتفورمين عند كبار السن. دراسة أدوية الضغط بينت أن هنالك استعمال أقل من اللازم لتعدد أدوية الضغط، وأدوية الثيازيد ومضادات مستقبلات الأنجيوتينسن 2. لوحظ بعض الوصفات غير العلمية مثل: مثبطات بيتا + ومدرات الثيازيد، مثبطات انزيم أ س ي + مثبطات بيتا، مثبطات انزيم أ س ي + مثبطات الكالسيوم من نوع دايهيدروبيريدين. النتيجة هو أن هذه الدراسة تشير الى أن هنالك بعض الاستعمالات الصحيحة والبعض غير صحيح أو غير متوافق مع الدراسات الحديثة. التعليم الطبي المستمر مطلوب لتحسين الممارسات الدوائية والعلاجية لمرضى السكري والضغط معا".

Abstract: The objective of this study was to determine the utilization pattern of antidiabetic and antihypertensive medication among diabetic hypertensive patients. The medical profile of three hundred and forty two patients diagnosed with type 2 diabetes mellitus and hypertension were reviewed and analyzed. Among the tested sample, antidiabetic monotherapy was prevalent (74.3%). Antihypertensive monotherapy was found among 47.3% of the tested sample. Analysis of the antidiabetic medications shows underutilization of insulin combination therapy and inappropriate use of metformin among the elderly. Analysis of the antihypertensive therapy shows that there is underutilization of combination therapy, low dose thiazides and angiotensin II receptor antagonists (ATIIRA). Some of the 2-drug antihypertensive combinations were irrational like beta blockers (BB) plus diuretics, angiotensin converting enzyme inhibitors (ACE-I) plus BB or ACE-I plus dihydropyridine calcium channel blockers (CCB). In conclusion, the study shows that some prescribing practices for diabetic hypertensive patients were appropriate while others were inappropriate and do not adhere to current recommendations in the literature. Continuing medical education is needed to improve the prescribing practices in Palestine.

Introduction:

It is estimated that (2.7%) of Palestinians living in *West-Bank* have hypertension and (2.1 %) have diabetes mellitus [(1)]. Although, no statistical information 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)]. In fact, according to the *American Heart Association*, diabetes mellitus is a cardiovascular disease [(3)]. 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) [(4)]. These vascular complications are augmented by the co-existence of hypertension [(5)]. To minimize and delay the vascular complications among diabetic hypertensive patients, a tight control of blood pressure, cholesterol and glucose levels is required [(4, 6)]. Although studies have indicated that tight blood glucose control can reduce microvascular end points, no experimental studies have yet shown a causal relationship between improved glycemic blood glucose control and reduction in serious cardiovascular outcomes [(7- 9)]. 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)].

There are a growing number of pharmacological treatment options for patients with hypertension. However, the choice of anti-hypertensive drug class in diabetic hypertensive patients is influenced by many factors like the presence of multiple co-morbid conditions and the possibility or risk of drug-drug interactions. To reach an optimum blood pressure level in these patients, combinations of two or more antihypertensive drug classes may be needed [(7, 11-13)]. The ideal antihypertensive drug to be used in diabetic hypertensive patients must have a favorable or at least a neutral effect on blood lipids, reduce the cardiovascular and renal deterioration and finally have no effect on blood sugar that would interfere with the glycemic control. Recent studies suggest that angiotensin II receptor antagonists (ATII-RA) have a reno-protective effect [(14-16)] and the *Losartan Intervention for Endpoint Reduction* (LIFE) study suggested that ATII-RA might even be superior to beta-blockers in reducing cardiovascular morbidity and mortality [(17)]. Studies were carried out to compare angiotensin converting enzyme inhibitors (ACE-I) with other drug classes like thiazide diuretics, beta blockers (BB) and calcium channel blockers (CCB). One study, CAPPP (Captopril Prevention Project), found that ACE-I inhibitors were superior to diuretics and BB [18], while the ALLHAT (*Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial*) study showed that diuretics and ACE-I are almost equivalent in all aspects [19]. The UKPDS (*United Kingdom Prospective Diabetes Study*) and STOP-2 (*Swedish Trial in Old Patients with Hypertension – 2*) indicated that ACE-I, diuretics and BB were equivalent in reducing cardiovascular events and mortality among diabetic patients [20, 21]. However, the UKPDS study showed that BB therapy was more frequently discontinued, the patients on BB gained more weight than those on ACE-I and the patients taking BB require the addition of newer glucose lowering agents more than those taking ACE-I [21]. Actually, based on the HOPE (*Heart Outcomes Prevention Evaluation)*, ACE-I were suggested as first line therapy for treatment of hypertension among diabetes mellitus [22, 23]. However, in this study, ACE-I were compared to placebo in high risk hypertensive patients and not with other pharmacological drug classes. Some studies have indicated that ACE-I have a hypertension-independent reno-protective effects among patients with diabetes mellitus [24, 25]. Finally, when BB are compared with ACE-I regarding their glucose metabolic effects, beta blockers adversely influence glucose homeostasis, blood lipid profile and delay recovery from hypoglycemia while ACE-I have favorable effect on insulin sensitivity and glucose homeostasis [26-28].

The current body of evidence suggests that thiazide diuretics, ACE-I and ATII-RA are superior to BB and CCB and thus they are preferred as first line therapy while CCB and BB are best used as second or third line treatment for hypertension treatment in diabetes mellitus [12, 20, 29-31].

The primary aim of the present study was to investigate the prescription of antidiabetic and antihypertensive medications among diabetic hypertensive patients with governmental medical insurance in Nablus city - Palestine. The appropriateness of antihypertensive and antidiabetic prescribing will also be analyzed based on current clinical studies and international guidelines and recommendations. Finally, the therapeutic consequences and implications of the prescribing pattern will be analyzed and discussed.

Methodology:

The medical files of three hundred forty two patients (342) patients who were diagnosed with diabetes mellitus type 2 and hypertension were reviewed and analyzed. Those patients are registered at the Ministry of Health (MOH) as chronic patients and they dispense their medications on regular basis. The data regarding age, gender, drug profile (all drugs prescribed for the patients) were extracted from the medical files and analyzed using SPSS 10. Data collection was made over a period of six months. The researcher took permission from the Ministry of Health officials before starting the collection of data. The chi-square test was used to determine the differences between proportions. A "p" *value* < 0.05 was considered to represent statistical significance.

Results:

Medications consumed by a sample of 342 diabetic hypertensive patients who were stabilized on anti-diabetic and anti-hypertensive therapy were analyzed and studied.

1. Age and gender distribution of patients:

A total of 1462 medications were prescribed for the 342 diabetic hypertensive patients with an average of 4.3 (SD = 1.3) medications per patient. The patients receiving those medications were 174 (50.9%) men and 168 (49.1%) women. The average age of the 342 patients was 64.4 years (SD = 8.7). The average age of the male patients was 65.1 years (SD = 8.4), while the average age of the female patients was 63.8 years (SD = 9.1). The total number of anti-diabetic and antihypertensive medications prescribed for the 342 patients was 430 (SD = 0.4) and 542 (SD = 0.7) respectively. The age distribution of the 342 patients studied shows that (244/342; 71%) of the patients were above the age of 60 years while the rest of the patients were between 41 and 60 years old (Table 1). No differences were observed between females and males with respect to the age distribution (Chi-square = 8.17; d.f. = 7, P > 0.05).

Table 1. Age and gender distribution of the 342 diabetic hypertensive patients.

Age	Male	Female	Total
40 – 50	8	12	20
50 – 60	32	46	78
60 – 70	74	72	146
70 – 90	60	38	98
Total	174	168	342

2. Prescribing "frequency" of antidiabetic and antihypertensive drugs:

The anti-diabetic medications constituted approximately 29.4% (430/1462) while anti-hypertensive medications constituted 37% (542 /1462) of all the medications that were prescribed to the patient population (Figure 1). Among the antidiabetic drugs, oral antidiabetic drugs accounted for (360/430; 83.7%) while insulin accounted for (70/430; 16.3%) of the total number of antidiabetic medications prescribed for the sample patients. Among the oral antidiabetic drugs, sulfonylurea (SFU) drug class accounted for (282/430; 65.6%) of the total antidiabetic medications used while biguanide accounted for (78/430; 18.1%) of the total number of antidiabetic medications prescribed for the sample patients as seen in Figure 2A. Among the anti-hypertensive drug classes, angiotensin converting enzyme inhibitors (ACE-I) accounted for (180/542; 33.2%), diuretics accounted for (150/542; 27.67%) calcium channel blockers (CCB) accounted for (114/542; 21%), beta-blockers (BB) accounted for (94/542; 17.3%) and alpha blockers accounted for (4/542; 0.7%) of the total antihypertensive medications prescribed to the patient population as seen in Figure 2B.

Figure 1: anti-diabetic and anti-hypertensive prescribing frequency among the 342 diabetic hypertensive patients

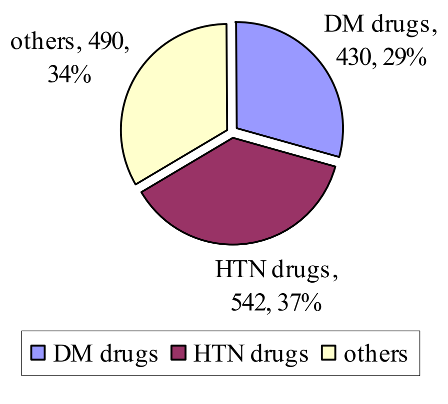

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Figure 2A: Antidiabetic drug classes prescribed for the 342 diabetic hypertensive patients

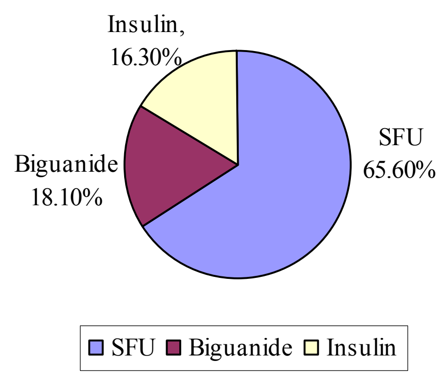
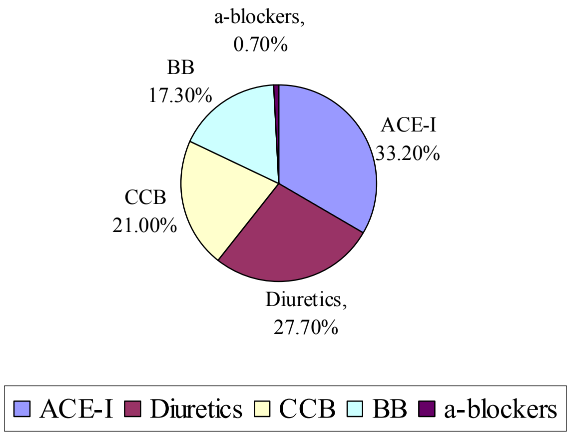
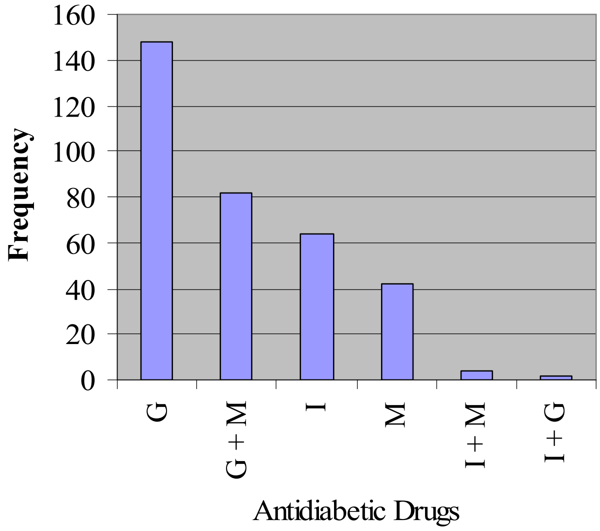


Figure 2B: Anihypertensive drug classes prescribed for the 342 diabetic hypertensive patients



3. Prescribing "pattern" of antidiabetic drugs
Among the study population, 254/342 (74.3%) patients were treated with either a single (monotherapy) oral anti-diabetic agent or insulin, and 88/342 (25.7%) patients were taking two antidiabetic drug combinations – either oral anti-diabetic drug combination or an oral anti-diabetic with supplementary insulin. Among those receiving antidiabetic monotherapy, the most frequently prescribed drugs were, in descending order, glyburide (G) (148/254; 58.3%), insulin (I) (64/254; 25.2%) and metformin (M) (42/254; 16.5%). Among those patients receiving combination antidiabetic therapy, oral antidiabetic drugs, glyburide plus metfomin was seen in (82/88; 93.2%), oral antidiabetic plus insulin combination was seen in (6/88; 6.8%): insulin plus metformin (4/88; 4.5%) and insulin plus glyburide (2/88; 2.3%). The prescribing pattern of antidiabetic drugs among the 342 patients is seen in Figure 3.

Figure 3: Frequency of various antidiabetic drugs prescribed for the 342 diabetic hypertensive patients.



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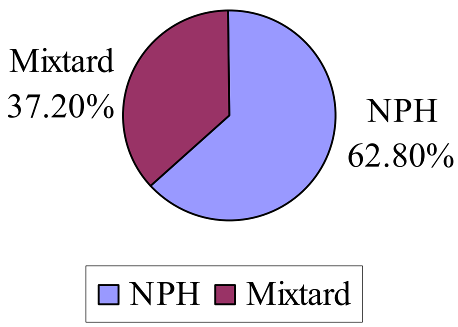
Among those receiving either mono or combination insulin therapy, (44/70; 62.8%) patients were receiving NPH insulin while (26/70; 37.2%) patients were receiving mixtard insulin preparation, as can be seen in figure 4.

Figure 4: Prescribing pattern of Insulin among the 342 diabetic hypertensive patients



The pattern of anti-diabetic drug utilization with the various combinations seen as well as the characteristics of the patients receiving those anti-diabetic drugs is summarized table 2. No differences were observed between gender and anti-diabetic mono / combination therapy while statistical difference was seen between age and antidiabetic mono / combination therapy (Chi-square = 0.092; d.f. = 1, $P > 0.05$ for gender versus diabetic therapy; Chi-square = 9.1; d.f. = 3 for age versus diabetic therapy; $P < 0.05$).

Table 2: pattern of anti-diabetic drug prescribing and patient characteristics. G = glyburide, M = metformin, I = insulin, f = female, m = male.

Drug Therapy	**Monotherapy** (74.3%); n = 342 patients	**Two drugs** (25.7%) n = 342 patients
Frequency	**254/342 (74.3%)** **G** = 148/254 (58.3%) **M** = 42/254 (16.5%)	**88/342 (25.7%)** **G + M** = 82/88 (93.1%) **G + I** = 2/88 (2.3%)

	I = 64 (25.2%)	**M + I** = 4/88 (4.5%)
Gender (m); (f)	**128/254 m (50.4%); 126/254 f (49.6%)** **G**: 72/128 m (56.3%); 76/126 f (60.3%) **M**: 18/128 m (14%); 24/126 f (19%) **I**: 38/128 m (29.6%); 26/126 f (20.6%)	**46/88 m (52.3%); 42/88 f (47.7%)** **G + M**: 40/46 m (86.9%); 42/42 f (100%) **M + I**: 4/46 m (8.6%) **G + I**: 2/46 m (4.3%)
Age (year)	**64 (25.2%) < 60; 190 (74.8%) > 60** **G** : 42/64 (65.6%)< 60; 106/190 (55.8%) > 60 **M** : 18/64 (28.1%) < 60; 24/190 (12.6%) > 60 **I** : 4/64 (6.25%) < 60; 60/190 (31.6%) > 60	**34 (38.6%) < 60; 54 (61.3%) > 60** **G + M** : 34/34 (100%) < 60; 48/54 (88.8%) > 60 **M + I** : 4/54 (7.4%) > 60 **G + I** : 2/54 (3.7%) > 60

4. Prescribing "pattern" of antihypertensive drugs

Among the study population, a total of 86 males and 76 females (162/342; 47.3 %) were receiving anti-hypertensive monotherapy. A total of 70 males and 78 females (148/342; 43.3%) were receiving two-drug antihypertensive therapy, whereas 16 males and 12 females (28/342; 8.2%) were receiving three-drug antihypertensive therapy. Four patients, two males and two females (4/342; 1.2%), were not receiving anti-hypertensive drug therapy. Among those receiving anti-hypertensive monotherapy, the most frequently prescribed antihypertensive drug classes were, in descending order, ACE-I (66/162; 40.7%), calcium channel blockers (42/162; 25.9%), beta-blockers (30/162; 18.5%) diuretics (22/162; 13.6%), alpha-blockers (2/162; 1.2%). Among those receiving 2-drug combination antihypertensive therapy, the most frequently prescribed antihypertensive drug classes were, in descending order, ACE-I + Diuretics (66/148; 44.5%), ACE-I + CCB (18/148; 12.2%), BB + Diuretics (18/148; 12.2%), BB + CCB (16/148; 10.8%), CCB + Diuretics (16/148;

10.8%), ACE-I + BB (12/148; 8.1%) and CCB + alpha blocker (2/148; 1.4%). Among those receiving 3-drug combination antihypertensive therapy, the most frequently prescribed antihypertensive drug classes were, in descending order, ACE-I + CCB + diuretics (10/28; 33.3%), ACE-I + BB + diuretics (10/28; 33.3%) and BB + CCB + diuretics (8/28; 26.6%). The pattern of anti-hypertensive drug utilization with the various combinations seen as well as the characteristics of the patients receiving those anti-hypertensive drugs is summarized table 3.

Table 3: Pattern of anti-hypertensive drug prescribing and patient characteristics. ACE-I = angiotensin converting enzyme inhibitors, D = diuretics, BB = beta-blockers, CCB = Calcium channel blockers, f = female, m = male. Note: four patients were not receiving anti-hypertensive drugs.

Drug Therapy	**Monotherapy** n = 342 patients	**Two-drug therapy** n = 342 patients	**Triple-drug therapy** n = 342 patients
Frequency	162/342 (47.3%)	148/342 (43.3%)	28/342 (8.2%)
Gender (m; f)	86/162 m (53%); 76/162 f (46.9%) **ACE-I**: 64/162 (39.5%) 30/86 m (34.8%); 34/76 f (44.7%) **CCB**: 44/162 (27.2%) 28/86 m (32.6%); 16/76 f (21%) **BB**: 30/162 (18.5%) 12/86 m (13.9%); 18/76 f (23.7%) **D**: 22/162 (13.5%) 14/86 m (16.3%); 8/76 f (10.5%) **-blockers**: 2/162 (1.2%) 2/86 m (2.3%)	70/148 m (45.8%) 78/148 f (54.2%) **ACE-I + D**: 66/148 (44.6%) 26/70 m (37.1%); 40/78 f (51.3%) **ACE-I + CCB**: 18/148 (12.2%) (10/18 m (55.6%); 8/18 f (44.4%) **BB + CCB**: 16/148 (10.8%) 6/16 m (37.5%); 10/16 f (62.5%) **BB + D**: 18/148 (12.2%) (10/18 m (55.6%); 8/18 f 44.4%) **CCB + D**: 16/148 (10.8%) 10/16 m (62.5%) 6/16 f	16/28 m (57.1%); 12/28 f (42.8%) **ACE-I + CCB + D**: 10/28 (35.7%) 6/10 m (60%); 4/10 f (40%) **ACE-I + BB + D**: 10/28 (33.3%) 8/20 m (80%); (2/10 f (20%) **BB + CCB + D**: 8/28 (28.6%) 2/8 m (25%); 6/8 f (75%)

		(237.5%) **ACE-I + BB**: 12/148 (8.1%) 6/12 m (50%); 6/12 f (50%) **CCB + -blocker**: 2/148 (1.4%) 2/2 m (100%)	
Age (year)	**56 < 60; 106 > 60** **ACE-I**: 64/162 (39.5%) 28/64 (43.8%) < 60; 36/64 (56.3% > 60 **CCB**: 44/162 (27.2%) 12/44 (27.3%) < 60; 32/44 (72.7%) > 60 **BB**: 30/162 (18.5%) 10/30 (33.3%) < 60; 20/30 (66.7%) > 60 **D**: 22/162 (13.6%) 6/22 (27.2%) < 60; 16/22 (72.7%) > 60 **-blockers**: 2/162 (1.2%) 2/2 (100%) > 60	**36 < 60; 112 > 60** **ACE-I + D**: 66/148 (44.6%) 18/66 (27.3%) < 60; 48/66 (72.7%) > 60 **ACE-I + CCB**: 18/148 (12.2%) 4/18 (22.2%) < 60; 14/18 (77.8%) > 60 **BB + D**: 18/148 (12.2%) 2/18 (11.1%) < 60; 16/18 (88.8%) > 60 **BB + CCB**: 16/144 (11.1%) 2/16 (12.5% < 60; 14/16 (8.75%) > 60 **CCB + D**: 16/148 (10.8%) 16/16 (100%) > 60 **ACE-I + BB**: 12/148 (8.1%) 10/12 (83.3%) < 60; 2/12 (16.6%) > 60 **CCB + a-blockers**: 2/148 (1.4%) 2/2 (100%) > 60.	**6 < 60, 22 > 60** **ACE-I + CCB + D** : 10/28 (35.7%) 2/10 (20% < 60; 8/10 (80%) > 60 **ACE-I + BB + D**: 10/28 (35.7%) 4/10 (40%) < 60; 6/10 (60%) > 60 **BB + CCB + D**: 8/28 (28.6%) 8/8 (100%) > 60

4. Most frequently prescribed antihypertensive drugs

Among those receiving anti-hypertensive monotherapy (162/342; 47.4%), the most frequently prescribed drug types were, in descending order, ACE-I: captopril (32/64; 50%) and enalapril (32/64; 50%); CCB: diltiazem (34/44; 77.3%), amlodipine (8/44; 18.2%) and nifedipine (2/44; 4.5%); BB: atenolol (30/30; 100%); diuretics: furosemide (18/22; 81.8%) and hydrochlorothiazide (4/22; 18.2%); alpha-blockers: prazocin (2/2; 100%).

Among those receiving 2-drug antihypertensive combination therapy (148/342; 43.3%), the most frequently prescribed type of combinations were, in descending order, <u>ACE-I + diuretics (66/148; 44.6%)</u>: captopril + furosemide (42/66; 63.6%) and enalapril + furosemide (24/66; 36.4%); <u>ACE-I + CCB (18/148; 12.2%)</u>: enalapril + amlodipine (10/18; 55.6%), enalapril + diltiazem (4/18; 22.2%), captopril + diltiazem (2/18; 11.1%) and captopril + nifedipine (2/18; 11.1%); <u>BB + diuretics (18/142; 12.2%):</u> atenolol + HCT (10/18; 55.6), atenolol + furosemide (6/18; 33.3) and furosemide + propranolol (2/18; 11.1%); <u>BB + CCB (16/148; 10.8%)</u>: atenolol + diltiazem (10/16; 62.5%), atenolol + nifedpine (4/16; 25%) and propranolol + verapamil (2/16; 12.5%); <u>CCB + diuretics (16/148; 10.8%)</u>: diltiazem + furosemide (12/16; 75%), nifedipine + furosemide (2/16; 12.5%) and amlodipine + furosemide (2/16; 12.5%); <u>ACE-I + BB (12/148; 12.1%)</u>: enalapril + atenolol (6/12; 50%); captopril + atenolol (4/12; 33.3%) and captopril + propranolol (2/12; 16.7%); <u>CCB + alpha-blocker (2/148; 1.4%)</u>: diltiazem + prazocin (2/2; 100%).

Among those receiving 3-drug antihypertensive combination therapy (28/342; 8.2%) the most frequently prescribed type of combinations were, in descending order, <u>ACE-I + CCB + diuretics (10/28; 35.7%)</u>: captopril + nifedipine + furosemide (4/10; 40%), captopril + diltiazem + furosemide (4/10; 40%) and enalapril + diltiazem + furosemide (2/10; 20%); <u>ACE-I + BB + diuretics (10/28; 35.7%)</u>: enalapril + atenolol + furosemide (8/10; 80%) and captopril + atenolol + furosemide (2/10; 20%); <u>BB + CCB + diuretics (8/28; 28.6%):</u> atenolol + diltiazem + furosemide (4/8; 50%), atenolol + nifedipine + HCT (2/8; 25%) and propranolol + amlodipine + HCT (2/8; 25%). The most frequently prescribed types of anti-hypertensive drugs within the mono and combination therapy are shown in table 4.

Table 4:

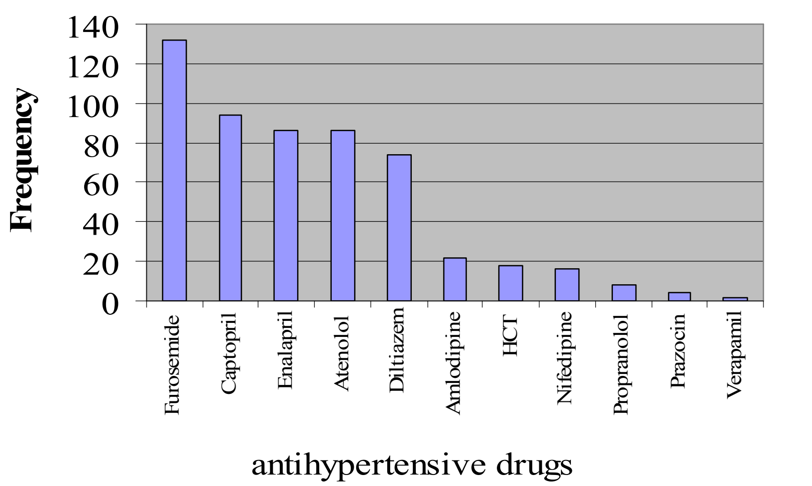
C = captopril, E = enalapril, Dt = diltiazem, N = nifedipine, A = amlodipine, At = atenolol, F = furosemide, H = hydrochlorothiazide, P = propranolol, Pr = prazocin, S = spironolactone.

HTN / Monotherapy 162/342 (47.9%)	**2-drug therapy** 148/342 (43.3%)	**3-drug therapy** (28/342; 8.2%)
ACE-I (64/162; 39.5%) **C** = 32 (50%) **E** = 32 (50%) **CCB (44/162; 27.2%)** **Dt** = 34/44 (77.3%) **A** = 8/44 (18.2%) **N** = 2/44 (4.5%) **BB (30/162; 18.5%)** **At =** 30/30 (100%) **D (22/162; 13.6%)** **F =** 18/22 (81.8%) **H =** 4/22 (18.2%) **-blockers**: 2/162 (1.2%) Pr = 2/2 (100%)	**ACE-I + Di (66/148; 44.6%)** C + F = (42/66; 63.6%) E + F = (24/66; 36.4%) **ACE-I + CCB (18/148; 12.2%)** E + A = (10/18; 55.6%) E + Dt = (4/18; 22.2%) C + Dt = (2/18; 11.1%) C + N = (2/18; 11.1%) **BB + CCB (16/148; 10.8%)** At + Dt = (10/16; 62.5%) At + N = (4/16; 25%) P + V = (2/16; 12.5%) **CCB + Di (16/148; 10.8%)** D + F = (12/14; 85.7%) N + F = (2/14; 14.3%) A + F = (2/14; 14.3%) **BB + D**: 18/148 (12.2%) At + H = 10/18 (55.6%) At + F = 6/18 (33.3%) P + F = 2/18 (11.1%)	**ACE-I + CCB + D** (10/28; 35.7%) C + N + F = (4/10; 40%), C + D + F = (4/10; 40%), E + D + F = (2/10; 20%) **ACE-I + BB + D** (10/28; 35.7%) E + At + F = (8/10; 80%) C + At + F = (2/10; 20%) **BB + CCB + D** (8/28; 28.6%) At + Dt + F = (4/8; 50%) At + N + H = (2/8; 25%) P + A + H = (2/8; 25%)

	ACE-I + BB (12/148; 8.1%) E + At = (6/12; 50%) C + At = (4/12; 33.3%) C + P = (2/12; 16.7%) **CCB + alpha-blocker (2/148; 1.4%** Dt + Pr = (2/2; 100%)	

Considering the overall utilization of anti-hypertensive therapy, the most frequently prescribed drug types were, in descending order, furosemide (132/542), captopril (94/542), enalapril (86/542), atenolol (86/542), diltiazem (74/542), amlodipine (22/542), HCT (18/542), nifedipine (16/542), propranolol (8/542), prazocin (4/542) and verapamil (2/542).

Figure 5: Most frequently prescribed anti-hypertensive drugs in mono and combination therapy of the 342 diabetic hypertensive patients



5. Pattern of anti-diabetic and antihypertensive treatment "regimens":

Among those patients receiving diabetic monotherapy, 110/254 (43.3%) were receiving hypertension monotherapy, 118/254 (46.5%) were receiving 2-drug combination antihypertensive therapy, 22/254 (8.7%) were receiving 3-drug combination antihypertensive drug therapy and finally 4/254 (1.6%) were receiving no antihypertensive drug therapy as seen in table (4).

Table 4: Pattern of anti-diabetic and antihypertensive treatment "regimens":

	DM Monotherapy	2-drug therapy	Total
no HTN therapy	4	0	4
HTN monotherapy	110	52	162
HTN 2-drug therapy	120	28	148
HTN 3-drug therapy	20	8	28
Total	254	88	342

Of particular interest, is the combination of anti-diabetic drugs with beta blockers since beta blockers have adverse effects on glucose homeostasis. Ninety four (94) patients were co-prescribed a BB with antidiabetic drugs. The most common combination was atenolol monotherapy with Glyburide monotherapy (16/94).

Discussion:

The drug utilization studies among diabetic hypertensive patients are important. It can help health policy makers in Palestine to determine the rationality and therapeutic implications for diabetic hypertensive patients. Furthermore, such a study will help health policy makers direct the economic scarcity in Palestine toward effective and efficient use of drugs.

A similar study conducted by a pharmacology research group in Bahrain on patients with type 2 diabetes mellitus and hypertension showed that the prescribing of antihypertensive medications differ in many instances from the world health organization guidelines especially regarding the choices and drug combinations of anti-hypertensive drugs and that the appropriateness of anti-diabetic drug choice is questionable in relation to the anti-hypertensive drug used [32]. A second study carried out in Bahrain by the same group mentioned above compared family physicians' and general practitioners' approaches to drug management of diabetic hypertension [33]. 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 for different drug classes for the management of diabetic hypertension and that there was suboptimal compliance among both FP and GP to international recommendations.

Antidiabetic drug choice :

In our study, glyburide (glibenclamide); a second generation sulfonylurea (SFU), and metformin, a biguanide were the only two oral antidiabetic drugs used among the sample studied. Glyburide was used alone or in combination with metformin or insulin. The extensive use of this second generation SFU, which has long duration of action, may not be appropriate especially among elderly diabetic hypertensive patients because of possible risk of drug-induced hypoglycemia. Shorter acting SFU were not prescribed or may be not available at the clinics of the Ministry of Health (MOH). The appropriateness of the metformin utilization can not be judged based solely on the data available in our hands. Metformin is best used for obese patients with type 2 diabetes mellitus and unfortunately updated information about body weight or body mass index (BMI) was not found in the medical record of every patient. Metformin monotherapy and metformin combination therapy were prescribed for 7% and 15.2% respectively of those patients who are above 60 years old in the tested sample. Those patients are at risk of developing lactic acidosis due to possible existence of hepatic and / or renal malfunction among elderly patients. Finally, the interest in antidiabetic combination therapy was renewed in the past decade [34]. In our study, a trend toward underutilization of combination of insulin with either a SFU or metformin was observed. Only (6.8%) of those receiving antidiabetic combination therapy were using insulin.

Antihypertensive drug choice:

Although several reports indicated that most diabetic hypertensive patients may require more than one antihypertensive agent to achieve an optimal blood pressure control, approximately, (~ 48%) were prescribed a single antihypertensive agent (monotherapy) while approximately 43% were prescribed 2-drug combination and approximately 8% were prescribed 3-drug combination. This underutilization of the antihypertensive drugs may be due to either lack of knowledge or economic reasons. In either case, the suboptimum use of antihypertensive drugs will increase risks of cardiovascular morbidity and mortality among the patients.

Despite the adverse effects of beta blockers on glucose homeostasis, beta-blockers, mainly as atenolol, accounts for (94 /542; 17.3%) of the total antihypertensive medications consumed by the tested sample. More than 80% (data not shown) of atenolol consumed by the diabetic hypertensive patients in the tested sample was prescribed at a high dose (100 mg daily) rather than the low dose (50 mg daily) which might increase the risk of beta-2 mediated insulin secretion blockade [35, 36].

ACE-I was the most commonly prescribed drug class both in mono and combination therapy (180/542; 33.2%). The use of ACE-I among diabetic hypertensive patients is in accordance with the current recommendations for the management of hypertension among diabetic patients. ACE-I are known to have favorable effect on blood glucose level and a renoprotective effect which makes this drug class to be preferred among hypertensive patients with diabetes mellitus. However, the expensive ATII-RA drug class was not prescribed indicating absence of such drug class from the clinics or lack of current knowledge about favorable effects of such drugs on diabetic hypertensive patients or tight control imposed by the authorities on prescribing such expensive drugs. Among the ACE-I drug class, captopril and enalapril were equally utilized among those patients receiving antihypertensive monotherapy. Captopril was more frequently utilized among those patients receiving two or three antihypertensive drug therapy. This popularity of captopril may be attributed either to the availability of this drug at the clinics of the MOH as a donation from other countries or to the low cost of captopril compared to other drugs in the ACE-I class.

Calcium channel blockers (CCB) ranked second in monotherapy (table 3) and ranked third in overall antihypertensive drug utilization (Figure 2B). The non dihydropyridine, diltiazem, was the most commonly prescribed CCB and verapamil being the least commonly prescribed. The dihydrpiridine, nifedipine and amlodipine, were in between. The popularity of the non-DHP diltiazem may be due to its reported positive effects on diabetic proteinuria [37].

Diuretics ranked second when considering overall utilization of antihypertensive drugs and ranked fourth when considering antihypertensive monotherapy (table 3). However, diuretics were extensively used in two and three drug combinations. Furosemide was the most commonly used diuretic followed by hydrochlothiazide (HCT). The overutilization of furosemide may be inappropriate. This might be attributed to the reluctance of physicians to prescribe HCT. It has been reported that HCT adversely affect glucose homeostasis, but such an effect is minimal at low HCT dose [38]. Combination of **ACE-I plus diuretic** was the most commonly seen among two and three antihypertensive drug combinations as seen in table (3). 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 [39]. Other commonly used antihypertensive combinations among the tested sample include a BB plus ACE-I, BB plus CCB, BB plus diuretic, ACE-I plus CCB and CCB plus an alpha blocker. **ACE-I plus CCB** combination ranked second among the 2-drug antihypertensive therapy (table 3), with the dihydropyridine, amlodipine, being the most common CCB used in this combination (table 4). This combination could provide better blood pressure level lowering, but their effects on proteinuria is comparable to ACE-I alone [40]. Non-DHP (e.g. diltiazem) plus ACE-I combination lowers insulin resistance and has an additive anti-proteinuric effect [41]. Combination of **CCB plus BB** ranked third among the 2-drug antihypertensive therapy. In this combination, diltiazem was the most common type of CCB used. A combination of diltiazem and beta blockers may have too much depressive effect on the heart while a combination of beta blocker with nifedipine might have beneficial compensatory mechanisms [42]. The utilization of **BB plus diuretics** combination which ranked fourth among the 2-drug combination is inappropriate since both drugs adversely affect lipid and glucose metabolism. [42]. The **CCB plus diuretics** or **alpha blocker** ranked fifth and seventh among the 2-drug antihypertensive combinations respectively. Only two patients were prescribed CCB plus alpha blocker. The CCB used in this combination was the non-DHP diltiazem while the alpha blocker used was prazocin. No clinical studies published in the literature that tests such combination. However both CCB and alpha blockers are tolerated classes of antihypertensive drugs for treating hypertension in diabetic patients [43, 44]. **ACE-I plus BB** combination which ranked sixth among the 2-drug combination is controversial since BB are know to block rennin release which is an early step where ACE-I acts [42].

Conclusion and Recommendation:

We concluded from this study that there are some inappropriate uses of medications among diabetic hypertensive patients that will increase the health and economical risk on the patient and the health system. We strongly recommend better drug monitoring for medications among this category of patients as well as patients with chronic diseases. This monitoring could be achieved through appointing new pharmacist whose responsibility is to review patient's medication and deliver continuing medical education in the field of current pharmacotherapy.

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