

**Influence of Disease and Drug Risk Factors on Metformin Dose Adjustment: A Retrospective Study of Outpatients in Nablus.**

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**Abstract:** Background: Metformin may, in the presence of certain risk factors, cause serious lactic acidosis. The aim of this study was to investigate the presence of risk factors for lactic acidosis among diabetic patients and to determine whether metformin daily dose was influenced by the presence of these risk factors or not. Methods: This is a retrospective study of one hundred and eighteen diabetic patients receiving metformin. Information about disease status and medication profile of the patients were retrieved from patients' medical files. Data were coded and entered using SPSS for analysis and graphics. Results: Approximately, two thirds (74/118, 62.7%) of the included patients had a least one disease risk factor for lactic acidosis. Of those patients, (48/74; 64.9%) had a dose adjustment, with congestive heart failure and renal impairment being the risk factors most likely to result in a dose adjustment. More than one third (38%) of metformin patients were co-prescribed ACE-I or NSAIDs. The dose of metformin was insignificantly influenced by the co-administration of drug risk factors. Conclusion: Metformin total daily dose was significantly influenced by the presence of disease risk factors and was insignificantly influenced by the co-administration of drug risk factors. Short running title: Risk Factors and Metformin Dose.

**Key words:** metformin, risk factors, dose, lactic acidosis.

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.(lactic acidosis)

SPSS

(%62.7)

%64.9

.lactic acidosis

NSAIDs ACE-I

. lactic acidosis

**Introduction:**

It is estimated that (2.1%) of Palestinians living in *West-Bank* have diabetes mellitus <sup>(1)</sup>. There are several pharmacological treatment options for diabetes mellitus. Biguanide agents have been used in the treatment of type 2 diabetes mellitus for more than 20 years. Phenformin, a member of biguanide family, was withdrawn from the market because of its association with lethal lactic acidosis <sup>(2)</sup>. Metformin, a member of biguanide family, is still in medical use and has also been linked with metabolic lactic acidosis but less frequently than phenformin <sup>(3, 4)</sup>. Metformin is extensively excreted by the kidneys with a half life of 1.5 – 4.9 h <sup>(5, 6)</sup>. The anti-hyperglycemic effect of metformin is largely due to inhibition of hepatic gluconeogenesis, increased insulin-mediated glucose disposal and inhibition of fatty acid oxidation <sup>(7, 8)</sup>. Although metformin is generally considered safe, it can, under certain conditions, cause serious lethal lactic acidosis <sup>(9)</sup>. Despite the very low prevalence of metformin-induced lactic acidosis, its prevention is of significant clinical importance due to a 50% mortality rate <sup>(10, 11)</sup>. The risk of lactic acidosis can be minimized by avoiding the use of metformin or adjusting its dose in patients with disease conditions that lead to high plasma metformin concentrations, and/or conditions that decrease removal of lactate such as renal impairment heart failure, severe infection, hepatic impairment and respiratory disease <sup>(12 – 15)</sup>. There are certain drugs that could lead to an increase in the metformin potential to cause lactic acidosis. Cimetidine, in conventional doses, have been shown to increase the metformin peak plasma level and thus dose of metformin should be reduced with cimetidine co-administration <sup>(16)</sup>. ACE-I are known to affect the renal

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function especially among diabetic patients with renal vascular disease and thus caution should be exercised when metformin is co-prescribed with ACE-I<sup>(17-19)</sup>. A published clinical case report has indicated that metformin and ACE-I have possible synergistic effect on the development of hyperkalemic lactic acidosis<sup>(20)</sup>. NSAIDs are known to precipitate acute renal failure, particularly in the elderly. Hence, caution should be exercised in the co-administration of NSAIDs with metformin<sup>(21)</sup>.

The aim of this study was (1) to investigate the presence of disease and drug risk factors for lactic acidosis among diabetics patients receiving metformin and (2) to investigate whether the presence of these risk factors will influence the selection or adjustment of total daily dose of metformin or not.

### **Methods and Materials:**

This study was carried out retrospectively using medical files of patients attending out-patient governmental clinics in Nablus/Palestine. The patients included in the study were registered at the Ministry of Health as chronic patients and they dispense their medications on regular time basis. All the medical files of patients who were diagnosed with diabetes mellitus were considered for the study. Medical files that contain full information regarding age, sex, diagnosis, drugs and their doses were included in the study. On the other hand, medical files that contain incomplete information were excluded from the study. Patients are considered positively diagnosed with diabetes mellitus if they were regularly attending the clinic for at least the past twelve months, their laboratory results indicate a fasting blood sugar higher than 126 mg/dl and have been receiving medications for diabetes mellitus. The medical files of three hundred forty two patients (342) patients who were diagnosed with diabetes mellitus type II and whose medical files contain all the information needed were reviewed and analyzed. Focus was made on 118 diabetic patients who were receiving metformin as mono or combination therapy for treatment of diabetes mellitus. Less than 10% of the patients included in the study were receiving metformin in combination with glibenclamide oral hypoglycemic agent. The patient's metformin total daily dose of either 850 mg or 1700 mg was recorded. The presence and nature of diseases or drugs that could be a risk factor for lactic acidosis were also obtained from the medical file and recorded. Risk factors considered were those discussed in literature and cited in references 12 through 15. The data regarding

age, gender, drug profile (all drugs prescribed for the patients) were extracted from the medical files, entered 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.

### Results:

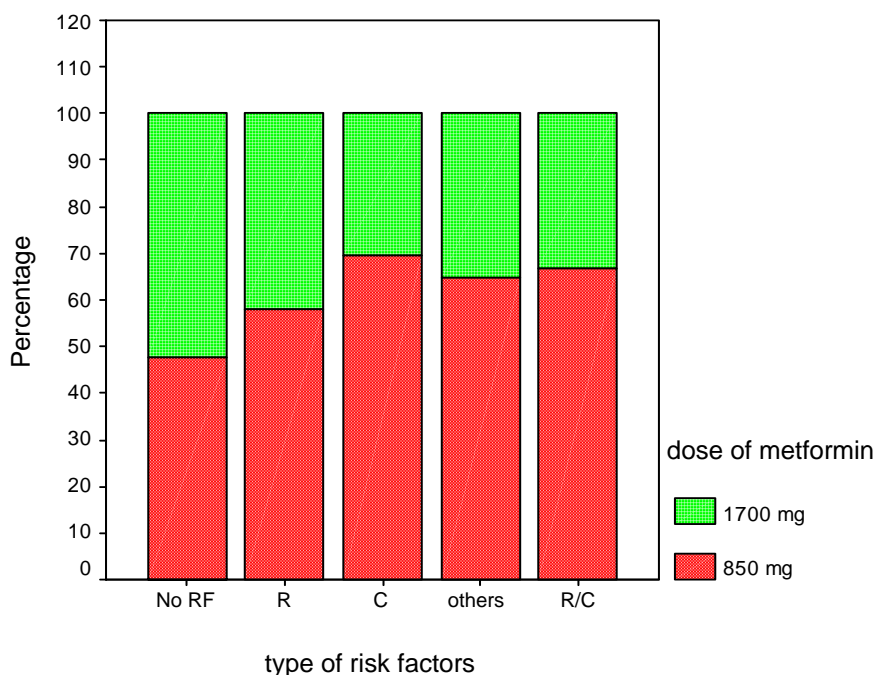
One hundred and eighteen (118) diabetic patients using metformin were enrolled in the study. Two thirds (74/118, 62.7%) of those patients had at least one risk factor for lactic acidosis. The mean age of the patients was 66.5 years (Std. Deviation = +/- 7.5). One third of the patients were above 70 years of age. Gender distribution was slightly in favor of males (51.7% for males versus 48.3% for females). Higher percentage of males (68%) were having risk factors than females (57%).

The patients were divided into two groups based on the presence or absence of disease risk factors. When disease risk factors are present, significantly more patients were using the low adjusted total daily dose of 850 mg daily. On the other hand, when disease risk factors are absent, the use of low and high daily dose of metformin (850 mg/daily versus 1700 mg/daily) was insignificantly different among the patients (Table 1). The use of low adjusted dose was most common in the presence of congestive cardiac failure followed by renal impairment (Fig. 1). Patients who had two or more disease risk factors were most likely to have a low adjusted daily dose of metformin followed by patients with one disease risk factor.

**Table 1:** Frequency of dose adjustment among patients with disease risk factors.

Category of patients	850 mg (%)	1700 mg (%)
No disease risk factors	21/44 ( 47.7)	23/44 (52.3 )
One disease risk factor	27/42 (64.3 )	15/42 (35.7 )
Renal Impairment	11/42 (26.2)	8/42 (19.0 )
Congestive Heart Failure	16/42 (38.1 )	7/42 (16.7 )
Two or more disease risk factors	21/32 (65.6 )	11/32 (34.4 )

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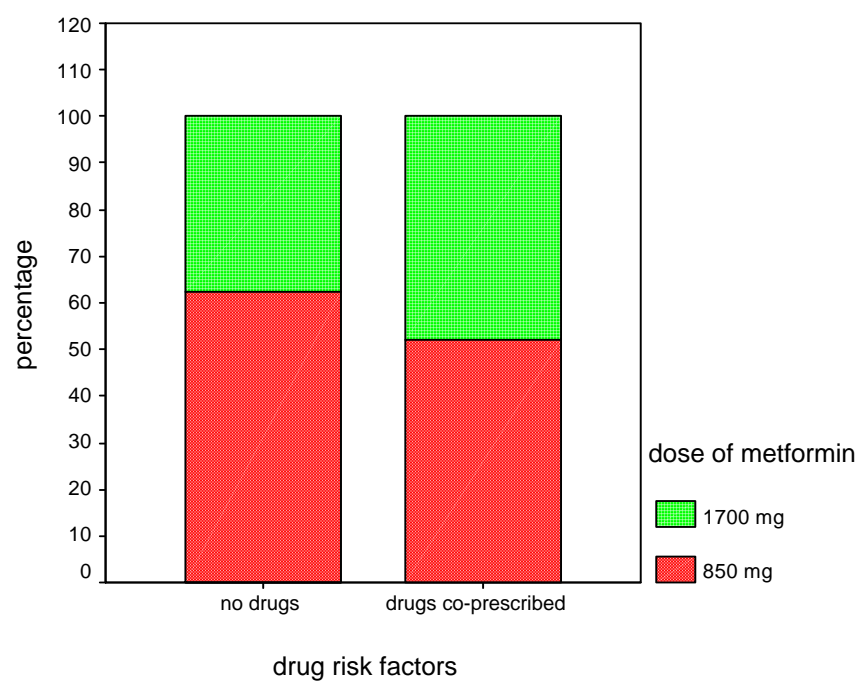


**Figure 1:** The percentage of patients with or without dose adjustments versus the type of risk factors. No RF = no risk factors, R = renal impairment, C = congestive cardiac failure, R/C = renal and cardiac problems, others: respiratory or hepatic problems or both.

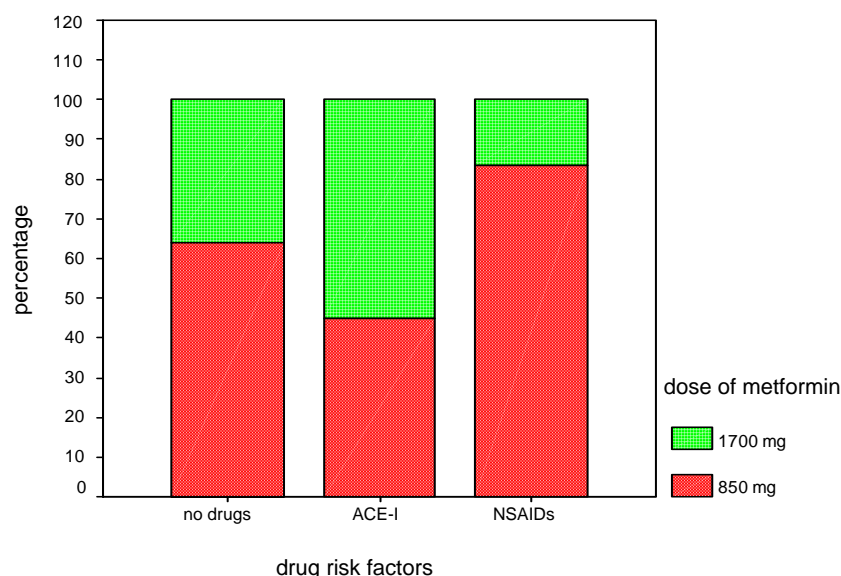
Analysis of drug risk factors for metformin associated lactic acidosis showed that 39% of the enrolled patients were co-prescribed angiotensin converting enzyme inhibitors (ACE-I) or non-steroidal anti-inflammatory drugs (NSAIDs). Doses of metformin were not significantly affected by the co-prescription of ACE-I that might enhance the risk of lactic acidosis. In contrast, approximately two thirds of the patient with no ACE-I co-prescribed, were using the reduced metformin daily dose (Table 2 & Fig. 2).

**Table 2:** Frequency of dose adjustment among patients with drug risk factors.

Category of patients	850 mg (%)	1700 mg (%)
No drug risk factors	46/72 (63.9 )	26/72 (36.1)
Metformin + ACE-I or NSAIDs	23/40 (50)	23/40 (50)

**(A)**

## Influence of Disease and Drug Risk Factors



(B)

**Figure 2:** The percentage of patients with or without dose adjustments versus medication risk factors. “no drugs” means that neither ACE-I or NSAIDs were co-prescribed with metformin. In part A, the data are presented such that ACE-I or NSAIDs were considered together while in part B, they were considered separately.

### Discussion:

On the basis of a recently published review article, advanced age per se, mild renal impairment and stable heart failure are no longer upheld as contraindications to the use of metformin<sup>(22)</sup>. Actually, metformin, alone or in combination, in subjects with heart failure and type 2 diabetes had been shown to lower morbidity and mortality compared with sulfonylurea monotherapy<sup>(23)</sup>. However, it is recommended to adjust the dose among those patients with classical contraindications and to withdraw metformin before radiological examinations with intravenous contrast media or surgical procedures under general anaesthesia in diabetics with normal renal function<sup>(22)</sup>. This study indicated that metformin total daily dosing was influenced by the presence of risk factors for lactic acidosis suggesting that physicians were aware of such

disease – drug interaction. The total daily dose was influenced by the number and type of risk factors. Congestive cardiac failure and renal impairment were the most important risk factors considered in dose adjustment. Unfortunately, the study sample did not include a large number of patients with respiratory problems to judge the influence of such risk factor on metformin daily dosing. Although the majority of patients with disease risk factors have dose adjustments the percentage of patients without dose adjustment is still higher than what has been indicated in other studies carried out in other countries<sup>(24)</sup>. Despite that some patients in the study were not having an adjusted dose of metformin, none of the patient's medical file indicated the occurrence of lactic acidosis at any time during therapy. Actually, the incidence of lactic acidosis among metformin users in general is very rare. The dose adjustment seen among the diabetic patients may be falsely interpreted since reduced metformin dose might be given if another oral hypoglycemic agent is prescribed to avoid risk of excessive hypoglycemia.

The study indicated adjustment of metformin daily dosing was not significantly affected by the co-prescribing of drug risk factors like those that might affect the renal function. This might suggest that prescribing physicians may be unaware of such potential drug drug interaction and the consequent risk of lactic acidosis. It is possible that the prescribing physicians chose the high (1800 mg/daily) metformin dose for patients with risk factors for lactic acidosis because of the need to maintain a better glycemic control. Such explanations can not be excluded given the retrospective nature of our study.

One limitation to this study is the lack of information regarding glycemic control. Another limitation is the lack of information on acid base and other laboratory data. The risk of metformin induced lactic acidosis is inferred from data rather than from the actual laboratory data. A better understanding of the choice of metformin dose could be made if the glycemic status of the patients over a certain period of time as well as laboratory data are known. Despite these limitations, this study gives us an idea about the metformin prescribing practices and that better understanding of both disease and drug factors is needed to avoid possible fatal lactic acidosis among diabetic patients.



## **Influence of Disease and Drug Risk Factors**

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