Lactate levels in Asian patients with type 2 diabetes mellitus on metformin and its association with dose of metformin and renal function

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SUMMARY

Aim: Our aims are to discover the average fasting plasma lactate level (FPL) in Asian patients with type 2 diabetes mellitus on metformin, with or without renal impairment and whether FPL is associated with the total daily dose of metformin (Tmet) and the degree of renal impairment in these patients. Methods: We conducted an observational cross-sectional study of Asian patients with type 2 diabetes, using measurements of FPL levels and glomerular filtration rate (GFR) calculated, using the abbreviated modification of diet in renal disease (MDRD) formula. The association between FPL, Tmet, GFR and other potential predictors was analysed. Results: A total of 97 subjects were recruited from our diabetes centre between July 2005 and February 2006. Sixty (61.9%) of the subjects were males; 69 (71.1%) Chinese, 21 (21.6%) Malays and 6 (6.2%) Indians. The mean (SD) age was 58.8 years (10.7) and the mean body mass index was 27.1 kg/m² (5.3). The mean FPL was 1.8 mmol/l (0.9) with 20 (20.6%) of subjects having an FPL beyond the upper limit of our reference range of 2.2 mmol/l. The mean FPL (two SE) of subjects with Tmet of ≤ 1000, 1001–2000 and > 2000 mg were 1.7 mmol/l (0.2), 1.6 mmol/l (0.2) and 2.1 mmol/l (0.5) respectively, (p = 0.119). The mean FPL of subjects with GFR of < 60, 60–90 and > 90 ml/min/1.73 m² was 1.7 mmol/l (0.3), 1.8 mmol/l (0.3) and 1.8 mmol/l (0.4) respectively, (p = 0.757). Among the potential predictors analysed, aspartate transaminase (p = 0.001) was found to be significantly associated with FPL. Conclusions: Our study shows no correlation between Tmet and GFR with FPL in Asian type 2 diabetic patients on metformin.

What’s known

Whether metformin-associated lactic acidosis (MALA) exists or is merely ‘guilty by association’ is a controversy. There are also conflicting views as to whether lactate levels in patients with diabetes with renal impairment on metformin are higher. Most, if not all of these studies, have been conducted in non-Asian patients.

What’s new

The fasting plasma lactate levels (FPL) in ambulatory Asian patients with type 2 diabetes mellitus on various doses of metformin, with renal function ranging from normal to impaired; the relationship between the FPL in these patients and the total daily dose of metformin (Tmet); and the relationship between FPL in these patients and the degree of renal impairment.

Introduction

Metformin is one of the most widely used oral medications for the treatment of patients with type 2 diabetes worldwide. It is an effective antihyperglycaemic agent, which is relatively of low cost, and its use has been shown to be associated with a decrease in macrovascular complications of diabetes mellitus. However, the use of metformin is often limited by the fear of metformin-associated lactic acidosis (MALA). There has been an ongoing debate on whether metformin is, indeed, the cause of lactic acidosis or if it is merely ‘guilty by association’ (1). Although clinical reports of MALA continue to be published (2), a recently updated systematic review of prospective trials and observational cohort studies involving metformin in patients with type 2 diabetes concluded that there was no evidence that metformin was associated with the increased risk of lactic acidosis if prescribed under study conditions (3).

Although many conditions are listed as contraindications to the use of metformin, these same contraindications are often ignored in clinical practice, not least of which is the one dictating against its use in renal impairment (4). In fact, Rachmani et al. (5) in a prospective study had suggested that lactic acid levels in patients with renal impairment who continued on metformin was not higher than those who discontinued metformin. This is in contrast to the case report of elevated blood lactate levels in elderly patients on metformin (with normal serum creatinine) which normalised after discontinuation of metformin (6).

The aim of our study was to look at the fasting plasma lactate level (FPL) in ambulatory Asian patients in Singapore, a population which consists...
predominantly of Chinese, Malay and Indians, with type 2 diabetes mellitus on various doses of metformin, with the renal function ranging from the normal to the impaired. We also wanted to explore whether any relationship exists between the FPL in these patients and the total daily dose of metformin (Tmet) and whether any relationship exists between FPL in these patients and the degree of renal impairment. As such, we conducted a ‘naturalistic’ cross-sectional study of Asian patients with a range of creatinine levels, who were on metformin.

Methods

A sample of 97 patients with type 2 diabetes, irrespective of age and gender, who were on follow-up in our diabetes centre and had been on metformin for at least a month were recruited. As our centre has a special interest in patients with diabetic nephropathy, we were able to recruit patients with normal renal function as well as those with impaired renal function. Given the awareness of the need for caution with metformin, besides patients with normal GFR who were on metformin, we were hoping to recruit at least a small number of patients with reduced GFR whose physicians were slower in reducing or discontinuing metformin. Patients who had chronic liver disease, congestive cardiac failure, respiratory failure, alcohol abuse, peripheral vascular disease, acute myocardial infarction or sepsis in the preceding month, and any illness requiring admission to hospital within the preceding month were also excluded.

The study protocol was reviewed and approved by the institutional review board. Written informed consent was obtained from all the participants. For all the subjects, the baseline characteristics of age, sex, race, body mass index (BMI), blood pressure and medications were recorded.

Fasting venous blood samples were collected for measurement of lactate, lipids, urea, electrolytes, creatinine, glycated haemoglobin (HbA1c) and full blood count. A sample of mid-stream urine was collected in a sterile container and sent for analysis of the creatinine, albumin–creatinine ratio. An electrocardiogram was run immediately for albumin, using immunoturbidimetry if the sample was clear. If it was turbid, it was centrifuged at 1800 g for 8 min prior to the assay. All the biochemistry tests were run on the Roche Diagnostics Integra 800 (Basel, Santz, Switzerland). Full blood count was analysed on whole blood via flow-cell cytometry on Sysmex XT1800I (Sysmex Corporation, Kobe, Japan).

The glomerular filtration rate (GFR) was calculated using the abbreviated MDRD formula (7). SPSS for Windows version 15 (SPSS, Chicago, IL, USA) was used for the data analysis. The association between FPL, Tmet, GFR and other potential predictors was analysed by univariate ANOVA, chi-squared test and multiple linear regression.

Results

A total of 97 subjects were recruited from our diabetes centre between July 2005 and February 2006. Sixty (61.9%) of the subjects were males. There were 69 (71.1%) Chinese, 21 (21.6%) Malays and six (6.2%) Indians. The mean (SD) age was 58.8 years (10.7) and the mean BMI was 27.1 kg/m² (5.3). The mean FPL was 1.8 mmol/l (0.9) with 20 (20.6%) of the subjects having a raised FPL, defined as > 2.2 mmol/l on the reference range in our laboratory. The basic characteristics of the subjects with and without a raised FPL are laid out in Table 1. Of the subjects with a raised FPL, 18 submitted to a repeat test with 10 showing increased FPL again.

All subjects had FPL values of < 5 mmol/l except one. His bicarbonate was 27 mmol/l. GFR was 123.96 ml/min/1.73 m². This did not satisfy the criteria for lactic acidosis, which is conventionally taken as a FPL ≥ 5 mmol/l with concomitant metabolic acidosis. A repeated FPL level 18 days later was 2.3 mmol/l.

The subjects were divided into three groups according to their Tmet: ≤ 1000, 1001–2000 and > 2000 mg. There were 29, 45 and 23 subjects in the respective groups, and they had a mean FPL (two SE) of 1.7 mmol/l (0.2), 1.6 mmol/l (0.2) and 2.1 mmol/l (0.5) respectively, (p = 0.119).

The subjects were also divided into three groups according to their GFR: < 60, 60–90, > 90 ml/min/1.73 m². There were 39, 34 and 24 subjects in each group respectively and they had a FPL of 1.7 mmol/l (0.3), 1.8 mmol/l (0.3) and 1.8 mmol/l (0.4) respectively, p = 0.757.
The subjects in each of the three GFR groups were categorised according to their Tmet, as shown in Figure 1. There was no statistically significant difference in FPL for the different Tmet categories in each of the GFR groups. The details of the data are in Table 2.

Using multiple linear regression, including the following: race, age, gender, Tmet, GFR, duration of metformin, HbA1c, alanine transaminase and aspartate transaminase (AST), only the latter was found to be significantly associated with FPL, \( p = 0.001 \) (data not shown).

**Discussion**

Ever since phenformin’s withdrawal on account of the relatively high mortality attributed to phenformin-associated lactic acidosis (8), the widespread use...
of metformin has been limited by myriad contraindica-
tions. Although a population-based study (9) and
systematic review (3) have indicated that the lactic
acidosis rate amongst patients prescribed metformin
is no higher than those not on metformin, case
reports of MALA continue to be published.

The mechanism by which biguanides cause lactic
acidosis is not known for certain. Even if metformin
does cause lactic acidosis, the incidence rate of lactic
acidosis is much lower than that of phenformin. The
reason why this is so is again not certain. It is
thought that phenformin’s metabolism is via the liver
whereas metformin is not metabolised significantly
by the liver but excreted mainly by the kidney (10).
In view of this, if metformin were to be the cause of
lactic acidosis, then, it follows that a decline in GFR
should lead to metformin accumulation, particularly
in patients with larger doses of metformin, leading
to a corresponding increase in FPL.

Our study did not show significant differences in
FPL between patients in the three GFR categories.
The mean values of the FPL in each of the individual
categories of GFR were within normal limits even for
the group with the lowest GFR of < 60 ml/min/1.73 m².
There were also no differences in FPL between
the three Tmet categories. Again, looking at
patients on the highest Tmet > 2000 mg, except for
the patients with GFR > 90 ml/min/1.73 m² who
unexpectedly had a mean FPL higher than the refer-
ence range, those with more severe degrees of renal
impairment had a normal mean FPL.

The Fremantle Diabetes Study (11) looked at a
community-based sample of patients with diabetes
and noted that there was a higher plasma lactate in
patients on metformin when compared with those
not on metformin. However, using a linear regression
model, the authors found no correlation between the
plasma lactate level and the daily metformin dose.
This latter finding is in broad agreement with our
results. Again, in accordance with the Fremantle
Diabetes Study, we did not find any increase in FPL
in our patients with GFR < 60 ml/min/1.73 m².

There are several plausible reasons for the FPL not
being higher in patients with a lower GFR. It may be
that physicians, mindful of being cautious with the
use of metformin, had intentionally decreased or dis-
continued the dose of metformin when prescribing
to patients with lower GFR. In fact, recruitment for
this study was particularly difficult, as most of the
patients with reduced GFR already had metformin
discontinued. This led to small numbers, particularly
in the categories of GFR < 60 ml/min/1.73 m² with
Tmet > 2000 mg; and possible type II error. Sec-
dondly, it has been noted that the liver is the main
organ for lactate metabolism with the kidney contri-
buting only an estimated 10–20%. In other words, it
may be possible that as long as the liver reserve was
good, excess lactate from metformin accumulation
could be disposed of by liver metabolism. Perhaps,
only at more advanced stages of renal failure would
metformin accumulation lead to a massive enough
degree of hyperlactataemia to overwhelm liver meta-
bolism. At this stage, the failure of renal disposal of
lactate could then add on to the hyperlactataemia,
leading to lactic acidosis. This may explain our cur-
rent findings of non-association of FPL with GFR as
we did not have patients with near end-stage renal
failure who were still on metformin in our study.

We found a correlation of AST with FPL despite
having excluded those with a history of any chronic
liver disease. The AST levels were all well within the
reference range. The mean value of AST for patients
with raised FPL was 13 U/l (10–30), while that for
patients with FPL who were not raised was 10 U/l.
We do not have any immediate explanation except
that perhaps this is again an indication that the liver
is extremely important in lactate metabolism.

There are some limitations to this study. As men-
tioned, some of the subgroups were small, in partic-
ular, subjects with GFR < 60 ml/min/1.73 m² who
were on Tmet of > 2000 mg. We expected this, and
were not able to improve on the numbers as physician
awareness of the need for caution with the use of met-
formin in renal impairment was high. In fact, we were
depending on the ‘naturalistic’ approach and the phy-
sicans being slower in reducing metformin in a few
patients with renal impairment for our observations.

We are aware of the fact that a wide range of
GFRs are still possible in < 60 ml/min/1.73 m²
group. However, there were only three patients with
GFR < 30 ml/min/1.73 m² and analysis of this sub-
group was hence not possible.

Another potential limitation is the use of the abbre-
viated MDRD formula for the estimation of GFR. The
estimation can be inaccurate, as it underestimates, in
general, GFR values of < 90 ml/min/1.73 m² (12). An
alternative method would have been to obtain the
24 h creatinine clearance (CCT). However, our sub-
jects were outpatients, and obtaining a CCT would
have been difficult and subject to errors of collection.
Moreover, a previous publication suggested that the
GFR, when estimated using the abbreviated MDRD
formula in a Chinese population (of which this study
has a predominance of) overestimates the GFR in
chronic kidney disease stages 4 and 5 and underesti-
mates the GFR in chronic kidney disease stage 1 (13).

Metformin is an effective oral antidiabetic agent.
In fact, it is now recommended as the initial oral
antidiabetic agent, even as lifestyle measures are
being encouraged in the patient with newly
diagnosed type 2 diabetes (14). Systematic review and population-based studies do not reveal any increase in the incidence of MALA amongst patients on metformin, prescribed according to the guidelines, when compared with those not on metformin (4,10). However, several studies have shown that FPL is increased in ambulatory patients on metformin compared with patients not on metformin (11,14), although not all are in agreement. Our report adds on to the body of information (5,11) that in mild-to-moderate renal impairment, moderate doses of metformin do not increase FPL further.

However, it may still be premature to encourage the widespread use of moderate doses of metformin in those with moderate renal impairment, as the incidence of MALA from previous studies is low (and may need a higher person-time exposure to uncover differences) but, important because of the potentially high fatality. Yet, the increasing number of patients with moderate renal impairment, from studies similar to ours, who are documented to have FPL within normal range while on moderate doses of metformin, should persuade institutional review boards to consider favourably, trials which propose studying the use of moderate dose metformin in patients with moderate renal impairment. In view of the low incidence of observed MALA, many centres will need to be involved, and perhaps a meta-analysis approach will need to be adopted.

In the longer term, if the safety of metformin in moderate renal impairment is indeed established, the large number of patients with mild-to-moderate renal impairment who now suffer the undesirable consequences of discontinuation of metformin (5), may look forward to better metabolic control of their diabetes.

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