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SHORT RESEARCH REPORT

Contraindications to metformin therapy among patients with type 2 diabetes mellitus

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Abstract
Objective The biguanide, metformin, is a commonly prescribed oral antihyperglycemic agent. However, there are several clinical conditions that are considered as contraindications to the use of metformin among patients with type 2 diabetes mellitus. The aim of this study was to investigate the presence and nature of contraindications to metformin therapy among patients with type 2 diabetes mellitus.
Method A retrospective study of the medical files of diabetic patients available at Alwosta clinic, north Palestine was carried out. Information about disease and medication profile of the patients was retrieved and analyzed using SPSS during the study period in 2004/2005. Focus was on metformin users who have contraindications to metfromin therapy.
Main outcome measure Presence and number of contraindications to metformin therapy.
Results Two hundred and seventy-two type 2 diabetic patients were identified. One hundred and twenty four of those diabetic patients were metformin users. Approximately, 60% of patients in the metformin group had a least one contraindication. Congestive heart failure and renal impairment were the most quantitatively present contraindications.
Conclusion Contraindications to metformin therapy are common among type 2 diabetic patients and mostly disregarded. Patients have to be critically assessed before starting therapy and in case of metformin prescribing; dose should be adjusted based on the presence of risk factors for metformin adverse effects.

Keywords Contraindications · Drug-related problems · Medication-related problems · Medication safety · Metformin · Palestine · Type 2 diabetes mellitus

Impact of findings on practice

- Diabetic patients with contraindications for metformin need to be screened better.
- It would be useful to establish follow-up programs for diabetic patients to screen for medication-related problems.

Introduction

Metformin, a biguanide, has become a preferred and well established medication for the treatment of type 2 diabetes mellitus, particularly in obese patients [1, 2]. It is often used alone or in combination with sulfonylurea (SFU) among patients who have not achieved glycemic control using dietary management alone. Metformin is believed to act through inhibition of hepatic gluconeogenesis, decreasing intestinal absorption of glucose, increasing the insulin-mediated glucose disposal and inhibition of fatty acid oxidation [3, 4]. The UK Prospective Diabetes Study (UKPDS) indicated that obese patients with newly diagnosed type 2 diabetes mellitus and who received metformin had a significant reduction in the rate of diabetes-related mortality and morbidity compared with patients given diet or

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sulfonylurea only [5]. Other positive aspects of metformin therapy include its beneficial effects on insulin resistance, obesity and hyperlipidemia [3, 6–9]. The apparent protective effects of metformin against vascular complications has stimulated the wide spread prescribing of metformin. However, metformin, like any pharmacological agent, has its own precautions and contraindications [10, 11]. Although gastrointestinal side effects may render the drug intolerable or limit the dose, the main concern with metformin is lactic acidosis which is fatal in 50% of the cases [12, 13].

The risk of lactic acidosis can be minimized by avoiding the use of metformin or adjusting its dose in patients with well-established contraindications. These contraindications mainly include renal impairment, tissue hypoxia as in the case of heart and respiratory diseases that require medications, hepatic impairment, elderly (>80 years), surgical procedures, and use of contrast media [4, 10]. Metformin contraindications are clearly stated in Arabic and in English language in the package leaflet of all metformin brand products available in the Palestinian pharmaceutical market. Despite these contraindications, metformin continues to be prescribed to patients at risk for developing adverse effects [14, 15].

Aim of the study

The aim of this study was to investigate the presence and nature of contraindications to metformin therapy among patients with type 2 diabetes mellitus.

Method

A retrospective study was carried out using medical files for patients attending Al-Wosta out-patient governmental clinic in north Palestine. The patients attending the clinic are those registered at the Ministry of Health as chronic patients, had governmental medical insurance and are residents of north Palestine. This clinic delivers pharmaceutical and medical care to patients with diabetes mellitus as well as other chronic diseases. Medical files for patients diagnosed with type 2 diabetes mellitus and treated with oral antihyperglycemic agents in the form of metformin or sulfonylurea were eligible for the study. Those patients were divided into two main groups: metformin group and sulfonylurea (SFU) group. The metformin group consisted of all patients using either metformin alone or in combination. The SFU group consisted of all patients using SFU alone. Information regarding age, sex, co-morbid conditions, and medications in general and oral antihyperglycemic agents in particular were obtained from the medical files. Data obtained regarding oral antihyperglycemic agents included the type and dose of medication dispensed. Data collection was made over 6 months and was authorized by the Ministry of Health.

Data obtained were analyzed regarding the presence of contraindications to metformin therapy. Contraindications to metformin therapy were defined as those present in the manufacturer's package leaflet as well as recent literature on metformin therapy. All data obtained were entered and analyzed using Statistical Package for Social Sciences (SPSS) program for windows version 13. Results were expressed as mean ± standard error of the mean. Chi square test was used to test for significant difference among groups. The level of significance was used at a P value < 5%. All graphs were made at SPSS and converted to WinWord format.

Results

Through the search of medical files available at the center, 272 type 2 diabetic cases were identified. Those 272 patients (130 women, 142 men) had a mean age of 63 ± 12.6 (42–89) years; 47% of them were older than 65 years and 16.6% were older than 75 years. The 272 patients were residents of north Palestine area. Their average visit to the clinic was once monthly. No data regarding duration of the disease or levels of glycosylated hemoglobin were available in medical files to be used as in indicator of glycemic control.

The antidiabetic regimens used for the 272 patients were either metformin alone (42), or metformin with sulfonylurea (SFU) (82) or SFU alone (148). The main SFU prescribed was glibenclamide. The total number of patients treated with metformin as mono or combo therapy was 124 (metformin group). Further analysis was made on this metformin group. Analysis focused on disease and drug contraindications and risk factors.

Of the 124 patients in the metformin group 52 patients had one contraindication, and 22 patients had two contraindications. Taking both data together, a total of 74 patients (60%) had at least one contraindication and 50 patients (40%) had no contraindications to metformin therapy. The most common contraindications were CHF, renal impairment followed by coronary artery diseases, hepatic and respiratory diseases (Fig. 1). The 50 patients with no contraindications to metformin therapy were characterized by lesser number of cardiac co-medications per

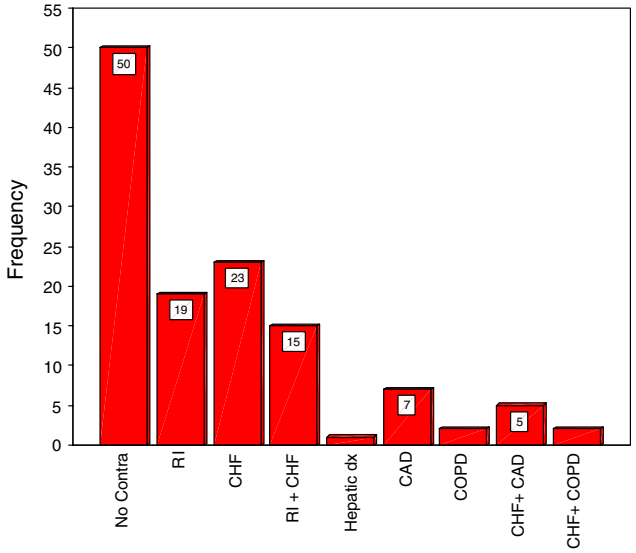

Fig. 1 Frequency and type of contraindications to metformin therapy among the patients in the metformin group. Contraindications are: RI, renal impairment; CHF, congestive heart failure; CAD, coronary artery disease including myocardial infarction; COPD, chronic obstructive pulmonary disease

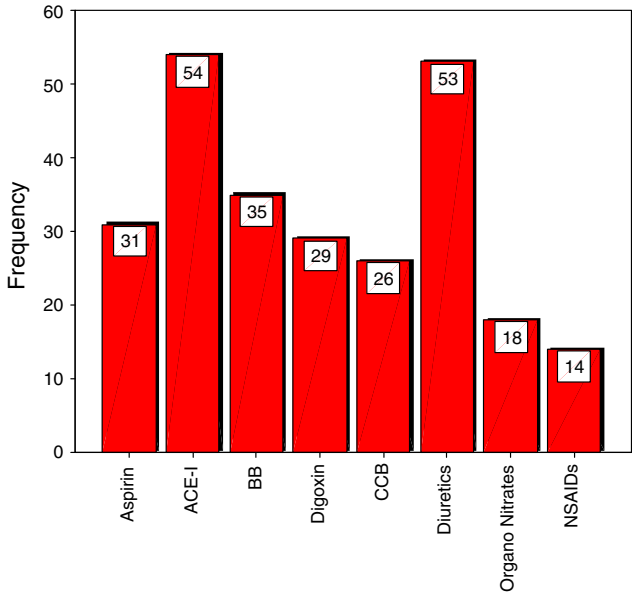

Fig. 2 Cardiovascular co-medications present among the 124 patients in the metformin group. Co-medications: ACE-I, angiotensin converting enzyme inhibitors; BB, beta blockers, CCB, calcium channel blockers; NSAIDs, non-steroidal anti-inflammatory drugs

patient and lower age range (39–57 years). Among the three different anti-diabetic regimens (metformin alone, metformin + SFU and SFU alone), there was no statistical difference ($P > 0.05$) in the prevalence of CHF or renal impairment.

The patients in the metformin group were prescribed a total of 226 cardiac medications, an average of 1.8 cardiac drugs per patient. Cardiac medications commonly prescribed include angiotensin converting enzyme inhibitors (ACE-I), beta blockers, calcium channel blockers, baby aspirin and diuretics. Other non-cardiac drugs, like NSAIDs, were co-prescribed with metformin in the study group (Fig. 2). Some of these medications might induce renal adverse consequences and hence should be administered with caution in this metformin group. Angiotensin converting enzyme inhibitors (ACE-I) were co-prescribed in 54 patients, diuretics in 53 patients and NSAIDs were co-prescribed in 14 patients.

Among the metformin group, only two dosing regimens were used, either a one tablet (850 mg) daily or two tablets (1700 mg) daily. The one tablet daily (850 mg) metformin regimen was prescribed for 71 of the patients, 20 of them were using metformin as a monotherapy (Table 1). The two tablets daily (1700 mg) metformin regimen was prescribed for 53 patients, 19 of them were using metformin as monotherapy. Among patients with no contraindications, the dose used was significantly in favor of the 850 mg daily dose. However, no significant dose preference was found among patients with no contraindications. Analysis of the total daily dose of metformin among patients with no contraindications, one contraindication and two contraindications to metformin therapy revealed that there was no significant difference ($P = 0.081$) in the use of 850 mg vs. 1700 mg daily dose (Fig. 3).

Discussion

Metformin therapy requires careful observation of contraindications. In the present study group of type 2 diabetic patients treated with metformin, approximately 60% were found to have contraindications which necessitate change of metformin regimen or caution. Other published studies yielded similar prevalence rate of contraindications. Of the 89 patients treated with metformin and admitted to a British university diabetes clinic, 54% had contraindications or risks precluding metformin treatment [14]. Another study in Germany found that 64% of the study population was having contraindications/precautions to metformin therapy [15].

Manufacturers of metformin containing products consider CHF that requires drug therapy as a contraindication [16, 17]. In our study, SCH was the most

Table 1 Demographic and clinical findings in patients receiving different oral drug therapy regimens for type 2 diabetes mellitus

Variable	Medication regimen				
	Metformin alone	Metformin plus SFU	SFU alone	Sub-total	Total
Number (*n*)	42	82	144		272
Gender					
F	18	40	71	130	272
M	24	42	73	142	
Age					
>70	24	50	39	114	272
<70	18	32	10	158	
Dose of metformin					
850 mg daily	20	51	–		71
1700 mg daily	19	34	–		53

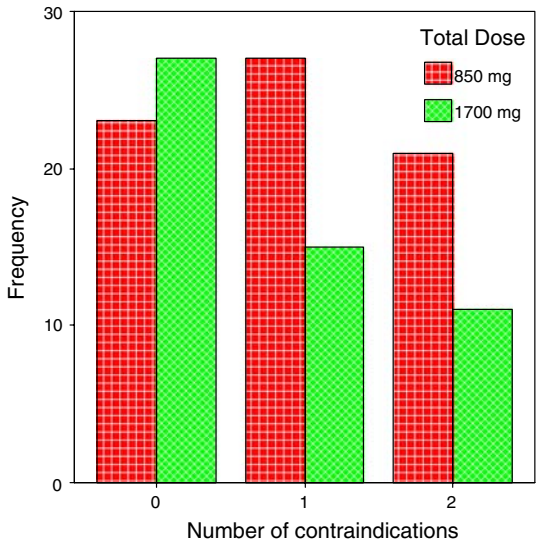

Fig. 3 Dose regimens of metformin for patients with different numbers of contraindications. No significant difference was found. 0, 1, 2: no, one and two contraindications, respectively

frequently occurring contraindication. This use of metformin in patients with CHF might have some advantages based on UKPDS findings. In the UKPDS, in overweight patients, metformin monotherapy led to a distinct reduction in the risk of diabetes-related endpoints, deaths and overall mortality among patients with cardiac diseases [5]. However, in our study, metformin monotherapy was applied to 34% (42/124) of the patients while in 66% (82/124) of the cases, metformin was combined with SFU, and for this combination the UKPDS found higher mortality. So, the use of metformin among patients with CHF was not against the manufacturer's advice, but also the recommendations of UKPDS findings regarding combining metformin and SFU [5].

Renal impairment was quantitatively, the second most common contraindication and was present in 34 (27%) of the patients. Renal impairment predisposes metformin patients to the most serious side-effect, type B lactic acidosis, which leads to death in 50% of cases [16]. The relationship between lactic acidosis and metformin use is still a controversial and debatable issue. A population-based study showed that similar rates of lactic acidosis are present in populations treated or untreated with metformin. The authors concluded that the association between metformin and lactic acidosis may be coincidental rather than causal [18]. However, further studies are required on the role of the disease conditions currently agreed to constitute risks of metformin induced lactic acidosis.

Other contraindications that were present in our study group include hepatic disease, chronic obstructive pulmonary disease and coronary artery diseases. Although, these contraindications were present in quantitatively fewer patients, they are considered very serious contraindications. In general, our study involved a group of patients mainly in their sixties with high co-morbidity and extensive co-medications indicative of compromised health state. Even, among patients with no absolute contraindications the use of metformin should be assessed critically.

Some medications co-prescribed with metformin might constitute a risk factor for serious metformin induced adverse effects. Angiotensin-converting enzyme inhibitors (ACE-Is) are commonly prescribed for diabetic nephropathy, hypertension and CHF. These diseases constitute risk factors for renal failure in diabetic patients and hence increase the risk of development of metformin induced lactic acidosis (MALA). Furthermore, combination of ACEI and metformin has been reported to have a possible synergistic effect on the development of hyperkalaemic lactic acidosis [19]. Non-steroidal anti-inflammatory drugs (NSAIDs) are also well known to precipitate acute renal failure, particularly in the elderly and susceptible individuals. Hence caution should be exercised in the co-administration of metformin and

NSAIDs. In a recent report, indomethacin therapy was associated with MALA in a middle age patient with normal renal function who had been treated with low dose metformin (500 mg twice daily) [20].

Analysis of metformin doses used among the patients showed that the group with contraindications was prudentially treated with lower total metformin daily dose than the group with no contraindications. This finding might suggests that although contraindications to metformin therapy might be disregarded, doses are adjusted to reduce risks.

There are limitations to this study, including the size of the metformin group, and the apparent lack of consideration of glycemic control, which would intuitively seem important as a factor for metformin selection. Of additional note is that in some cases, it is probable that the contraindications for using metformin were noted, but these were deemed to be outweighed by the benefits of the metformin therapy. Finally, a recent review study of pooled data from 206 comparative trials and cohort studies revealed no cases of fatal or non-fatal lactic acidosis in 47,846 patient-years of metformin use or in 38,221 patients-years in the non-metformin group [21]. The 95% confidence intervals of the upper limit for the true incidence of metformin-associated lactic acidosis was 6.3 cases per 100,000 patient-years, and the upper limit for the true incidence of lactic acidosis in the non-metformin group was 7.8 cases per 100,000 patient-years [21]. There was no difference in lactate levels, either as mean treatment levels or as a net change from baseline, for metformin compared to placebo or other non-biguanide therapies. The authors of the review concluded that there is no evidence from prospective comparative trials or from observational cohort studies that metformin is associated with an increased risk of lactic acidosis or with increased levels of lactate compared with other antihyperglycemic treatments [21]. Regardless of these limitations, the information from this study does represent prescribing practices in the clinic investigated over the study period, and is of interest to those working to improve medication safety in the ministry of health.

Conclusion

Contraindications to metformin therapy were common among type 2 diabetic patients and mostly disregarded. Patients have to be critically assessed before starting therapy and in case of metformin prescribing; dose should be adjusted based on the presence of risk factors for metformin adverse effects. This study should encourage better screening for diabetic patients with contraindications and precautions to metformin therapy, improve prescribing pattern of medications in general and that of metformin in particular, establish follow up programs for diabetic patients to screen for medication problems, and finally to invest more in clinical pharmacist who can help improve medication use and prescribing pattern.

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