Renal failure and use of metformin in people with type 2 diabetes: An audit

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Article points

1. Metformin therapy for people with renal impairment can lead to lactic acidosis, a rare but life-threatening condition.
2. An indicator of renal impairment is a high serum creatinine concentration.
3. In this audit, 2% of people with type 2 diabetes were taking metformin despite having serum creatinine above indicated levels.
4. People on metfomin should have regular renal function monitoring.

Key words

- Renal impairment
- Serum creatinine

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Despite the efforts to address the increasing incidence of both type 1 and type 2 diabetes, the diabetic population is set to increase by 15% between 2001 and 2015 (DoH, 2006). The first-line treatments for type 2 diabetes are education and lifestyle changes, which include diet, weight control and physical activity. Metformin is the first-line drug of choice in overweight individuals in whom strict dieting has failed to control diabetes. If appropriate, it may also be considered as an option in people who are not overweight (British Medical Association and the Royal Pharmaceutical Society of Britain, 2007). A potential complication of metformin is the development of type B (non-hypoxic) lactic acidosis. This complication, although rare (0.03 cases per 1000 patient years), has a reported mortality of 50% (Price, 2003).

How metformin causes lactic acidosis is unclear and is not necessarily related to the accumulation of metformin, as was previously thought, because metformin is excreted unchanged in the urine. Tissue hypoxia has been noted to be a trigger of lactic acidosis and, therefore, metformin should be discontinued when tissue hypoxia is suspected, regardless of renal function (Jones et al, 2003).

Putative risk factors for lactic acidosis with biguanide treatment include: age >60 years; decreased cardiac, hepatic or renal function; diabetic ketoacidosis; surgery; respiratory failure; ethanol intoxication; and fasting (Luft, 2001).

NICE states that metformin is contraindicated in those with renal impairment (serum creatinine levels >130µm/l) and in those at risk of sudden deterioration of renal function (NICE, 2002). However, the British National Formulary recommends avoiding metformin in mild renal impairment, where mild renal impairment is defined as a glomerular filtration rate (GFR) of 20–50ml/min/1.73m^2 or serum creatinine levels in the range 150–300µm/l (British Medical Association and the Royal Pharmaceutical Society of Britain, 2007).

There are various reasons why renal impairment occurs in people with diabetes. One of the long-term complications of diabetes is diabetic nephropathy, which can progress to renal failure in some cases. The main focus of therapy in diabetic nephropathy is blood pressure. Guidelines have

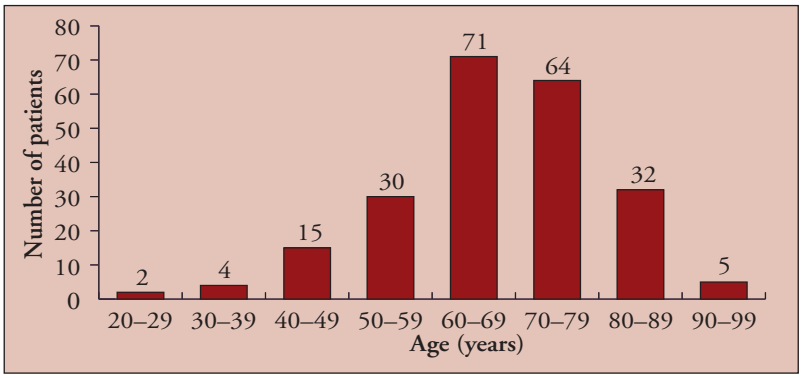

Figure 1. Ages of people with type 2 diabetes on metformin audited by the Asplands Medical Centre, Milton Keynes.

progressively revised the target blood pressure goal downwards and they currently stand at 130/80 mmHg in people with chronic renal failure and recommend either angiotensin converting enzyme (ACE) inhibitors or angiotensin-II receptor blocker (ARB) therapy as first-line renoprotective antihypertensive therapy (British Cardiac Society et al, 2005). Many people with type 2 diabetes are therefore prescribed ACE inhibitors. Although ACE inhibitors now have a specialised role in some forms of renal disease, they also occasionally cause impairment of renal function that may progress and become severe (at particular risk are the elderly; British Medical Association and the Royal Pharmaceutical Society of Britain, 2007). Concomitant treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) increases the risk of renal damage (British Medical Association and the Royal Pharmaceutical Society of Britain, 2007). We also know that NSAIDs are popular drugs in individuals with arthritis (Longmore et al, 2004).

Unfortunately, normal aging is accompanied by a reduction in GFR by 6–10 ml/min/1.73 m^2 per decade after the age of 40 years, so those over 70 years of age may have a GFR less than 75 ml/min/1.73 m^2 (National Kidney Association).

Study aims

This retrospective study, performed at Asplands Medical Centre in Milton Keynes (total registered population: 10 026), compares current practice in primary care with NICE guidelines on the management of type 2 diabetes and the recommendations from the British National Formulary with regards to the use of metformin in people with renal failure (NICE, 2002; British Medical Association and the Royal Pharmaceutical Society of Britain, 2007). The aim is to improve treatment and routine monitoring of people with diabetes on metformin.

Method

The clinical notes of people who were on metformin when the audit commenced and who also had serum creatinine levels above 150 µm/l at any time since commencing metformin treatment were reviewed. Data on the latest serum creatinine levels (within last 6 months) were also examined.

The age, duration of diabetes, concurrent drug therapy and BMI of people with current serum creatinine levels above 130 µm/l were also taken into account. Metformin therapy was considered inappropriate if the serum creatinine level was more than 150 µm/l. The value of 150 µm/l was used in accordance with recommendations from the British National Formulary (British Medical Association and the Royal Pharmaceutical Society of Britain, 2007) and is also used in current local practice.

Results

Individuals with type 2 diabetes comprise 2.6% (n = 262) of the total practice-registered population (10 026). Of these, 223 (85.1%) have been on metformin at some time since diagnosis. Most individuals on metformin were aged 60–80 years (60.5%; n = 135; *Figure 1*).

In total, 43 (19.3%) individuals who have taken metformin had serum creatinine levels >130 µm/l on one or more occasion since diagnosis; 25 (58.1%) of these were in the range 130–150 µm/l and 18 (41.9%) had a concentration >150 µm/l. Review of the clinical notes of the 18 people on metformin who had serum creatinine levels >150 µm/l revealed that ten were not taking metformin and were instead using insulin or another hypoglycaemic agent. However, the remaining eight were still taking metformin. *Table 1* shows the baseline characteristics of these eight individuals. In these individuals, the latest serum creatinine levels from within the previous 6 months revealed that three had serum creatinine levels <130 µm/l, two had concentrations in the range 130–150 µm/l and three >150 µm/l. *Table 2* shows up-to-date information on the latest GFR

1. Guidelines have progressively revised the target blood pressure goal downwards and they currently stand at 130/80 mmHg in people with chronic renal failure.
2. Concomitant treatment with nonsteroidal anti-inflammatory drugs increases the risk of renal damage.
3. Review of the clinical notes of the 18 people on metformin who had serum creatinine levels >150 µm/l revealed that ten were not taking metformin and were instead using insulin or another hypoglycaemic agent.

and serum creatinine levels, and current medications of these eight people.

Discussion

This study shows that five people (2.2%) with type 2 diabetes had serum creatinine levels >130 µm/l while currently taking metformin.

Furthermore, all but one of these five people were aged >70 years and were on concurrent therapy with ACE inhibitors. The BMIs of these people varied from 22 to 32 kg/m^2 *(Table 2)*. Available data on latest GFR for three of these people confirmed chronic renal impairment (30, 33 and 40 ml/min/1.73 m^2). Unfortunately, there were no data on the latest GFRs of the other two patients.

Possible explanations for the use of metformin in people with renal impairment include the following.

- Normal serum creatinine levels at time of first prescription and development of renal impairment later went unnoticed.
- The benefits of continuing metformin therapy were greater than any associated risks.

In view of the clear contraindication to metformin in these five individuals and after discussion with treating physicians, the following management changes were decided upon.

- Individuals will be contacted to discuss replacing metformin with either insulin or another oral hypoglycaemic regimen in order to avoid the associated risks of metformin therapy in the presence of renal impairment.
- Monitoring of serum creatinine levels will be included in the routine check up of people with

Table 1. Baseline characteristics of eight people with type 2 diabetes currently on metformin and with serum creatinine levels above 150 µm/l at any time since diagnosis.

Patient	Age at diabetes diagnosis (years)	Sex	Earliest available serum creatinine level (µmol/l)
A	75	Male	108
B	60	Male	49
C	72	Male	111
D	79	Male	152
E	60	Female	88
F	65	Male	114
G	81	Male	121
H	60	Male	146

Table 2. Characteristics of eight people with type 2 diabetes currently on metformin who have experienced serum creatinine levels >150 µm/l at any time since diagnosis.

Patient	Age in years	Diabetes duration in years	Latest BMI	Latest GFR (ml/min/1.73 m^2)	Latest serum creatinine (µm/l)	Current medications
A	81	6	21	53	120	Metformin Ramipril
B	67	7	31	90	75	Glibenclamide Metformin
C	77	5	28	54	125	Metformin Lisinopril
D	85	6	29	33	147	Metformin Ramipril
E	76	16	32	No data	161	Metformin Ramipril
F	74	9	25	40	153	Metformin Ramipril
G	85	4	23	30	193	Metformin Perindopril Losartan
H	60	Newly diagnosed	22	No data	144	Metformin

Page points

1. If the results of this audit are representative of management of people with diabetes nationally, they would imply that a large number of people with diabetes are receiving metformin inappropriately.
2. In the author's opinion, renal function should be monitored regularly in people with type 2 diabetes who are taking metformin with a view to cease metformin therapy at the recommended levels of glomerular filtration rate or serum creatinine.
3. The high mortality rate associated with lactic acidosis is a very good reason to stop metformin at the first sign of renal impairment in individuals who are on concomitant ACE inhibitor therapy (especially the elderly).

diabetes using metformin.

One drawback of the audit is that it does not assess whether or not serum creatinine levels were measured before starting metformin. Most individuals were on metformin for several years before the audit and these data were not available.

If the results of this audit are representative of management of people with diabetes nationally, they would imply that a large number of people with diabetes are receiving metformin inappropriately.

The danger of using nephrotoxic drugs (aminoglycosides, tetracyclines, amphotericin B, NSAIDs or ACE inhibitors) in these individuals also needs to be kept in mind (Longmore et al, 2004). ACE inhibitors, being nephrotoxic, are recommended for microalbuminurea; therefore, renal function of these individuals should be monitored closely with a view to stop metformin at recommended creatinine levels (British Medical Association and the Royal Pharmaceutical Society of Britain, 2007).

A population-based study in Tayside Scotland (population 349303) by Emslie-Smith et al (2001) showed that 24.5% of people prescribed metformin have contraindications to its use. Development of contraindications rarely results in discontinuation of metformin therapy. It also showed that despite this lactic acidosis remains rare (one episode of lactic acidosis in 4600 patient years).

Conclusion

A small percentage (2.2%) of people with diabetes audited were receiving metformin inappropriately. In the author's opinion, renal function should be monitored regularly in people with type 2 diabetes who are taking metformin with a view to cease metformin therapy at the recommended levels of glomerular filtration rate or serum creatinine.

In view of the low incidence of lactic acidosis with metformin in people with renal failure, the benefit–risk ratio favours the use of concomitant therapy with ACE inhibitors. However, the high mortality rate associated with lactic acidosis is a very good reason to stop metformin at the first sign of renal impairment in individuals who are on concomitant ACE inhibitor therapy (especially the elderly).

In conclusion, the following contraindications to metformin are as follows (British Medical Association, Royal Pharmaceutical Society of Britain, 2007).

- Avoid metformin in mild renal impairment (serum creatinine 150–300 µm/l).
- Withdraw if tissue hypoxia likely (sepsis, respiratory failure, recent myocardial infarction or hepatic impairment).
- Stop when using iodine-containing x-ray contrast medium and do not restart metformin until renal function returns to normal.
- Stop metformin 2 days before general anaesthesia and restart when renal function returns to normal.
- Avoid in pregnancy and breast feeding. ■

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