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ASPIRIN THERAPY AMONG DIABETIC HYPERTENSIVE PATIENTS:

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التداوي بالأسبرين عند المرضى المصابين بالسكري والضغط معا"

ملخــص: الهدف من هذة الدراسة هو تحديد نسبة المرضى المصابين بالسكري والضغط والذين يتناولون الأســبرين وتحديــد اذا ما كان هنالك فروق في الجنس أو العمر من حيث تناول الأسبرين. تمت الدراسة بواسطة تحليل الملفات الدوائية ل 342 مريضا" بالسكري والضغط. معدل أعمار المرضى في العينة كان 64.4 ونسبة الذكور الى الأناث كانت 1.03 : 1 . فقط 31.5% من العينة كانوا يتناولون الأسبرين. وجد فروق بين الجنسين في تناول الأسبرين(38% بين الذكور و 25% بين الأناث) ولكن لم يوجد فروق في تــناول الأسبرين بين الفئات العمرية المختلفة. في المحصلة فان استعمال الأسبرين اقل من اللازم في هذه الفــئة مــن المرضـــى. علـــى الأطباء وصف الأسبرين بصورة أكثر كوقاية أولى أو ثانوية عند هؤلاء المرضى.

Abstract The objective of this study was to determine the percentage of diabetics with hypertension who are using aspirin, and to report on any differences between males and females and age groups. Medical records of the 342 diabetic hypertensive patients were analyzed. The mean age of the patients in the sample was 64.4 years and male: female ratio was 1.03 : 1. Among the sample population studied, only 108/342 (31.5%) were using aspirin. Gender differences in aspirin therapy was noticed. Aspirin was used in 42/168 (25%) females versus 66/174 (38%) males. No significant age differences were seen in aspirin therapy. As a conclusion, aspirin use is low in diabetics with hypertension. Physicians in Palestine should be encouraged to use aspirin more in diabetics for both primary and secondary prevention of cardiovascular disease.

Key Words: Aspirin, Clinical Pharmacology, Diabetic Hypertensive Patients, Palestine.

Introduction

According to the *American Heart Association,* it is possible to say that diabetes mellitus is a cardiovascular disease [(1)]. One reason for this description is that 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) [2]. Studies have shown an increased platelet adhesiveness and aggregability, with a concomitant increased release of thromboxane, in diabetic subjects [3]. Furthermore, these vascular complications are augmented by the co-existence of hypertension [4]. Due to this elevated risk of vascular complications among diabetic hypertensive patients, the use of proven cardiovascular preventive therapies is imperative. One of the cardiovascular preventative strategies that can be used to lower vascular incidence is administration of a safe and inexpensive drug like aspirin [5-7]. In fact, since 1970s, more than 200 randomized controlled trials have been carried out to investigate the benefit of aspirin in primary and secondary prevention of all types of vascular diseases [8 - 10]. A study carried out by Yudkin JS. compared four different approaches to reduce cardiovascular risk among patients with and without diabetes. This study concluded that aspirin treatment would provide approximately an extra one year of life expectancy in diabetes similar to the potential benefit of anti-hypertensive treatment [11]. Other studies have suggested that individuals with diabetes benefit from aspirin use as those without diabetes, however, due to the fact that diabetics have markedly higher baseline risk, the absolute benefit of aspirin therapy may be two to four times higher among diabetics compared with non-diabetics [5, 7, 9]. Furthermore, the use of aspirin, does not increase risk of retinal or vitreous hemorrhage and can be safely used in patients with diabetes who do not have other contraindications (e.g., allergy, bleeding tendency, anticoagulant therapy, active liver disease) [12, 13]. The first recommendation for the use of low dose aspirin in primary and secondary prevention of high risk diabetics (e.g. patients with diabetes mellitus and hypertension) was published in 1997 by the American Diabetes Association [14]. This recommendation was further emphasized by the ADA 2000 publication in which aspirin was recommended for any one with diabetes mellitus and above the age of 30 and with no known aspirin contraindications [15].

The objectives of this study was to determine the percentage of patients diagnosed with diabetes mellitus type 2 and hypertension who are using aspirin, to determine the conformity of aspiring prescribing to the current recommendation and finally to report on any differences between males and females in using aspirin therapy.

Methodology

This study was carried out on patients attending governmental clinics. Patients attending private clinics or hospitals were not studied because they were not accessible at the time of the study. Several thousands of patient's files were screened. All the medical files of patients who were diagnosed with diabetes mellitus and hypertension in Nablus/West-Bank governmental clinics were considered for the study. Medical files that contain full information regarding age, sex, history of the disease, name and specialization of the physician who diagnose the patient, drugs prescribed and dates of regular visits with the all laboratory results attached were included in the study. On the other hand, medical files that contain incomplete information or missing laboratory data (e.g. fasting blood sugar, blood pressure, lipid profile etc.) were excluded from the study. Patients are considered positively diagnosed with diabetes mellitus and hypertension if they were regularly attending the clinic for at least the past twelve months, their laboratory results indicate a fasting blood sugar higher than 120 mg/dl, resting blood pressure higher than 140/90 mmHg and have been receiving medications for diabetes mellitus and hypertension. The medical files of three hundred forty two patients (342) patients who were diagnosed with diabetes mellitus type 2 and hypertension and whose medical files contain all the information needed 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:

1. Age, Gender and Drug Profile of the 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 prescribed 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

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 montherapy, 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 prescribed 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%). Among those prescribed either mono or combination insulin therapy, (44/70; 62.8%) patients were prescribed NPH insulin while (26/70; 37.2%) patients were prescribed mixtard insulin preparation.

Among the study population, a total of 86 males and 76 females (162/342; 47.3 %) were prescribed anti-hypertensive monotherapy. A total of 70 males and 78 females (148/342; 43.3%) were prescribed two-drug antihypertensive therapy, whereas 16 males and 12 females (28/342; 8.2%) were prescribed three-drug antihypertensive therapy. Four patients, two males and two females (4/342; 1.2%), were not prescribed anti-hypertensive drug therapy. Among those prescribed 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 prescribed 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 combinational 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%).

2. Prescribing "frequency" of Aspirin:

One hundred and eight patients (108) patients out of the three hundred forty two patients (342) were prescribed low dose (100 mg) aspirin daily therapy. So the majority of the patients in the sample were not prescribed aspirin or any other anti-platelet therapy (234/342; 68.4%). Statistical analysis indicate that patients who were prescribed aspirin are significantly lower than those who were not prescribed aspirin (*$P<0.001$).*

3. Prescribing "pattern" of Aspirin therapy:

The age gender characteristics of those patients prescribed low dose aspirin therapy is shown in table 2. Analysis shows statistical difference in the gender versus low dose aspirin therapy (d.f = 1, $P < 0.05$). Less females were receiving low dose aspirin therapy (25%) versus males (32%).

Table 2: Low dose aspirin therapy versus gender distribution.

Anti-platelet Therapy	Gender		Total
	Male	Female	
None	108/174 (62%)	126/168 (75%)	234
Aspirin	66/174 (38%)	42/168 (25%)	108
Total	174	168	342

Age versus low dose aspirin therapy distribution (table 3) shows that only 29% of patients aged 60 or above were prescribed low dose aspirin or any other anti-platelet. Among patients aged less than 60 years, 37% were prescribed low dose aspirin therapy. However, analysis for significance shows no statistical difference of age versus aspirin therapy distribution (d.f. = 3, $P > 0.05$).

Table 3: Low dose aspirin therapy versus age distribution.

Age (years)	Anti-platelet Therapy		Total
	None	Aspirin	
< 60	68/108 (63%)	30/108 (37%)	108
> 60	166/234 (71%)	78/234 (29%)	234
Total	234	108	342

4. Disease Profile of Patients Prescribed Low-Dose Aspirin:

Analysis of other co-morbid conditions present in the three hundred forty two patients sowed that: 21.6% were having a history of coronary artery diseases (CAD), 11.1% were having congestive heart failure (CHF), 9.9% were having renal problems as indicated by creatinine results, 57% were smokers, 69% were overweight (BMI> 25) and 43.3% were having dyslipidemia as indicated by total triacylglycerol, LDL and HDL levels. The disease characteristics of those prescribed low dose aspirin is shown in table 4. Other factors like family history of cardiac diseases were not included in the patient's file making it difficult to study the influence of such factor on the prescribing of aspirin.

Statistical analysis indicate that there is significant correlation between aspirin prescribing and the presence of a history of CAD ($P < 0.005$) while no significant correlation exist between aspirin prescribing and the presence of other disease conditions like CHF, renal problems, dyslipidemia, smoking and body weight ($P > 0.1$). These results suggest there is little consideration to the total disease condition of the patient when prescribing aspirin. It seems that a history of CAD is the strongest positive motivation for physicians to prescribe aspirin, however, other factors have little or no effect.

Table 4: Low dose aspirin therapy versus disease conditions present in the sample patients diagnosed with diabetes mellitus and hypertension. Note that the numbers are overlapping and thus the total patients prescribed aspirin is greater than 108 patients.

Other Co-morbid Condition	Anti-platelet Therapy		
	None	Aspirin	Total
CAD	13/74 (17.6%)	61/74 (82.4%)	74
CHF	16/38 (42%)	22/38 (58%)	38
Renal problem	26/34 (76.4%)	8/34 (23.5%)	34
Dyslipidemia	67/148 (45.3%)	81/148 (54.7%)	148
Smoking	112/195 (57%)	83/195 (43%)	195
Overweight (BMI> 25)	169/236 (71.6%)	67/236 (28.4%)	236

Pooling of these data to fully characterize the patients prescribed low dose aspirin, we find that more than 65% (72/108) of those patients have the following characteristics: diabetic hypertensive with a history of CAD, dyslipidemic and smokers.

5. Characteristics of Physicians Prescribing the Low-Dose Aspirin:

The physicians prescribing the medications for the patients were cardiologists and endocrinologists. No data available on their year or country of graduation. It is difficult to draw conclusions or correlation between aspiring prescribing and physician's factors like country and year of graduation. However, the prescribing physicians are specialists who have been working in the clinics for at least the past five years.

6. West Bank versus Gaza:

This study is carried in West-Bank. Up to our knowledge, no published data is available on the situation in Gaza. Therefore, it is not possible to compare the aspirin prescribing among diabetic hypertensive patients in West-Bank versus those in Gaza.

Discussion

This survey found that less than one third (31.5%; 108/342) of the patients with diabetes mellitus type 2 and hypertension were on low dose (100 mg) aspirin therapy. This is not in accordance with the ADA guidelines as well as the current clinical trial outcome recommendations. The ADA recommended that the presence of at least one of the following risk factors in a patient with diabetes confers eligibility for aspirin therapy: family history of heart attack, smoking, body weight in excess of 120% of normal, hypertension, micro- or macroalbuminuria, or dyslipidemia. In our study, all the patients analyzed have at least one cardiovascular factor which is hypertension.

We can suggest several possible reasons for the low rates of aspirin use among people with diabetes type 2 and hypertension: (1) the lack of up-dated knowledge among practicing physicians about ADA guidelines and recommendations as well as the current clinical trials on aspirin on diabetic patients; (2) Physicians might have an exaggerated perception of the risks of aspirin therapy for people with diabetes, particularly those with retinopathy or hypertension. Results from the Early Treatment Diabetic Retinopathy Study (ETDRS) and the Hypertension Optimal Treatment (HOT) trial should be clarified to physicians. The ETDRS used a relatively high dose of aspirin (650 mg/day) in people with diabetes and retinopathy, yet showed no significant increase in the risk of severe complications [13]. In the HOT study, which included 1,501 patients with diabetes, 75 mg/day of aspirin reduced the risk of myocardial infarction, with no effect on stroke or fatal bleeds [5]. It is also possible that patients with more severe diabetes may be less motivated to comply with recommendations for aspirin therapy. Such patients are often prescribed multiple antihypertensive and anti-diabetic therapies. Aspirin may be perceived as relatively unimportant or unnecessary. Although, it was statistically insignificant, our findings indicate that aspirin was less likely to be used by patients above 60 years old than by younger patients who are less than 60 years old. This difference could not be due to differences in income or education since aspirin therapy is in-expensive and promoted and sold as over-the-counter cardio protective drug in community pharmacies in Palestine. In fact, we were expecting the opposite. In our study, aspirin was also less commonly used by women than by men. The *Early Treatment Diabetic Retinopathy Study* (ETDRS) and the *Hypertension Optimal Treatment* (HOT) study contained many women with diabetes and showed significant reductions in the risk for the first myocardial infarction with aspirin therapy. Elderly women have similar cardiovascular risk factors as men and should use a cardioprotective therapy as vigorously as men. Although, our study is limited by the fact that the complete diseases profile is not fully known, it is clear that there is suboptimal use of aspirin in this high risk group of patients.

An extensive plan for diabetic hypertensive patients must be carried out. Those registered patients must be screened and evaluated for the potential use of low dose aspirin. The ministry of health need to organize continuing medical education in the field of clinical pharmacology and therapeutics for working physicians. Emphasis should be made on recent findings and recommendations regarding primary and secondary cardio-protection with anti-platelet drugs.

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