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Obesity independently predicts responders to biphasic insulin 50/50 (Humalog Mix50 and Insuman Comb 50) following conversion from other insulin regimens: a retrospective cohort study

J Mamza,[1] R Mehta,[2] I Idris[1]

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[1]Division of Medical Sciences & Graduate Entry Medicine, School of Medicine, University of Nottingham, Derby, UK
[2]Trent Research Design Services, University of Nottingham, Nottingham, UK

Correspondence to
Dr Iskandar Idris;
Iskandar.idris@nottingham.ac.uk

ABSTRACT

Aims: This study aims to examine the metabolic effects of intensification or initiation of insulin treatment with biphasic insulin 50/50, and determine the predictors of responders or non-responders to biphasic insulin 50/50.

Methods: A cohort of 2183 patients ≥18 years with diabetes, newly treated with biphasic insulin 50/50 between January 2000 and May 2012, were sourced from UK General Practices via The Health Improvement Network (THIN) database. Baseline clinical parameters of 1267 patients with suboptimal glycated hemoglobin (HbA1c) >7.5% (>58 mmol/mol) who had received background insulin regimens for at least 6 months preceding biphasic insulin 50/50 were compared against 12-month outcome data. Responders were defined as those with HbA1c <7.5% (58 mmol/mol) and/or HbA1c reduction of ≥1% (10.9 mmol/mol) at 12 months. Comparative analyses were carried out on subgroups of 237 patients initiating insulin therapy with biphasic insulin 50/50, and between users of the Humalog Mix50 (HM50) versus Insuman Comb 50 (IC50). Associations were examined using t tests and multivariate logistic regression techniques.

Results: The overall mean HbA1c reduction at 12 months as a result of intensification and initiation with biphasic insulin 50/50 was 0.5% (5.5 mmol/mol) and 1.6% (17.5 mmol/mol), respectively. Adjusted ORs show obesity (body mass index >30 kg/m^2), treatment duration for ≥9 months, and baseline HbA1c are independent determinants of responders. In addition, stratified for baseline HbA1c levels, HM50 was associated with better HbA1c outcome compared with IC50.

Conclusions: biphasic insulin 50/50 is effective for achieving glycemic control in suboptimal HbA1c levels, especially among obese patients with insulin-treated diabetes. Stratified for baseline HbA1c, HM50 was associated with improved HbA1c outcome compared with IC50.

KEY MESSAGES

- Limited data are available to determine the appropriate place of use for premixed biphasic insulin 50/50 (Humalog Mix50 and Insuman Comb 50) in routine clinical practice, compared with other lower mix insulin formulations (eg, mix30 or mix25).
- Using real-world clinical data from a UK primary care cohort, we have shown that biphasic insulin 50/50 is effective for achieving glycemic control in suboptimal glycated hemoglobin (HbA1c) levels, especially among obese (body mass index >30) patients with insulin-treated diabetes.
- Humalog Mix50 is more effective than Insuman Comb 50.
- These findings could form a basis for a randomized clinical trial on obese insulin-treated patients with diabetes.

INTRODUCTION

The introduction of insulin therapy to achieve adequate glycemic control in patients with type 2 diabetes mellitus (T2DM) is inherent to the progressive deterioration of the pancreatic β-cell function.[1 2] There is no consensus about the most appropriate insulin regimen to be chosen,[3] but National Institute for Health and Care Excellence (NICE) guidelines recommend initiating insulin therapy with human neutral protamine Hagedorn insulin or a long-acting analog (basal insulin) injected at bedtime or twice daily according to the patient's need.[4] When glycemic control is inadequate with basal insulin, therapy can be intensified with prandial insulin (which may include a premixed therapy or basal–bolus regimen). Basal–bolus insulin has been shown to be useful for controlling preprandial and postprandial blood glucose levels, as well as for lowering glycated hemoglobin (HbA1c) levels,[5 6] although we have shown that in routine practice, glycemic control remains suboptimal in many patients receiving a basal–bolus insulin regimen.[7]

In people without diabetes, basal insulin secretion represents approximately 50% of

the total secretion, with the remaining 50% being meal related.[8] Among patients with T2DM requiring intensive insulin therapy regimens in the form of multiple daily injections or insulin pump therapy, both regimens required 50% basal and 50% rapid-acting insulin following dose titration.[9] Based on these, a biphasic insulin 50/50 containing 50% each of rapid-acting and basal insulin (a mid-mix regimen) was developed to provide the physiological advantages of rapid-acting and long-acting insulin in the convenience of a premixed formulation.[10] Indeed, intensification of insulin therapy (where patients' blood glucose levels remain suboptimal after receiving biphasic insulin aspart 30/70, biphasic human insulin 30/70, or biphasic insulin lispro 25/75) has been shown to be achieved by switching to premixed regimens with greater prandial coverage (HM50).[11–13] Insuman Comb 50 (IC50)—a combination of 50% soluble insulin and 50% crystalline protamine insulin—is also available as a biphasic insulin 50/50 regimen. There is, however, limited postmarket surveillance and/or real-world evidence assessing the effectiveness of switching to HM50 or IC50 regimens in patients with suboptimal HbA1c levels. This study aims to investigate the effectiveness of the biphasic insulin 50/50 regimen (HM50 and IC50) in patients with persistently suboptimal HbA1c and examine the clinical and metabolic parameters that predict glycemic response in people with T2DM.

METHODS

Study design and data source

We conducted a retrospective cohort analysis of data from The Health Improvement Network (THIN) database, which contains anonymous patient data from more than 400 general practices throughout England and Wales. The database has been validated at the practice and dataset levels by comparing its demographics, morbidity, mortality, prevalence, and geographical rates with various national data sources. The database contains information on all past and current medical diagnoses (coded using read codes) and prescribed medications (coded using British National Formulary).

Study population

The study population comprises a cohort of patients who were identified to have T2DM, and were registered to a practice for more than 12 months before the index date (ie, between January 1, 2000 and the end of the study— May 16, 2012). The cohort comprised patients with a suboptimal glucose control (HbA1c) level above 7.5% (58 mmol/mol), who were prescribed other forms of insulin regimens before the index date and were ≥18 years. Standardized computerized routines to include programing language and use of algorithms were used to obtain the relevant data using Read codes. Information was extracted on patients diagnosed with diabetes and previous insulin prescriptions for at least 6 months preceding conversion to biphasic insulin 50/50 regimen. Six months duration was used because THIN data suggests 95% of repeat prescriptions for insulin have a periodicity of less than 6 months.

Exposure and outcomes

Exposure was defined as two or more prescriptions of HM50 or IC50, with a follow-up period of 12 months from the index date. Alternatively, the 90th day recording of HbA1c levels was used, or the date of switching to, or adding another glucose-lowering drug. The primary outcome was a change in HbA1c levels after exposure. Responders are defined as patients whose 12-month HbA1c fell below 7.5% (58 mmol/mol) or who experienced HbA1c reduction of more than 1% (10.9 mmol/mol) at 12 months when compared with baseline. The secondary outcome was a measure of the association between changes in HbA1c level and absolute change in weight at 12 months after the index date.

Covariates

Covariates were selected a priori on the basis of clinical significance. These are baseline demographic and clinical parameters, referred to as 'predictors' of interest. They include age, gender, social deprivation (measured using Townsends index scores),[14] body weight, body mass index (BMI), baseline HbA1c, total cholesterol levels, low-density lipoprotein, high-density lipoprotein (HDL), triglycerides, systolic and diastolic blood pressures, smoking status, lipid-lowering therapies, antihypertensive drugs, aspirin, oral antidiabetic drugs (OADs), drugs, duration of diabetes drug treatment, and comorbidity. In addition, the background insulin treatments the patients received prior to index date, for example, basal, bolus, or premixed regimens, were included as determinants of interest.

Statistical analysis

Baseline characteristics that might distinguish between responders and non-responders to HM50/IC50 therapy were analyzed using the χ^2 and t tests. Multiple logistic regressions were carried out to identify covariates that predict a response (HbA1c change) within 12 months. ORs for predictors and confounding variables were calculated and expressed as point estimates with a 95% CI, at the conventional statistical significance level of 0.05. Missing data were accounted for with multiple imputations using chained equations.[15]

Subgroup and secondary analyses

Correlation and linear regression analyses were performed to assess the relationship between changes in HbA1c and weight at 12 months. Analysis was carried out on a subgroup of patients who were not prescribed any insulin prior to study entry (initiation group). Subgroup analysis for efficacy in end point changes in HbA1c from baseline was performed between HM50 and IC50 treatment groups. Baseline HbA1c was

categorized into three strata: <8% (<64 mmol/mol), 8 to <9% (64–75 mmol/mol), and ≥9% (≥75 mmol/mol).

Sensitivity analysis

Sensitivity analysis was carried out to compare results of multiply imputed data with complete data, and to assess the reliability of the outcomes and the impact of missing data. All analyses were conducted using Stata Software, V.13.[16]

Bias

Our analysis employed the 'new user' design to minimize biases associated with prevalent use of insulin.[17] Prior exposure to basal, bolus, and other premixed insulin regimens could also be a factor on the causal pathway for response, thereby introducing confounding by indication.[18] These potential biases were minimized by conducting analysis within a cohort of new users who did not receive prescriptions for biphasic insulin 50/50 in the 12 months prior to study entry. The cohort was restricted to patients with at least two repeat prescriptions of biphasic insulin 50/50 for an estimated 12-month follow-up to reduce the risk of bias introduced by the different durations of treatments.[17] We also restricted the cohort to individuals whose treatment with insulin for at least 6 months preceding conversion had failed.

RESULTS

General patient characteristics

Of the 2183 users of biphasic insulin 50/50, 1267 patients fulfilled the criteria for cohort entry as outlined in figure 1 and 237 people formed the subgroup of patients who had not received insulin prior to the index date. The cohort had a mean age of 61 years and 54% were men. In total, 684 (54%) of the cohort were prescribed HM50.

Response to intensification therapy

Our analysis focused on HbA1c response to intensification with biphasic insulin 50/50. In total, 457 (36%) of patients responded to intensification therapy, based on criteria for responders described previously. Responders were not significantly different with age, sex, weight, social deprivation strata, smoking status, or previously prescibed medications. In addition, responders were unrelated to the majority of comorbid conditions and clinical parameters. Baseline mean HbA1c was significantly higher among responders compared with non-responders (10.2% (88 mmol/mol) vs 9.3% (78 mmol/mol), p<0.001), and responders had a slightly lower HDL at baseline (1.3 vs 1.4 mmol/L, p=0.03; table 1). Overall, intensification with biphasic insulin 50/50 resulted in a 0.5% (5.5 mmol/mol) reduction in HbA1c, 0.9 kg increase in weight, and 0.3 kg/m^2 increase in BMI at 12 months. Responders had a significantly

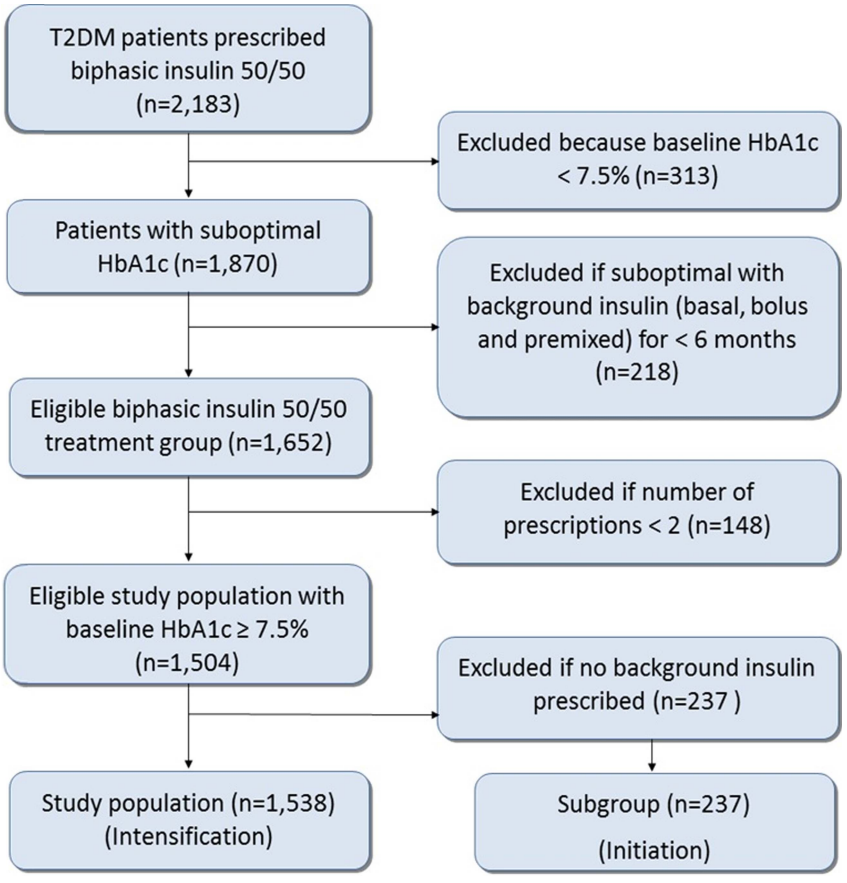

Figure 1 Study selection flow diagram. HbA1c, glycated hemoglobin; T2DM, type 2 diabetes mellitus.

Table 1 Baseline characteristics of Humalog Mix50 users

Characteristics	Total (n=1267)	Responders (n=457)	Non-responders (n=810)	OR (95% CI) (unadjusted)	p Value
Exposure/predictors					
Age (years)	61 (15)	62 (14)	61 (15)	1.01 (1.00 to 1.01)	0.1
Sex					
Male	682 (54)	251 (37)	431 (63)	1	
Female	585 (46)	206 (35)	379 (65)	0.93 (0.74 to 1.17)	0.9
Townsend deprivation					
I—least deprived	226 (18)	84 (37)	142 (63)	1	
II	269 (21)	94 (35)	175 (65)	0.91 (0.63 to 1.31)	0.6
III	284 (22)	103 (36)	181 (64)	0.96 (0.67 to 1.38)	0.8
IV	274 (22)	94 (34)	180 (66)	0.88 (0.61 to 1.27)	0.5
V—most deprived	214 (17)	82 (38)	132 (62)	1.05 (0.71 to 1.54)	0.8
BMI (kg/m^2)	30.4 (6.8)	31 (6.9)	30 (6.7)	1.02 (1.00 to 1.04)	0.01
BMI categories (kg/m^2)					
Normal	259 (20)	79 (31)	180 (70)	1	
Overweight	406 (32)	140 (34)	266 (66)	1.20 (0.86 to 1.68)	0.3
Obese	602 (48)	238 (40)	364 (40)	1.49 (1.09 to 2.03)	0.01
Weight (kg)	85.8 (2.)	87 (20)	85 (20)	1.00 (1.00 to 1.01)	0.1
Baseline HbA1c (%)	9.6 (1.5)	10.2 (1.7)	9.3 (1.3)	1.54 (1.41 to 1.68)	<0.001
BP (mm Hg)					
Systolic BP	139 (19)	139 (19)	139 (19)	1.00 (1.00 to 1.01)	0.6
Diastolic BP	76 (11)	76 (11)	76 (11)	1.00 (1.00 to 1.01)	0.6
Total cholesterol (mmol/L)	4.7 (1.3)	4.7 (1.3)	4.7 (1.2)	1.01 (0.92 to 1.10)	0.9
HDL (mmol/L)	1.3 (0.6)	1.3 (0.6)	1.4 (0.5)	0.78 (0.63 to 0.98)	0.03
LDL (mmol/L)	2.6 (1.1)	2.6 (1.1)	2.6 (1.1)	1.02 (0.92 to 1.14)	0.7
Triglyceride (mmol/L)	2.4 (6.6)	2.7 (4.9)	2.2 (7.3)	1.01 (0.99 to 1.03)	0.2
Smoking status					
Never smoked	577 (46)	204 (35)	373 (65)	1	
Current smoker	226 (18)	76 (34)	150 (66)	0.93 (0.67 to 1.28)	0.6
Ex-smoker	464 (37)	177 (38)	287 (62)	1.13 (0.87 to 1.45)	0.9
Use of medications					
Antihypertensive	1076 (85)	381 (35)	695 (65)	1.83 (0.61 to 1.13)	0.2
Lipid-lowering therapy	911 (72)	341 (37)	570 (63)	1.24 (0.96 to 1.60)	0.1
Aspirin	693 (55)	255 (37)	438 (63)	1.07 (0.85 to 1.35)	0.5
Oral antidiabetic					
Gliptin	44 (3)	16 (36)	28 (63)	1.01 (0.54 to 1.89)	0.9
GLP1	61 (5)	25 (41)	36 (59)	1.24 (0.73 to 2.10)	0.4
Metformin	1115 (88)	400 (36)	715 (64)	0.93 (0.66 to 1.32)	0.7
Sulfonylurea	465 (37)	177 (38)	288 (62)	1.15 (0.90 to 1.45)	0.3
Thiazolidinedione	133 (11)	49 (37)	84 (63)	1.04 (0.72 to 1.51)	0.8
Other	95 (8)	35 (37)	60 (63)	1.03 (0.67 to 1.60)	0.9
Previous insulin therapy					
Premixed regimen	925 (73)	325 (35)	600 (65)	1	
Basal insulin	253 (20)	95 (38)	158 (62)	1.11 (0.83 to 1.48)	0.5
Bolus	89 (7)	37 (42)	52 (58)	1.31 (0.84 to 2.05)	0.2
Comorbid conditions					
CHD	636 (50)	237 (37)	399 (63)	1.11 (0.88 to 1.40)	0.4
PAD	313 (25)	120 (38)	193 (62)	1.14 (0.87 to 1.48)	0.3
Cerebrovascular	252 (20)	87 (35)	165 (65)	0.92 (0.69 to 1.28)	0.6
Heart failure	228 (18)	96 (42)	132 (58)	1.37 (1.02 to 1.83)	0.04
Hypoglycemia	549 (43)	193 (35)	356 (65)	0.93 (0.74 to 1.18)	0.6
Number of Mix50 Rx					
2–5	406 (32)	131 (32)	275 (68)	1	
6–8	315 (25)	95 (30)	220 (70)	0.91 (0.66 to 1.25)	0.5
9–12	284 (22)	104 (37)	180 (63)	1.21 (0.88 to 1.67)	0.2
≥13	262 (21)	127 (48)	135 (52)	1.97 (1.43 to 2.72)	<0.001

Continued

Table 1 Continued

Characteristics	Total (n=1267)	Responders (n=457)	Non-responders (n=810)	OR (95% CI) (unadjusted)	p Value
Duration of therapy (months)					
0–3	111 (9)	27 (24)	84 (76)	1	
3–6	106 (8)	33 (31)	73 (69)	1.41 (0.77 to 2.56)	0.3
6–9	133 (11)	48 (36)	58 (64)	1.76 (100 to 3.07)	0.05
9–12	917 (72)	349 (38)	568 (62)	1.91 (1.21 to 3.01)	0.005

BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; GLP1, glucagon-like peptide-1 agonis; HbA1c; glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PAD, peripheral artery disease.

higher mean (SD) weight increase (1.6 (7.1) vs 0.5 (4.9) kg, p<0.001) and significant mean HbA1c reduction of 1.9% (20.8 mmol/mol) vs 0.3% (3.3 mmol/mol) increase seen in non-responders (p<0.001).

Main results

After adjusting for the effects of confounders, the independent predictors of response to intensification with biphasic insulin 50/50 were obesity (BMI >30 kg/m^2; OR, 1.50 (95% CI 1.08 to 2.09), ≥9 months of intensification therapy (OR, 1.98 (95% CI 1.23 to 3.20)), and baseline HbA1c (OR, 1.55 (95% CI 1.42 to 1.69); table 2).

Comparison between HM50 vs IC50

We compared the metabolic effects of HM50 vs IC50 according to baseline strata for HbA1c values. Overall, HM50 was associated with a better HbA1c response compared with IC50 (mean reduction in HbA1c of 0.6% vs 0.4% (6.6 vs 4.4 mmol/mol), p<0.001; table 3). The difference in mean change of HbA1c was approximately 0.5% (95% CI 0.02% to 0.94%) or 5.5 mmol/mol (95% CI 0.2 to 10.3) lower with HM50 treatment group compared with IC50 in the baseline HbA1c category below 8% (<64 mmol/mol). The IC50 group had a 0.06% (95% CI −0.22% to 0.34%) or 0.7 mmol/mol (95% CI 2.4 to 3.7) lower reduction in HbA1c compared with HM50 at baseline HbA1c category of 8% to <9% (64 to <75 mmol/mol). The greatest treatment benefit was observed in patients within the baseline HbA1c category of 9% and above (≥75 mmol/mol), where HM50 was associated with a non-significant lower mean difference (−0.2% (95% CI −0.03% to 0.39%) or −2.2 mmol/mol (95% CI −0.3 to 4.3)) when compared with the IC50 treatment group. Mean weight increase at 12 months was not significantly different between HM50 and IC50 users (table 3).

Other analyses

Tests for interactions between sex, social deprivation, and responders were not significant at the 5% level, indicating no evidence of effect modification across these groups. A scatter plot of individual patient data shows a significantly negative but weak association between change in HbA1c and change in weight at 12 months

Table 2 Results of multiple logistic regression analyses

Predictors of response	OR (95% CI) (unadjusted)	p Value	OR (95% CI) (adjusted)	LRT p Value
Baseline HbA1c (%)	1.53 (1.40 to 1.67)	<0.001	1.55 (1.42 to 1.69)	<0.001
BMI categories (kg/m^2)				
Normal	1		1	
Overweight	1.35 (0.94 to 1.94)	0.1	1.40 (0.98 to 2.00)	0.06
Obese	1.35 (0.95 to 1.91)	0.09	1.50 (1.08 to 2.09)	0.02
HDL (mmol/L)	0.91 (0.70 to 1.12)	0.3	–	–
Comorbid conditions				
Heart failure	1.20 (0.88 to 1.64)	0.2	–	–
Number of Mix50 Rx				
2–5	1		–	–
6–8	0.72 (0.50 to 1.04)	0.08		
9–12	0.94 (0.64 to 1.37)	0.7		
≥13	1.27 (0.85 to 1.91)	0.2		
Duration of therapy (months)				
0–3	1		1	
3–6	1.64 (0.88 to 3.04)	0.1	1.51 (0.80 to 2.82)	0.2
6–9	1.90 (1.05 to 3.44)	0.04	1.70 (0.94 to 3.07)	0.08
9–12	1.95 (1.15 to 3.31)	0.01	1.98 (1.23 to 3.20)	0.005

BMI, body mass index; HDL, high-density lipoprotein; HbA1c; glycated hemoglobin; LRT, likelihood ratio test.

Table 3 Comparing treatment effects of intensification with IC50 and HM50 at 12 months

	IC50			HM50			Difference in mean change (95% CI)
	n (%)	Mean change (SD)	95% CI	n (%)	Mean change (SD)	95% CI	
Outcome							
Responders	184 (32)	−1.91 (1.1)	(−2.07 to −1.75)	273 (40)	−1.97 (1.0)	(−2.09 to −1.86)	0.07 (−0.13 to 0.26)
Non-responders	399 (68)	0.34 (1.1)	(0.23 to 0.45)	411 (60)	0.26 (0.9)	(0.17 to 0.35)	0.08 (−0.06 to 0.22)
HbA1c (%) (mmol/mol)	583 (46)	−0.37 (1.5)	(−0.49 to −0.25)	684 (54)	−0.63 (1.5)	(−0.74 to −0.52)	−0.26 (−0.43 to −0.10)
		−4.00 (16.4)	(−5.40 to −2.70)		−6.90 (16.4)	(−8.10 to −5.7)	−2.80 (−4.70 to −1.10)
HbA1c subgroups (%) (mmol/mol)							
HbA1c (<8%) (<64)	84 (14)	0.57 (1.3)	(0.28 to 0.85)	41 (6)	0.09 (1.0)	(−0.23 to 0.41)	0.48 (0.02 to 0.94)
		6.20 (14.2)	(3.10 to 9.3)		1.00 (10.9)	(−2.50 to 4.50)	5.20 (0.20 to 10.3)
HbA1c (8 to <9%) (64 to <75)	177 (30)	−0.05 (1.5)	(−0.27 to 0.17)	190 (28)	0.01 (1.2)	(−0.16 to 0.17)	−0.06 (−0.34 to 0.22)
		−0.50 (16.4)	(−3.00 to 1.90)		0.10 (13.1)	(−1.7 to 1.9)	−0.720 (−3.70 to 2.40)
HbA1c (≥9%) (≥75)	322 (55)	−0.79 (1.5)	(−0.95 to −0.63)	453 (66)	−0.97 (1.5)	(−1.11 to −0.83)	0.18 (−0.03 to 0.39)
		−8.60 (16.4)	(−10.40 to −6.9)		−10.60 (18)	(−12.1 to −9.10)	2.00 (−0.30 to 4.30)
Weight (kg)		0.94 (4.9)	(0.54 to 1.34)		0.87 (6.5)	(0.38 to 1.36)	0.07 (−0.58 to 0.71)

HbA1c; glycated hemoglobin; HM50, Humalog Mix50; IC50, Insuman Comb 50.

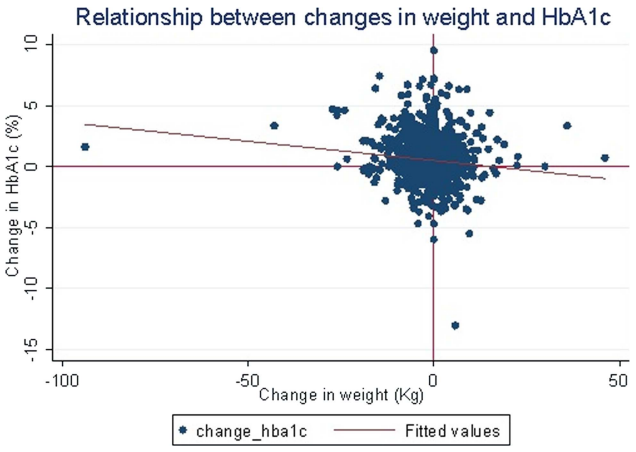

Figure 2 Relationship between change in glycated hemoglobin (HbA1c) and change in weight at 12 months.

(Pearson's correlation coefficient, r=−0.13; p<0.001; figure 2). Change in weight accounts for approximately 1.7% of the total variation in HbA1c change, and for every unit increase in weight, HbA1c increased by an estimated 0.04% (0.4 mmol/mol). The subgroup of 237 patients who initiatied insulin therapy with biphasic insulin 50/50 were examined, and 149 (59%) patients responded to treatment. The mean (SD) reduction in HbA1c in the subgroup was 1.6 (2.1) % or 17.5 (23.0) mmol/mol.

DISCUSSION

Overall, this study showed a significant 0.5% (5.5 mmol/mol) reduction in HbA1c at 12 months after patients with suboptimal HbA1c from background insulin were converted to biphasic insulin 50/50. Multiple regression analysis showed that the presence of obesity and baseline HbA1c were independent predictors of responders to biphasic insulin 50/50 therapy. Results showed that responders to biphasic insulin 50/50 in the main study cohort were more likely to experience weight gain and reduction in cholesterol levels, compared with non-responders. HM50 appears to be superior to IC50 in glycemic outcomes, when stratified for baseline HbA1c.

Although mean HbA1c improved following conversion to biphasic insulin 50/50, only 36% of patients responded to the intensification based on our strict definition of responders. This relatively low percentage of responders to biphasic insulin 50/50 may reflect the difficulties in lowering HbA1c in a challenging cohort of patients with insulin-treated diabetes. This was similar to our previous study of responders to any insulin therapy among patients with newly diagnosed diabetes, where 47% of patients responded to any insulin therapy.[19]

The link between intensification of insulin treatment and weight gain is well recognized.[6 20] We[7] and others[21 22] have previously shown that low BMI is a significant predictor of response to insulin therapy. A study by Nichols *et al* on insulin-treated patients with T2DM, for example,

showed that lower BMI, younger age, and female gender were predictors of good glycemic response to insulin. Furthermore, we have previously shown a threshold BMI of 34.7 kg/m^2, above which patients appeared to have a reduced response to insulin therapy.[7] Thus, the management of obese insulin-treated diabetes presents a significant therapeutic challenge as clinicians strive to achieve optimal glycemic targets. To this end, a novel and important finding from this study was the observation of improved HbA1c response to biphasic insulin 50/50, among obese (BMI >30 kg/m^2) compared with non-obese patients with insulin-treated diabetes. The reason for this is unclear, as our data cannot be analyzed for the total amount or frequency of insulin being used per day. We would speculate, however, that the intensification of insulin therapy by conversion to biphasic insulin 50/50 regimen (from a basal–bolus insulin or a low-mix biphasic insulin regimen) is often associated with a reduction in the total amount of insulin used per day (unpublished preliminary observation from our ongoing UK multicentre audit of HM50 use in clinical practice), which would facilitate weight loss, improved compliance, and would confer glycemic benefits. This is highly relevant given the high prevalence of obesity among insulin-treated patients with diabetes. The mean weight gain of 1.6 kg at 1 year induced by conversion to biphasic insulin 50/50 was comparable, if not slightly less than the weight gain of 2.2 kg with any insulin regimen, observed in our previous study.[7] Moreover, in the previous study,[7] we observed a mean BMI increase of 1.13 kg/m^2 with any premixed insulin compared with a BMI gain of 0.3 kg/m^2 with biphasic insulin 50/50 in the present study. This favorable effect of biphasic insulin 50/50 on weight observed in this study is supported by a previous finding from another study. Kazda *et al*[23] found that, among patients who started insulin therapy with either HM50 or Humalog, BMI gain was significantly less in the former (0.6±1.1 vs 0.9±1.5, p<0.005), despite patients taking a higher daily dose of insulin in the HM50 group (0.59±0.3 U/kg vs 0.50±0.23 U/kg, p<0.005). In addition, previous studies have shown benefits of HM50 compared with human insulin 70/30[13] or Humalog 75/25[23] in reducing postprandial glucose excursion.[10] These benefits were augmented when HM50 was given thrice daily compared with 70/30 twice daily,[11] or 70/30 thrice daily,[24] but equivalent when compared with a basal–bolus insulin regimen.[25] Our data however did not include ethnicity and hence our findings cannot be generalized to all ethnic groups. Socioeconomic factors did not affect glucose control.

In the sensitivity analysis of missing data, the association between response and baseline predictors gave similar results for the complete and incomplete cases, which indicates that missing data were unlikely to bias the outcome of the study. Nonetheless, our analyses were subject to some limitations inherent to observational studies. Potential residual confounders such as compliance, diabetes duration, indications for insulin therapy, and differences in insulin regimens or titration protocols used across different areas in the UK were not accounted for. We attempted to minimize compliance bias by restricting the analysis to those who received more than 6 months of biphasic insulin 50/50 prescription from the index date. Also, we did not fully account for the role of comorbid illnesses, but previous data suggest that this factor did not affect glycemic control.[25] Despite these limitations, our study highlights the effectiveness of biphasic insulin 50/50 in real-world practice. We have shown how simple clinical and demographic parameters that are available to clinicians and researchers may influence biphasic insulin 50/50 treatment among patients with suboptimal glucose control.

In summary, the results of this study support the use of biphasic insulin 50/50 as a therapeutic option, especially among obese patients with insulin-treated diabetes whose glucose control remains suboptimal. Improvements in HbA1c were associated with weight gain and reduction in cholesterol levels. Our findings also showed that when stratified for baseline HbA1c, HM50 was associated with greater HbA1c reduction compared with IC50. A robust randomized controlled trial is required to fully investigate the effectiveness of biphasic insulin 50/50 among patients with obesity and diabetes who are unresponsive to other insulin treatment.

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