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REVIEW

The use of metformin in type 1 diabetes: a systematic review of efficacy

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Abstract
Aims/hypothesis As adding metformin to insulin therapy has been advocated in type 1 diabetes, we conducted a systematic review of published clinical trials and clinical trial databases to assess the effects on HbA_{1c}, weight, insulin-dose requirement and adverse effects.
Methods We constructed evidence tables and fitted a fixed-effects model (inverse variance method) in order to assess heterogeneity between studies and give a crude measure of each overall treatment effect.
Results Of 197 studies identified, nine involved randomisation with informed consent of patients with type 1 diabetes to metformin (vs placebo or comparator) in either a parallel or crossover design for at least 1 week. We noted marked heterogeneity in study design, drug dose, age of participants and length of follow-up. Metformin was associated with reductions in: (1) insulin-dose requirement (5.7–10.1 U/day in six of seven studies); (2) HbA_{1c} (0.6–0.9% in four of seven studies); (3) weight (1.7–6.0 kg in three of six studies); and (4) total cholesterol (0.3–0.41 mmol/l in three of seven studies). Metformin was well tolerated, albeit with a trend towards increased hypoglycaemia. Formal estimates of combined effects from the five trials which reported appropriate data indicated a significant reduction in insulin dose (6.6 U/day, $p<0.001$) but no significant reduction in HbA_{1c} (absolute reduction 0.11%, $p=0.42$). No reported trials included cardiovascular outcomes.
Conclusions/interpretation Metformin reduces insulin-dose requirement in type 1 diabetes but it is unclear whether this is sustained beyond 1 year and whether there are benefits for cardiovascular and other key clinical outcomes.

Keywords Cardiovascular disease · HbA_{1c} · Insulin · Metformin · Obesity · Systematic review · Type 1 diabetes

Abbreviations

AMPK	AMP-activated protein kinase
CVD	Cardiovascular disease
MeSH	Medical search headings
SMD	Standardised mean difference
TW	Text word
UKPDS	UK Prospective Diabetes Study

Introduction

Tight glycaemic control using intensive insulin therapy was shown in the DCCT to reduce rates of microvascular complications in type 1 diabetes [1]. However, achieving and maintaining such control in type 1 diabetes using standard insulin therapy requires a high level of support and is associated with more hypoglycaemia, increased weight gain and, in some patients, aggravation of cardiovascular risk factors including dyslipidaemia [2, 3].

Metformin is an inexpensive and established oral glucose-lowering agent widely used in the treatment of type 2 diabetes [4]. Metformin, a biguanide agent, is first-line oral pharmacotherapy for type 2 diabetes in the UK and elsewhere, in accordance with guidance from the National

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Institute for Health and Clinical Excellence/National Collaborating Centre for Chronic Conditions (NICE/NCC) [5] and international guidelines, such as those issued jointly by the American Diabetes Association and the European Association for the Study of Diabetes [6] and the International Diabetes Federation [7].

Activation of the energy-regulating enzyme AMP-activated protein kinase (AMPK), principally in muscle and the liver, is considered a major mode of metformin action [8]. Therapy in type 2 diabetes is associated with decreased hepatic glucose production, decreased fasting plasma glucose, a reduction in HbA_{1c} level, weight stabilisation/loss, modest reductions in serum triacylglycerol, VLDL and LDL levels, as well as decreased C-reactive protein, platelet activation and procoagulant factors (such as factor VII and fibrinogen) [9]. In the UK Prospective Diabetes Study (UKPDS) [10, 11] and the A Diabetes Outcome Progression Trial (ADOPT) [12], patients randomised to metformin therapy experienced less weight gain than those allocated to other oral therapies, together with equivalent or lower rates of hypoglycaemia [12, 13]. Importantly metformin therapy was associated with a substantial 33% reduction in the rate of myocardial infarction in people with type 2 diabetes in the UKPDS, and this was sustained to 10 years after the end of randomisation [14]. Metformin therefore has properties that make it an attractive potential adjunct agent in type 1 diabetes.

The published summaries of the evidence on the effects of metformin in type 1 diabetes are incomplete. A recent review [15] did not include the two largest trials to date [16, 17] but did include data from a non-randomised controlled study [18]. A recent Cochrane review [19] only included the two trials [20, 21] conducted in adolescents. We have therefore conducted a systematic review aimed at capturing all published data from randomised trials that involved using metformin in people of any age with type 1 diabetes.

Methods

Our objective was to capture all trial data for metformin in type 1 diabetes where the trial was: (1) randomised; (2) lasted at least 1 week; (3) used either a comparator drug or placebo or used a crossover design; and (4) included consenting patients. We extracted any data on cardiovascular disease (CVD), HbA_{1c}, body weight or BMI, insulin dose, lipids and adverse effects.

Search strategy We first captured all publications pertaining to type 1 diabetes and metformin for any outcomes as follows in PubMed (1950 to week 4 January 2009, updated 6 October 2009) and EMBASE (1974 onwards). The search was conducted as follows using medical search headings (MeSH):

1. 'Diabetes Mellitus, Type 1' [MeSH]
2. (DIABET*) AND (TYPE 1 [TW] OR IDDM [TW]) OR ('INSULIN DEPENDENT' not 'NON-INSULIN DEPENDENT')
3. 1 OR 2
4. 'Metformin' [MeSH]
5. Metformin [TW]
6. 4 OR 5

This search was run by two independent researchers (P. Royle and H. M. Colhoun), and was repeated and updated by S. Vella. The abstracts of all identified publications were manually searched for studies that attempted to evaluate the effect of metformin on any clinically relevant outcome whether in a randomised trial or open-label or other design. The citations of all relevant publications were manually searched (H. M. Colhoun and L. Buetow) for any additional studies. Where uncertainty existed, the full text of the article was obtained and reviewed. S. Vella and L. Buetow independently assessed all potentially relevant studies and performed data extraction. The resulting tables of evidence were reviewed by J. R. Petrie and H. M. Colhoun. Disagreement was resolved by discussion; independent adjudication was not required.

In addition we searched for ongoing and unpublished trials as follows:

- Cochrane Library 2009 issue 1
- Science Citation Index meeting abstracts (includes European Association for the Study of Diabetes and American Diabetes Association meetings) 1980-October 2008
- Diabetes UK meeting abstracts 2002–2008
- Endocrine Society Abstracts 2005–2008
- Science Citation Index meeting Abstracts 1980–2008
- National Research Register (NRR)
- Controlled-trials.com

Five trials were registered on the UK NRR, all with glycaemic/metabolic outcomes with end dates in 2005 or earlier. All leading investigators were emailed to request data: N0176113569, completed but unpublished (pilot study); N0231133055, completed and published [22]; N0394131469, not completed; N0301111201, completed and published [23]; N0046091476, not completed.

An online reference to trial N0394131469, initially accessed in the first search (week 4 January 2009), was no longer accessible on searching across multiple research registers on relevant websites (www.nrr.org.uk; www.controlled-trials.com) in the updated search (6 October 2009).

On the controlled-trials.com meta-register, one additional glycaemic/metabolic trial was found: NCT00145379, not completed, still recruiting (n=50).

Participants Participants were those of any age described by the authors of the publications as having type 1 diabetes or insulin-dependent diabetes or youth-onset diabetes.

Analysis We decided to summarise the data mostly in text and tabular form as there was obvious heterogeneity between studies in methods, design and outcome measures. However, we also present some data using standard meta-analysis techniques [24]; the two trials of very short duration [25, 26] were excluded from these. Strictly speaking these formal meta-analysis techniques should be used only when a group of studies is sufficiently homogeneous in terms of participants, interventions and outcomes to provide a meaningful summary [24]. Nevertheless, we considered it useful to have a measure of the statistical significance of apparent effects.

With these reservations, a fixed-effects model using the inverse variance method was fitted to give a crude measure of the overall treatment effect, to assess its statistical significance and to assess the heterogeneity of treatment effect between studies. We examined the outcomes of effect on %HbA_{1c} and on insulin dose. The metan STATA user command was used, which quantifies heterogeneity using the I^2 measure [27]. Of the eight eligible studies, one study [23] was excluded as it may have been incorrectly analysed as if it were a parallel-group study (in which case the standard deviations would not be valid). Three other studies could not be included as they either did not report the outcomes of interest [25, 26], or because the data items necessary for inclusion in a combined analysis were not reported [17]. The data were extracted as %HbA_{1c} and as U/day for insulin dose (using mean weight at baseline in each treatment group to convert insulin in U kg^{-1} day^{-1} to U/day). For some studies, only attained mean levels were available rather than changes from baseline by treatment group; therefore, we derived treatment effect as the net difference in absolute units of outcome between metformin and placebo groups. The obvious methodological heterogeneity in study design, drug dose, age of participants and length of follow-up render the combined estimates of effect somewhat imprecise.

Results

The initial electronic search identified 187 studies (Fig. 1). A manual review of the citations yielded an additional ten studies. In total, 47 of these publications were judged to be relevant to metformin therapy in type 1 diabetes. Analysis of publications revealed: 17 were observational studies with no random allocation and/or no comparator group [18, 22, 28–42]; 11 were reviews, letters or commentaries [43–53]; two did not contain any quantitative estimates of effects [54, 55]; one concerned an outcome (erythrocyte binding of insulin) not judged relevant [56]; and four were abstracts of papers subsequently published [57–60]. Of the remaining 12 publications, one concerned insulin-requiring type 2 diabetes rather than type 1 diabetes (noted after translation) [61], and one covered a treatment period of fewer than 7 days [62]. Only ten studies were therefore identified [16, 17, 20, 21, 23, 25, 26, 63–65]. One of these, which was conducted on participants living in a children's home and did not mention informed consent, was excluded from further analysis [64].

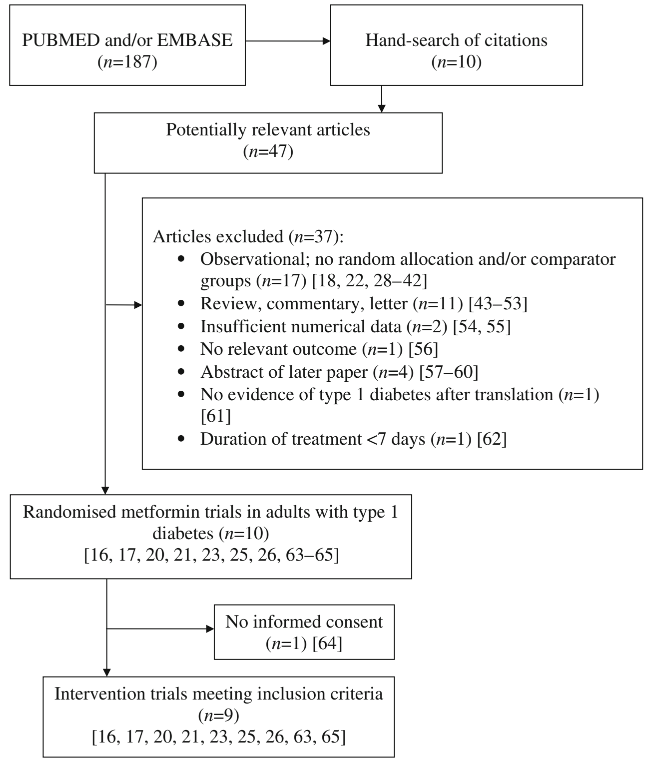

Fig. 1 Flow chart of the literature search

The final nine studies [16, 17, 20, 21, 23, 25, 26, 63, 65] covered a total of 192.8 patient years, and the number of completed participants ranged from ten to 92 (median 26) (two studies did not report number completed [17, 26]) (Table 1). The total maximum daily metformin dose varied from 1,000 to 2,550 mg; duration of therapy ranged from 7 days to 12 months (median 4 months). Two studies were available only in abstract form [17, 26], including one of the largest studies (n=80), which dated from 2000 [17].

All nine studies evaluated at least one glycaemic control or blood glucose variable in association with metformin treatment (Table 2), but only seven reported mean change

Table 1 Study design and baseline characteristics of participants

First author [reference]	Year	Form of publication	Design	Random allocation sequence	Comparison group	Blinding of investigator/patient	Number of patients randomised (completed)	Duration in months (or as stated)	Mean age (years)	Mean weight (kg)	HbA_{1c} (%) at baseline	Daily dose metformin (mg)
Gin [25]	1985	Full	Crossover	[b]	Placebo	No/No	10 (10)	(7 days)	41	62	10.0[a]	1,700
Keen [26]	1987	Abstract	Crossover	[b]	Placebo	Yes/Yes	8 ([b])	(3 weeks)	‘Adults’[b]	84	[b]	1,500
Walravens [17]	2000	Abstract	Parallel group	[b]	Placebo	Yes/Yes	80 ([b])	6	16	68	9.6	1,000
Meyer [63]	2002	Full	Parallel group[c]	[b]	Placebo	Yes/Yes	62 (59)	6	41	76	7.6	1,700
Hamilton [20]	2003	Full	Parallel group	Computer generated	Placebo	Yes/Yes	30 (27)	3	16	63 (MF), 71 (PL)	9.4 (MF), 8.9 (PL)	Up to 2,000 (weight-dependent)
Särnblad [21]	2003	Full	Parallel group	[b]	Placebo	Yes/Yes	30 (26)[d]	3	17	68	9.3	Forced titration to 2,000
Khan [23]	2006	Full	Crossover	Computer generated	Placebo	Yes/Yes	15 (15)	4	48	92	8.6	Forced titration to 2,550
Lund [16]	2008	Full	Parallel group[c]	Computer generated	Placebo	Yes/Yes	100 (92)	12	46	80	9.5	Forced titration to 2,000
Jacobsen [65]	2009	Full	Parallel group	[b]	Placebo	Yes/Yes	24 (23)	6	40	90	8.9 (MF), 9.3 (PL)	Forced titration to 2,000

[a] HbA_1

[b] Further data unavailable

[c] Intention-to-treat analysis

[d] 24 completed the hyperinsulinaemic–euglycaemic clamp procedure

MF, metformin; PL, placebo

in HbA_1 or HbA_{1c} [16, 17, 20, 21, 23, 63, 65], which was reduced by 0.6–0.9% in four studies [17, 20, 21, 23], with no significant change in three [16, 63, 65] (overall range +0.13% [16] to −0.9% [21]). The remaining two (shorter-term) studies reported other glycaemic benefits, including an 18% increase in glucose uptake (artificial pancreas hyperinsulinaemic–euglycaemic clamp) [25], and improved postprandial glucose handling [26].

Of the seven studies in which insulin dose was not fixed by design [16, 17, 20, 21, 23, 63, 65], insulin-dose requirement was reduced by 5.7–10.1 U/day in six of seven studies (the study which reported no change was conducted in adolescents) [21]. The same seven studies were of sufficient duration to report data on changes in weight or BMI. Metformin reduced weight by 1.7–6.0 kg in three [16, 17, 65] of six studies [16, 17, 21, 23, 63, 65]. A sustained and statistically significant reduction (mean 1.74 kg) was reported in the largest study, which was also of the longest duration [16].

Total cholesterol was reported in seven studies: it was reduced by 0.37 mmol/l in comparison with placebo in the largest study [66], and by 0.3–0.41 mmol/l with respect to baseline (but not placebo) in two others [23, 63]. 'No change' was reported in the other four studies [20, 21, 25, 65].

For formal meta-analysis, only five studies reported the necessary means and standard deviations for insulin dose and HbA_{1c} [16, 20, 21, 63, 65]; there were insufficient data for weight and lipids. Figures 2, 3, 4 and 5 summarise the data in standardised mean differences (SMDs) between treatment groups (i.e. the mean difference/standard deviation of mean difference). Analysing all five studies, the overall effect on $\%HbA_{1c}$ was a standardised mean difference between treatment groups of −0.10 (i.e. 0.10 standardised units lower in the metformin group 95% CI: standardised mean difference reduction of –0.36 to 0.15, p=0.42). This translates into an absolute difference of 0.11 units lower $\%HbA_{1c}$ in the metformin than placebo groups (not statistically significant) (Fig. 2). As there was some suggestion of heterogeneity (p=0.175), we carried out a sensitivity analysis of the four smaller and shorter studies [20, 21, 63, 65]. Thus, excluding the largest study [16] the overall effect on $\%HbA_{1c}$ was a standardised mean difference between treatment groups of −0.30 (i.e. 0.30 standardised units lower in the metformin group 95% CI: standardised mean difference of −0.64 to 0.037, p=0.081). This translates into an absolute difference of 0.28 units lower $\%HbA_{1c}$ (not statistically significant) in the metformin than the placebo groups, with little evidence of heterogeneity (p=0.353) (Fig. 3).

All five studies [16, 20, 21, 63, 65] showed a reduction in daily insulin dose with metformin, with the overall measure of the treatment effect being a standardised mean difference between treatment groups of −0.65 (i.e. 0.65 standardised units lower in the metformin group 95% CI: standardised mean difference of –0.92 to –0.39 units, p<0.001). This translates into an absolute difference in insulin-dose requirement of 6.6 U/day lower in the metformin than placebo groups. The χ^2 test of heterogeneity was not statistically significant (p=0.41), with most of the information coming from the Lund et al. study [16] (Fig. 4). A similar sensitivity analysis of the four smaller and shorter studies [20, 21, 63, 65], excluding Lund et al. [16] confirmed a reduction in daily insulin dose with metformin, with the overall measure of the treatment effect being a standardised mean difference between treatment groups of −0.55 (i.e. 0.55 standardised units lower in the metformin group 95% CI: standardised mean difference of −0.90 to −0.21 units, p=0.002). This translates into an absolute difference of 7.16 U/day lower in the metformin than placebo groups. The χ^2 test of heterogeneity was not statistically significant (p=0.365) with most of the information coming from Meyer et al. [63] (Fig. 5).

There were trends for increased major and/or minor hypoglycaemia with metformin therapy in six [16, 20, 23, 26, 63, 65] out of seven studies in which this adverse effect was mentioned [16, 20, 21, 23, 26, 63, 65] (Table 2); this reached statistical significance in two of the smaller studies [20, 65]. There were no reports of lactic acidosis associated with metformin therapy. Rates of gastrointestinal adverse effects were not systematically reported except in two studies [16, 65], with rates being nearly identical in metformin and placebo groups in the largest study [16].

No studies of any design evaluating cardiovascular function, structure or events were identified.

Discussion

We found only nine randomised studies of metformin therapy in type 1 diabetes, two of which were small and experimental. There were only 192.8 patient years of randomised follow-up in the literature which compares adversely with the evidence for statin therapy in type 1 diabetes (over 6,000 patient years), although even this is inconclusive [67]. Reflecting the paucity of the evidence underpinning metformin in type 1 diabetes, recent publication of a single study [16] from the Steno Diabetes Centre almost doubled the available patient years of randomised follow-up. Overall, the grade of evidence according to the Cochrane GRADE system for our main outcomes of glycaemic control and insulin dose is, at best, moderate [24].

Only five studies [16, 20, 21, 63, 65] could be formally combined in a meta-analysis: there are obvious constraints to the interpretations of such sparse and heterogeneous data. Nonetheless, there was evidence of a significant effect of

Table 2 Study outcomes

First author [reference]	Year	Main outcome	Effect on HbA_{1c} level	Effect on insulin dose	Effect on weight/ anthropometry	Other main effect(s)	No. of hypoglycaemic events	Lipids
Gin [25]	1985	Glucose uptake	[a]	Fixed by design (HEC with Biostator)	[a]	18% increase in insulin sensitivity (p<0.01)[b,c]	[a]	No significant differences with MF[b]
Keen [26]	1987	Fasting and postprandial glucose	Not measured (reduced mean 7 point capillary glucose –1.6[c] [MF] vs 0.1[c] [PL] mmol/l; p<0.05)	No change (fixed CSII)	No significant change[b]	No significant difference in change in fasting venous plasma glucose (–1.7[c] [MF] vs –0.9[c] [PL] mmol/l; *p*=NS)	7 (MF), 0 (PL); 'trend towards more hypos' *p*=NS; severity of events not specified	[a]
Walravens [17]	2000	HbA_{1c}	0.7% lower with MF at 3 months (*p*<0.05); no difference at 6 months[c,d]	Reduced by 10% with MF in men at 6 months only[a]	Wt: MF 64 kg[d], PL 70 kg[d]; *p*<0.05 at 3 months WC: MF 74 cm[d], PL 77 cm[d]; *p*<0.05 at 3 months No significant effects at 6 months	[a]	[a]	HDL increased by 7 mmol/l[c,d] (22%) with MF (*p*='significant')[a]
Meyer [63]	2002	Insulin dose (CSII)	No significant difference –0.13%[c] (MF) vs –0.11%[c] (PL) ('remained unchanged'[b])	6.0 fewer U/day[c] with MF compared with PL (*p*=0.0043)	No significant change[a]	4.5 fewer U[c] of basal insulin dose/day with MF compared with PL (*p*=0.023)	Minor: similar for MF and PL; 47.2[c] (MF) vs 45.1[c] (PL) events patient^{-1} month^{-1} (*p*=NS) Major: 19 (MF) vs 8 (PL); 'no significant difference'	MF: TC reduced by 0.41 mmol/l[c] (*p*=0.04) PL: no data[b]
Hamilton [20]	2003	Insulin sensitivity (FSIGT); HbA_{1c}	0.6%[c] lower with MF compared with PL (*p*=0.03)	0.16[c] U kg^{-1} day^{-1} lower with MF compared with PL (*p*=0.01)	'Trend towards lower BMI in MF group' –0.05[c] (MF) vs 0.2[c] (PL) kg/m^2 (*p*=NS)	No significant difference in the change in insulin sensitivity from baseline between MF and PL 2.6×10^{-4} min^{-1} (μU/ml)$^{-1}$ (1.0–4.1)[e] (MF) vs 2.5×10^{-4} min^{-1} (μU/ml)$^{-1}$ (1.9–2.9)[e] (PL) (*p*=NS)	Minor: 1.8[c] (MF) vs 0.9[c] (PL) events patient^{-1} week^{-1} (*p*=0.03) Major: 2 (MF), 1 (PL)	'No significant change'[d]
Särnblad [21]	2003	HbA_{1c}	0.9% (–1.6, –0.1)[e] lower with MF (p<0.05)[b]	No significant change over time for either treatment group[b]	No significant change in wt: 66 to 67 kg[c] (MF), 65 to 66 kg[c] (PL)[b] No significant change in BMI, WC or WHR[b]	Statistically significant (but variable) increase in insulin sensitivity from baseline with MF, not with placebo (HEC) (*p*=<0.05)[b]	Minor[a] Major: none reported	'No significant change over time for either treatment group'[a]
Khan [23]	2006	HbA_{1c}	0.7 %[a] lower with MF compared with PL (*p*<0.005)	8 U[a] fewer per day with MF compared with PL (*p*<0.05)	–2 kg[c] (MF) vs –1 kg[c] (PL) (*p*=NS)	Fasting plasma glucose 4.3 mmol/l[c] lower with MF compared with PL (*p*<0.001)	Minor: 12 (MF) vs 11 (PL) episodes per patient per 4 weeks (*p*=NS) Major: 'none were reported'	TC and LDL lowered by 0.3 mmol/l[c] and 0.2 mmol/l[c], respectively, by MF (*p*=NS for the difference between MF and PL)
Lund [16]	2008	HbA_{1c}	No significant effect with MF (0.13% [–0.19, 0.44][e], *p*=NS)	5.7 U (–8.6, –2.9)[e] fewer per day with MF (*p*<0.001)	Wt reduced by 1.74 kg (–3.32, –0.17)[e] with MF compared with PL (*p*=0.03) BMI reduced by 0.56 kg/m^2 (–1.06, –0.05)[e] with MF compared with PL (*p*=0.03) HC reduced by 2.90cm (–5.03, –0.77)[e] with MF compared with PL (*p*=0.008)	Significant reduction in cobalamin (–83.3 pmol/l [–139.3, –27.3][e]; *p*=0.004) and alkaline phosphatase (5.91 U/l [–10.77, –1.05][e]; *p*=0.018) from baseline with MF compared with PL Significant increase in potassium (0.20 mmol/l [0.02, 0.38][e]; *p*=0.029) with MF compared with PL	Minor: 48% of patients (MF) vs 49% of patients (PL) (not compared statistically) Major: 15% of patients (MF) vs 10% of patients (PL) (*p*=NS) Borderline increase in patients experiencing unconsciousness: 6% (MF) vs 1% (PL) (*p*=0.06) Major hypoglycaemic events leading to unconsciousness during follow-up: 10 (MF) vs 2 (PL) (*p*<0.05)	Significant reductions in TC and LDL in MF-treated patients compared with PL[f] TC: –0.37 mmol/l (–0.67, –0.06)[e] (*p*=0.021) LDL: –0.33 mmol/l (–0.61, –0.06)[e] (*p*=0.018)

Jacobsen [65]	2009	HbA_{1c}	No significant difference (–0.48[c] [MF] vs –0.17[c] [PL]%; *p*=NS)	8.8 U (–14.62, –3.04)[e] fewer per day with MF (*p*=0.004)	Wt was 3.9 kg (–7.01, –0.71)[e] lower with MF compared with PL (*p*=0.02)	No significant difference in systolic or diastolic blood pressure (daytime or night-time) compared with baseline or between treatment groups Comparing with baseline values: DSBP: –1.1[c] (MF) vs –4.2[c] (PL) mmHg (*p*=NS) DDBP: –2.4[c] (MF) vs –8.7[c] (PL) mmHg (p = NS) NSBP: –4.8[c] (MF) vs –0.4[c] (PL) mmHg (*p*=NS) NDBP: –4.5[c] (MF) vs 2.4[c] (PL) mmHg (*p*=NS)	[g]Significantly higher frequency with MF (0.7[c] [MF] vs 0.3[c] [PL] events $patient^{-1}$ $week^{-1}$ [*p*=0.005]) 'the increased frequency was most distinct in the first 8 weeks'[a]	No significant differences in change in TC, LDL, between treatment groups[f] TC: –0.09[c] (MF) vs 0.03[c] (PL) mmol/l (*p*=0.80) LDL: –0.23[c] (MF) vs –0.10[c] (PL) mmol/l (*p*=NS)

To convert values for insulin sensitivity to SI units ($\times 10^{-4}$ min^{-1} $[pmol/l]^{-1}$) multiply by 0.167

[a] Further data unavailable

[b] No *p* value reported for between-treatment comparison

[c] 95% CI unavailable

[d] No variance estimates stated

[e] 95% CI

[f] Lipid data published separately [66]

[g] Only biochemical hypoglycaemia was registered

CSII, continuous subcutaneous insulin infusion; DDBP, daytime diastolic blood pressure; DSBP, daytime systolic blood pressure; FSIGT, frequently sampled intravenous glucose tolerance test; HC, hip circumference; HEC, hyperinsulinaemic–euglycaemic clamp; MF, metformin; NDBP, night-time diastolic blood pressure; NSBP, night-time systolic blood pressure; PL, placebo; TC, total cholesterol; WC, waist circumference; Wt, weight

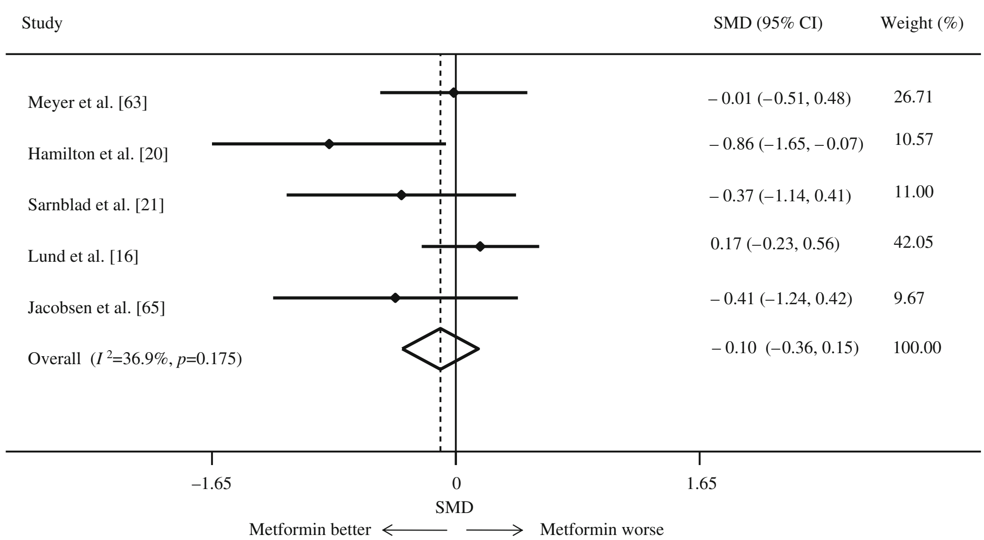

Fig. 2 Standardised mean difference of HbA_{1c} level between metformin-treated and metformin-free type 1 diabetes patients from five randomised controlled studies, including the largest study to date [16] (see text for equivalent $\%HbA_{1c}$ units)

metformin in reducing daily insulin dose requirement. There was no significant effect on HbA_{1c}, which might be expected as, over time, patients would tend to self-titrate their insulin dose towards their usual HbA_{1c}, unless this was prohibited by the protocol. Overall, the evidence we have reviewed is consistent with a whole-body insulin-sensitising effect of metformin. A predicted concomitant attenuation in weight gain with lowering of required insulin doses was seen in the largest and longest trial [16], which was of twice the duration of any other study. A reduction in weight was also reported over 6 months' treatment in the most recently published study [65], in which use of a specific algorithm for insulin titration resulted in a mean dose reduction of 20%. In keeping with the evidence in type 2 diabetes, as recently reviewed by Wulffele et al [68], there was also a relatively consistent signal that metformin may reduce total cholesterol and LDL-cholesterol in adults with type 1 diabetes [66].

In terms of adverse effects, we noted trends towards increased rates of hypoglycaemia in association with adjunct metformin therapy, although this reached statistical significance in only two of the smaller trials [20, 65]. Furthermore, although the largest trial did not report increased rates of metformin-associated major or minor hypoglycaemia, there were significantly more major hypoglycaemic events leading to unconsciousness among metformin-treated individuals with type 1 diabetes [16]. Clearly, even with this weak evidence, physicians contemplating a recommendation of metformin therapy for their patients with type 1 diabetes should advise them carefully regarding insulin-dose adjustment and blood-glucose monitoring. Surprisingly, gastrointestinal adverse effects were infrequently mentioned by investigators. In the largest trial, two of 108 patients screened dropped out for this reason in a run-in period; thereafter, these effects occurred in almost half of the remaining patients, but in almost exactly equal

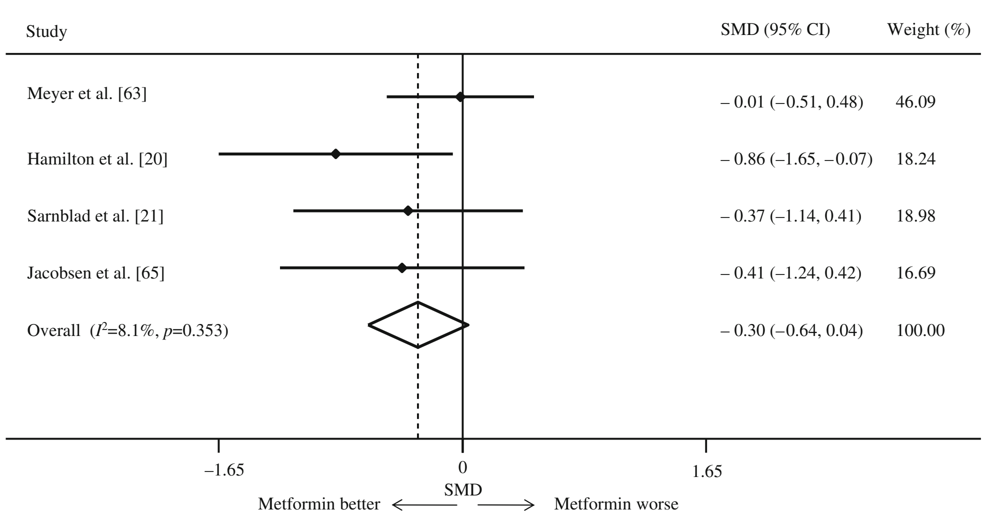

Fig. 3 Standardised mean difference of HbA_{1c} level between metformin-treated and metformin-free type 1 diabetes patients from four randomised controlled studies, excluding the largest study to date [16] (see text for equivalent $\%HbA_{1c}$ units)

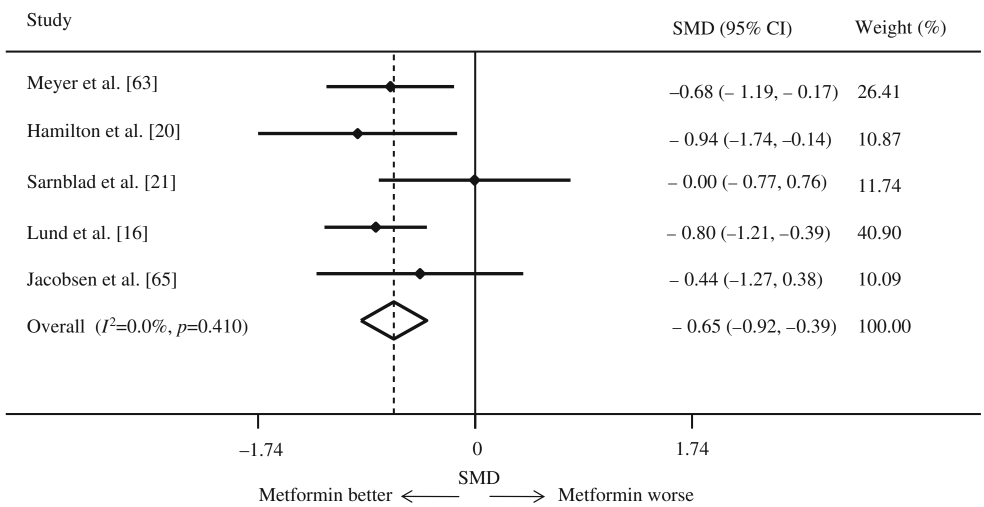

Fig. 4 Standardised mean difference of insulin dose between metformin-treated and metformin-free type 1 diabetes patients from five randomised controlled studies, including the largest study to date [16] (see text for equivalent insulin dose units)

proportions in the active and placebo groups [16]. No cases of lactic acidosis were reported in any of the trials. Although evidence from a Cochrane review has been reassuring on this account in type 2 diabetes [69], randomised follow-up is clearly insufficient in type 1 diabetes, and concern continues to be expressed by some physicians [46].

The findings of the present review disagree to some extent from those of another recent review [15]. Pang and Narendran reported a reduction in HbA_{1c} with metformin therapy in type 1 diabetes on the basis of their meta-analysis of the three smaller trials on this topic [20, 21, 23] which they chose to combine with one of the three larger trials [63], (but not the two largest [16, 17]), along with an observational (controlled but non-randomised) trial that did not meet our inclusion criteria [18]. At the time of their review, the largest trial [16] was only available in abstract form [60]. Thus, although our own review has the limitation of being based on only 192.8 patient years of follow-up, it is a significant advance on the 54 patient years available in the only comparable publication to date. The conclusions of both reviews on outcomes other than HbA_{1c} (weight reduction, insulin dose requirement and cholesterol) were, however, generally similar. While acknowledging that studies of duration as short as 1 to 3 weeks are unlikely to yield information on efficacy, we opted to include them in this review simply as potential sources of information on safety and tolerability, particularly given the paucity of evidence available. These studies were excluded from the formal meta-analysis.

As potential chance differences (randomisation error) at baseline between groups allocated to treatment can influence the outcome of smaller studies, an ideal approach for meta-analysis is to base calculations on data adjusted for baseline values. As such information was not available for all studies, we derived the treatment effects reported from

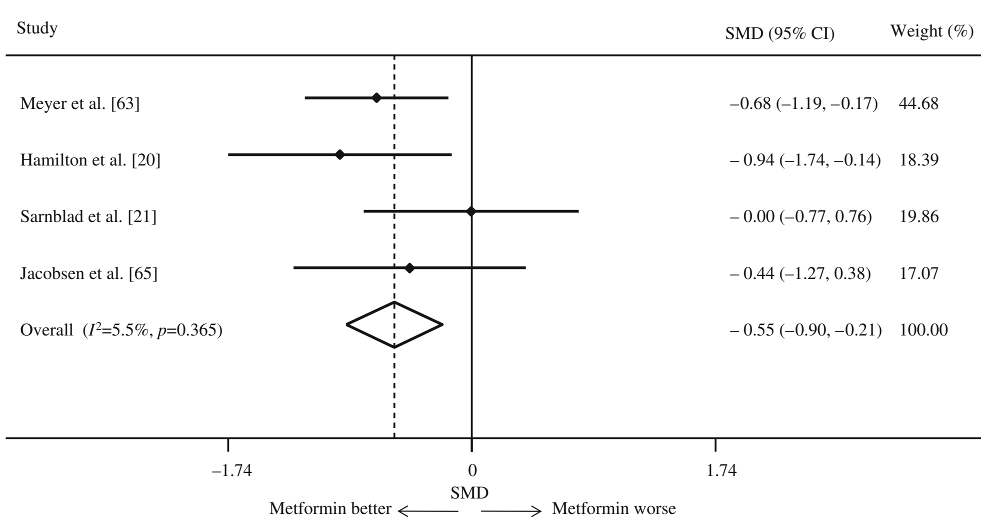

Fig. 5 Standardised mean difference of insulin dose between metformin-treated and metformin-free type 1 diabetes patients from four randomised controlled studies, excluding the largest study to date [16] (see text for equivalent insulin dose units)

absolute units of outcome; we acknowledge this as a limitation, but believe it unlikely to have significantly impacted on the conclusions. A further constraint is that magnitude of treatment effect can be influenced by differences in entry criteria between trials (e.g. for HbA_{1c}): we believe that such methodological issues inherent to meta-analysis only strengthen the case for further larger trials.

Following UKPDS [10] and its more recent 10 year post-randomisation follow-up [14], metformin is widely considered to protect against cardiovascular complications in type 2 diabetes. This is the principal reason for its current status as first-line therapy in this condition. It should be recalled that only 753 patients were included in this specific UKPDS randomisation, and that an effect in the other direction was observed when it was combined with a sulfonylurea [10, 70]. Recently published results from the Hyperinsulinaemia: the Outcome of its Metabolic Effects (HOME) trial have shown that metformin improves macrovascular outcomes in insulin-treated type 2 diabetes patients [71]. This is consistent with some data, including from one of the present authors (J. R. Petrie), that metformin may have intrinsic (and possibly direct) beneficial effects independent of glucose lowering on the cardiovascular system via activation of AMPK [72–74] in a number of conditions [72, 75, 76]. If this is accepted, the hypothesis that metformin might prevent cardiovascular complications in type 1 diabetes should also be tested formally, as even young adults with this condition have an extremely high relative risk of CVD [77–79]. The data reviewed herein provide useful information to guide the design of such a future trial.

To our knowledge metformin therapy is not advocated in any major national or international guidelines for the management of type 1 diabetes, nor in our own regional guidelines. However, routine searches we recently conducted of anonymised type 1 diabetes prescription data in Tayside, Scotland [80] (population 400,000, with approximately 1850 classified as having type 1 diabetes and diagnosed aged <35 years), estimated that 7.9% with BMI> 27 kg/m^2 were receiving metformin, rising to 13.0% for those with BMI>30 kg/m^2. Even allowing for any residual misclassification, it is therefore likely that many thousands of people with type 1 diabetes worldwide are receiving an unproven therapy of unknown long-term efficacy (albeit a familiar one with an attractive theoretical underpinning and the potential to result in reductions in rates of CVD). Considering that type 1 diabetes is usually diagnosed in childhood or adolescence and is a lifelong condition, we believe that properly designed randomised controlled clinical trials of sufficient size and duration to have the power to show reductions in CVD should be conducted forthwith. Given that metformin use in type 2 diabetes has also been associated with reduced cancer risk [81], it would additionally be desirable to investigate this relationship in metformin-treated people with type 1 diabetes.

In summary, our systematic review and meta-analysis of the randomised trials in the literature indicates that metformin therapy in type 1 diabetes is associated with a reduced insulin-dose requirement but no clear evidence of an improvement in glycaemic control. In addition, there may be small reductions in weight and total cholesterol/LDL-cholesterol, but there are no data on cardiovascular outcomes or their surrogates. We suggest this is an important area for future study.

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