Management & prevention of type 2 diabetes

DIABETIC MEDICINE

eGFR in place of creatinine as marker of renal impairment in metformin users

Readability	✓✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! factor	✓✓✓✓

1 Currently, UK guidelines use a cut-off point of serum creatinine >150 µmol/l as a marker of when metformin treatment for type 2 diabetes should be discontinued due to renal impairment.

2 This study set out to assess the clinical implications of changing the current definition of renal impairment to one based on estimated glomerular filtration rate (eGFR).

3 Serum creatinine levels were taken and eGFRs calculated for 11 297 individuals with type 2 diabetes on the Lothian diabetes register who were taking metformin according to local practice guidelines.

4 Using classification from the National Kidney Foundation, 82% of participants had stage 2 or 3 renal impairment (eGFR <90 ml/min/1.73 m^2).

5 The authors calculated that changing the cut-off point for metformin use in renal impairment to an eGFR of 36 ml/min/1.73 m^2 would have a neutral effect on the number of people with type 2 diabetes eligible for metformin treatment.

6 Changing the threshold to 36 ml/min/1.73 m^2 would also allow metformin use in people with serum creatinine levels up to 179 µmol/l. Rounding this up to 40 ml/min/1.73 m^2 would permit metformin use up to serum creatinine levels of 163 µmol/l and would mean 2.8% would be recommended to cease metformin therapy.

7 The authors recommend using a cut-off point of 36–40 ml/min/1.73 m^2, as this is consistent with current practice

Warren RE, Strachan MW, Wild S, McKnight JA (2007) Introducing estimated glomerular filtration rate (eGFR) into clinical practice in the UK: implications for the use of metformin. *Diabetic Medicine* **24**: 494–7

Classifying renal impairment for metformin use

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Metformin is the recommended initial glucose lowering therapy for the majority of people with type 2 diabetes. It has the reputation of being a safe drug, with its main side effects being on the GI tract where it can cause diarrhoea and abdominal pain. There is an association between metformin therapy and the rare but potentially fatal condition of lactic acidosis. Metformin is excreted through the kidney, therefore it is possible that if metformin is given when there is significant renal impairment, levels will build up in the blood and increase the risk of lactic acidosis. It has therefore always been considered prudent not to give metformin to people with significant renal impairment and to stop it if significant renal impairment develops. But what constitutes significant renal impairment?

The NICE glycaemic guidelines for type 2 diabetes of 2002 recommend not starting metformin if the serum creatinine is above 130 µmol/l and stopping metformin if it rises above 150 µmol/l.

However, it is known that serum creatinine may not be an accurate guide to renal impairment and estimated glomerular filtration rate (eGFR) has been introduced as a more accurate guide. So how do the 2002 figures relate to eGFR levels?

In the paper summarised to the right, the authors looked at a database of nearly 20 000 Scottish people with type 2 diabetes of whom 11 297 were taking metformin. eGFR values were calculated and 2880 (25.5%) had at least stage 3 renal impairment. Using an eGFR cut-off for metformin of 36 ml/min/1.73 m^2 would have a neutral effect on the number of patients eligible for metformin therapy and would permit its use in individuals who have creatinine concentrations as high as 179 µmol/l

If the eGFR threshold were set at 40 ml/min/1.73m^2 it would result in 312 patients in this study having to discontinue metformin.

This study suggests that the eGFR threshold for discontinuing metformin could be around 36 ml/min/1.73 m^2.

NICE (2002) *Inherited clinical guideline G. Management of type 2 diabetes. Management of blood glucose.* NICE, London

ANNALS OF INTERNAL MEDICINE

HbA_{1c} and weight reduced by exenatide where TZD therapy inadequate

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 This was a double-blind, placebo-controlled trial set over 16 weeks at sites in the US, Canada and Spain.

2 The aim was to compare the impact of exenatide versus placebo on glycaemic control in people with type 2 diabetes suboptimally controlled by a TZD (with and without metformin).

3 Baseline HbA_{1c} of the 233 individuals involved was 7.9±0.1%.

4 Participants were randomised to received either 10 µg exenatide (n=121) or placebo (n=112) twice daily in addition to their TZD treatment (with and without metformin).

5 At 16 weeks, exenatide had reduced HbA_{1c} by on average 0.89±0.09% compared with an increase of 0.09±0.10% in the placebo group. For difference between HbA_{1c} outcome, $P<0.001$.

6 No significant impact of the existing therapy (TZD alone or plus metformin) was found on changes in HbA_{1c} ($P=0.87$).

7 Decrease in body weight was significantly greater with exenatide (1.51 kg; $P<0.001$).

8 Seventy-six per cent of exenatide users reported at least one adverse event, compared with 65.2% taking placebo.

Zinman B, Hoogwerf BJ, Durán García S et al (2007) The effect of adding exenatide to a thiazolidinedione in suboptimally controlled type 2 diabetes: a randomized trial. *Annals of Internal Medicine* **146**: 477–85

"Furthermore, 22% of participants were classified with depressive symptoms as per the CEDS, but of these 70% were not clinically depressed."

DIABETIC MEDICINE

Self-management training has greater benefits than didactic education

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓✓

1 Compared in this trial were a didactic education programme for people with type 2 diabetes (n=62), a group self-management programme (n=56) and an individualised self-management programme (n=64).

2 Compared with the didactic education, the group self-management approach significantly reduced HbA_{1c} at 15 months ($P<0.05$).

3 Individualised education reduced HbA_{1c} at 3 months but this effect was not sustained 15 months after the intervention ($P=0.73$).

4 The conclusion reached in the study states that self-management training has significant benefits in the medium term at controlling diabetes over a didactic approach.

Kulzer B, Hermanns N, Reinecker H, Haak T (2007) Effects of self-management training in Type 2 diabetes: a randomized, prospective trial. *Diabetic Medicine* **24**: 415–23

DIABETES CARE

Nonalcoholic fatty liver disease associated with CVD risk

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 The authors of this study set out to document the prevalence of nonalcoholic fatty liver disease (NAFLD) among people with type 2 diabetes attending the Sacro Cuore Hospital, Italy, and to examine the possible link between NAFLD and CVD.

2 The investigation involved 2839 individuals who were screened for NAFLD and manifest CVD.

3 Unadjusted prevalence of NAFLD was 69.5%. The rate of occurrence of NAFLD was found to significantly positively correlate with age ($P<0.001$).

4 Prevalence of the following vascular diseases were significantly higher ($P<0.001$ in all cases) among those with NAFLD: coronary (2.6 versus 18.3%); cerebrovascular (20.0 versus 13.3%); and peripheral (15.4 versus 10.0%).

5 The authors concluded that this study had confirmed the high prevalence of NAFLD in type 2 diabetes and that the condition is associated with an increased risk of CVD.

Targher G, Bertolini L, Padovani R et al (2007) Prevalence of nonalcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients. *Diabetes Care* **30**: 1212–8

"Both doses of vildagliptin significantly reduced HbA1c from baseline at 24 weeks (P<0.001), however GI adverse events occurred significantly more frequently than with placebo (P=0.022)."

DIABETES CARE

Vildagliptin reduces HbA_{1c} but increases GI side-effects

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 The efficacy and safety of vildagliptin plus metformin over a 24-week period was investigated in this double-blind, randomised, multicentre, parallel-group study.

2 Recruited were people with type 2 diabetes inadequately controlled by metformin. In total, 177 individuals were randomised to receive 50mg vildagliptin daily; 185 to receive 100mg vildagliptin daily; and 182 to receive placebo.

3 Both doses of vildagliptin significantly reduced HbA_{1c} from baseline at 24 weeks ($P<0.001$), however GI adverse events occurred significantly more frequently than with placebo ($P=0.022$).

4 The authors concluded that vildagliptin is a well-tolerated add-on therapy to metformin in cases of inadequately-controlled type 2 diabetes.

Bosi E, Camisasca RP, Collober C et al (2007) Effects of vildagliptin on glucose control over 24 weeks in patients with type 2 diabetes inadequately controlled with metformin. *Diabetes Care* **30**: 890–5

DIABETES CARE

Distress not depression found in people with type 2 diabetes

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓

1 This study assessed 506 individuals with type 2 diabetes for: major depressive disorder (MDD) using the Composite International Diagnostic Interview; depressive symptoms using the Center for Epidemiological Studies Depression Scale (CEDS); and distress using the Diabetes Distress Scale.

2 Also recorded were demographic variables, HbA_{1c}, non-HDL-c, time spent doing physical activity and consumption of kilocalories, saturated fat and fruit and vegetables.

3 Mean age of participants was 57.83 ± 9.86 years; mean BMI was 32.73 ± 7.74 kg/m^2; and mean duration of type 2 diabetes was 8.1 ± 7.54 years.

4 MDD was diagnosed in 9.9% of participants. Furthermore, 22% of participants were classified with depressive symptoms as per the CEDS, but of these 70% were not clinically depressed.

5 Participants with depressive symptoms on the CEDS had a significantly higher kilocalorie intake (1636.30 ± 819.74 kcal versus 1294.40 ± 608.54 kcal; $P<0.001$); a significantly greater proportion of saturated fats in their diet (12.7 ± 3.54% versus 11.86 ± 3.54%; $P<0.05$); and took significantly less exercise as measured by the International Physical Activity Questionnaire (1970.8 ± 2637.1 versus 2565.8 ± 2704.2; $P<0.05$).

6 The authors concluded that most people who have diabetes and high levels of depressive symptoms are not clinically depressed and may instead be experiencing diabetes-specific distress.

Fisher L, Skaff MM, Mullan JT et al (2007) Clinical depression versus distress among patients with type 2 diabetes: not just a question of semantics. *Diabetes Care* **30**: 542–8

'The calculated adjusted indirect comparison of rosiglitazone to pioglitazone revealed a 3-fold higher risk of oedema with rosiglitazone.'

DIABETES RESEARCH AND CLINICAL PRACTICE

TZDs give 2-fold increase in risk of oedema

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓

1 Previous research has found an association between the use of TZDs in type 2 diabetes and an increased risk of peripheral oedema. Consequently, this meta-analysis was carried out in order to assess the overall risk of oedema secondary to TZD use.

2 Five electronic databases were searched for prospective, randomised studies that were either placebo-controlled or comparative and documented the incident rate of oedema with TZD use.

3 In total, 36 studies were included in this meta-analysis, with a total of 15332 individuals with type 2 diabetes involved.

4 The reported pooled odds ratio for oedema caused by TZD use was 2.26 (95% CI: 2.02–2.53).

5 Separating out into odds ratios for the two different TZDs gave the following results: rosiglitazone 3.75 (95% CI: 2.70–5.20) and pioglitazone 2.42 (95% CI: 1.90–3.08).

6 The calculated adjusted indirect comparison of rosiglitazone to pioglitazone revealed a 3-fold higher risk of oedema with rosiglitazone.

7 The authors highlight that the conclusions from an analysis comparing data from trials containing multiple-intervention groups should be taken in context.

Berlie HD, Kalus JS, Jaber LA (2007) Thiazolidinediones and the risk of edema: a meta-analysis. *Diabetes Research and Clinical Practice* **76**: 279–89

DIABETOLOGIA

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

Link found between SMBG and CV mortality in type 2 diabetes

1 Using an Australian community-based cohort, the authors set out to ascertain whether or not self-monitoring of blood glucose (SMBG) is an independent predictor of improved outcomes in type 2 diabetes.

2 Data were taken from 1280 individuals recruited to the Fremantle Diabetes Study. Further investigated were a subset of these (n=531) who attended >6 annual assessments.

3 Diabetes-related morbidity, cardiac death and all cause mortality were recorded on an annual basis.

4 The authors collected 12491 patient-years of data (mean: 9.8 ±3.5 years). During this time, 486 participants died (38%). Cardiac causes were cited as reason for death in 15.3% (n=196).

5 The prevalence of SMBG was significantly lower in individuals who died during the follow-up period than those who survived to June 2006 (65.4% versus 73.0%; P=0.005)

6 The authors adjusted the data for confounding explanatory variables and used a Cox proportional hazard model to find any independent association between SMBG and mortality.

7 SMBG was not independently associated with all-cause mortality end points ($P \geq 0.11$).

8 An increased risk of 79% for cardiovascular mortality was found in individuals not treated with insulin who did not carry out SMBG.

9 Findings also showed a time-dependent 48% decreased risk of retinopathy in the individuals followed for more than six annual reviews.

10 In conclusion, the authors report no independent association between SMBG and survival in type 2 diabetes.

Davis WA, Bruce DG, Davis TM (2007) Does self-monitoring of blood glucose improve outcome in type 2 diabetes? The Fremantle Diabetes Study. *Diabetologia* **50**: 510–5

'The authors hypothesise that BMD does not account for all fracture risk in the type 2 diabetes population.'

DIABETES CARE

Elevated risk of hip fracture in type 2 diabetes

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 Following previous findings that people with type 2 diabetes have higher bone mineral density (BMD) than controls, this study sought to compare the risk of hip fractures in people with and without type 2 diabetes.

2 A retrospective cohort design was utilised. Inclusion criteria included age ≥66 years and residence in Ontario, Canada.

3 In total, 197412 people with type 2 diabetes were compared to 401400 age-matched individuals without the condition.

4 After the data had been adjusted to take into consideration factors such as previous BMD test and medications increasing the risk of falling and decreasing BMD, hip fracture risk was still elevated in those with diabetes. The hazard ratio for men was 1.18 (95% CI: 1.12–1.24; P<0.0001) and 1.11 for women (95% CI: 1.08–1.15; P<0.0001).

5 This study confirmed previous findings that among people with diabetes, women are at the highest risk of hip fractures (incidence per person-years: 9.09 versus 4.13 for men with diabetes).

6 The authors hypothesise that BMD does not account for all fracture risk in the type 2 diabetes population and other factors relating to the likelihood of an individual falling may be involved, including: visual impairment from retinopathy; neuropathy; and cerebrovascular disease.

Lipscombe LL, Jamal SA, Booth GL, Hawker GA (2007) The risk of hip fractures in older individuals with diabetes: a population-based study. *Diabetes Care* **30**: 835–41