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Article

Insulin analogues versus human insulin in type 1 diabetes: direct and indirect meta-analyses of efficacy and safety

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All patients with Diabetes Mellitus (DM) receive insulin therapy. In this study, we evaluated the efficacy, safety and tolerability of human insulin and insulin analogues. We performed a systematic review of the literature and a meta-analysis according to the Cochrane Collaboration methodology. In the absence of clinical studies comparing insulins, we performed a mixed treatment comparison to establish the differences between the active treatments. We included studies published from 1995 to 2010. HbA1c results, episodes of hypoglycemia and nocturnal hypoglycemia data were extracted and analyzed. Thirty-five randomized clinical trials were selected after examining the abstract and a full text review. These studies included 4,206 patients who received long-acting insulin analogues and 5,733 patients who received short-acting insulin analogues. Pooled data regarding efficacy indicated no significant differences in HbA1c values between glargine or detemir (once daily) and NPH insulin. However, a twice-daily dose of detemir produced differences in HbA1c values that favored detemir (-0.14% [95% CI: -0.21 to -0.08]; $p<0.0001$; $I^2=0\%$). Direct and indirect comparisons are consistent and show that there were no significant differences between human insulin and insulin analogues in efficacy or safety. Our results indicate that long- and short-acting insulin analogues offer few clinical advantages over conventional human insulin.

Uniterms: Insulins/meta-analysis. Diabetes mellitus/type 1. Insulin/treatment efficacy. Insulin/safety use.

Todos os pacientes com Diabetes Mellitus (DM) tipo 1 recebem insulina. Neste estudo, avaliaram-se eficácia, segurança e tolerabilidade de insulinas humanas e análogas. Realizou-se uma revisão sistemática e meta-análise, de acordo com o preconizado pela Colaboração Cochrane. Na ausência de estudos clínicos comparando insulinas entre si, realizaram-se meta-análises de comparações indiretas a fim de estabelecer diferenças entre tratamentos ativos. Incluíram-se estudos de 1995 a 2010. Resultados de HbA1c, episódios de hipoglicemia e hipoglicemia noturna foram extraídos e analisados. Após leitura de resumos e, posteriormente, de artigos na íntegra, selecionaram-se 35 ensaios clínicos randomizados, totalizando 4206 pacientes utilizando insulina análoga de longa duração e 5733 pacientes insulina análoga de curta duração. Os resultados não demonstraram diferença estatisticamente significativa para redução de HbA1c entre glargina e detemir (uma vez ao dia) comparados a NPH. No entanto, insulina detemir utilizada duas vezes ao dia reduz a HbA1c (-0.14% [95% CI: -0.21 to -0.08]; $p<0.0001$; $I^2=0\%$). Comparações diretas e indiretas indicam que não existem diferenças significativas na médica de redução de HbA1c, independente da posologia de detemir, sendo estes resultados de eficácia e segurança consistentes. Os resultados indicam que insulinas análogas de longa ou curta duração apresentam pequenas vantagens, quando comparadas às insulinas tradicionais. Ademais, não existem diferenças entre eficácia e segurança quando comparamos insulinas análogas entre si.

Unitermos: Insulinas/meta-análise. Diabetes mellitus tipo 1. Insulina/eficácia. Insulina/segurança no uso.

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INTRODUCTION

Diabetes mellitus is associated with serious long-term complications and premature death (Singh *et al.*, 2009). The Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study confirmed the benefits of improved glycemic control (DCCT, 1993; UKPDS, 1998). To implement intensive insulin therapy, a physiologic model of insulin replacement is applied to most patients with type 1 diabetes mellitus (Pieber *et al.*, 1995).

There are many good insulin formulations; however, metabolic control in many patients remains unsatisfactory (Plank *et al.*, 2005).

For many years, the most commonly used type of insulin that provided a basal insulin supply was NPH (Neutral Protamine de Hagedorn); however, it has been shown to frequently result in nocturnal hypoglycemia due to unintended plasma insulin peaks (Rosenstock *et al.*, 2005). Injection of regular human insulin does not replicate the postprandial endogenous secretion of insulin. Insulin analogues are modified forms of human insulin that have been developed to address this limitation (Singh *et al.*, 2009). Since 2000, long-acting insulin analogues have been available. They are progressively replacing NPH insulin as the preferred form of basal insulin for type 1 diabetes because of their favorable pharmacokinetics and pharmacodynamics, namely a less pronounced peak concentration and longer duration of action, which results in lower HbA1c levels and fewer episodes of hypoglycemia (Bolli *et al.*, 2009a).

Unmodified human insulin hardly mimics the physiologic post-prandial insulin peak of non-diabetic people because there is a high tendency for it to aggregate as a hexamer at the injection site. Short-acting insulin analogues have reduced tendencies toward oligomerization, which allows them to be more quickly absorbed into the blood; as a consequence, they have faster onsets of action (Plank *et al.*, 2005).

Numerous clinical trials have demonstrated the pharmacokinetic advantages of insulin analogues. However, a recent meta-analysis suggested that the rapid-acting analogues provide only small advantages in terms of HbA1c (glycated hemoglobin or glycosylated hemoglobin) reductions and no advantages for hypoglycemia compared with unmodified human insulin (Gough, 2007). Although insulin analogues are commonly prescribed for the management of diabetes mellitus, there is uncertainty regarding their optimal use (Singh *et al.*, 2009).

Systematic reviews of insulin analogues have been published previously (Brunelle *et al.*, 1998; Siebenhofer A *et al.*, 2004; Warren *et al.*, 2004; Plank *et al.*, 2005; Gough, 2007; Monami *et al.*, 2009; Singh *et al.*, 2009). However, through our comprehensive search of the literature, we did not encounter any reviews delving into the efficacy, safety and tolerability of both short- and long-acting insulin analogues for the management of type 1 diabetes in adults. Within this context, the aim of this work was to evaluate these characteristics of short- and long-acting insulin analogues in comparison with the conventional human insulins.

METHODS

We performed a systematic review of the literature and a meta-analysis that compared the efficacy and safety of various long-acting insulin analogues, Neutral Protamine Hagedorn (NPH) and regular human insulin in type 1 diabetic adults (≥ 18 years). All studies used the same long-acting insulin for both treatments.

A systematic review of the literature was conducted in accordance with the methodology of the Cochrane Collaboration guidelines (Higgins *et al.*, 2009). We performed a comprehensive search for randomized controlled trials using several combinations of keywords, including "glargine," "lantus," "detemir," "levemir," "aspart," "novorapid," "lispro," "humalog," "glulisine," "apidra," "type 1 diabetes," "insulin-dependent diabetes" and "random,"* in the following databases: Scopus, Medline, Cochrane Library, Lilacs and International Pharmaceutical Abstracts (IPA). The literature search was supplemented with a hand search of references and other systematic reviews that have already been published. The search included studies performed between January 1995 and December 2010 without language restriction.

Selection and quality assessment of trials

Two reviewers (A.S. and R.V.) independently selected the studies initially by reviewing the titles and abstracts. These studies included exclusively double-blinded randomized controlled trials (RCTs) of adult patients with established type 1 diabetes who received a long-acting insulin analogue (glargine or detemir), a short-acting insulin analog (aspart, lispro or glulisine), NPH insulin (either alone or in combination with rapid-acting human insulin [regular]) or insulin analogues (lispro or aspart) for at least 4 weeks. We included detemir with a treatment regimen of once- or twice-daily. We excluded studies that used a crossover methodology.

Data extraction was performed by two independent authors (A.S. and C.C.) in accordance with the recommendations of the Cochrane Handbook for

Systematic Reviews of Interventions (Higgins *et al.*, 2009). Extracted data included study design, baseline characteristics, health intervention, drug regimen, concomitant treatments and outcomes. Any disagreement in data collection was resolved through consensus and with a third reviewer (R.V.) when necessary. The quality of each trial was evaluated using a method assessment tool published by Jadad *et al.* (1996).

Outcomes

Two major outcomes were obtained: efficacy, defined as a change (%) in HbA1c concentration at the end of the study, and safety, including overall hypoglycemia episodes and nocturnal hypoglycemia episodes, as defined by the number of patients with at least one episode during the study for long-acting insulin or the number of patients with at least one episode during a month for short-acting insulin.

Statistical analyses

The efficacy results are described as the mean difference (MD) with an associated 95% confidence interval (CI) for the HbA1c changes at the end of the studies. For the safety results (hypoglycemia) and withdrawals (because of adverse events or a lack of efficacy), the odds ratio (OR) method was used with the associated 95% CI of the event rates.

The data of the included studies were pooled across the trials using the random effect model (inverse variance method). Heterogeneity was evaluated by the inconsistency index (I^2). Values of I^2 lower than 25% were considered low heterogeneity, whereas values of 25-50% were considered moderate to high heterogeneity. In meta-analyses that showed I^2>50% (high heterogeneity), several sensitivity analyses were performed to determine whether the study characteristics (including low methodological quality) and statistical methods could have influenced the results.

When it was not possible to perform meta-analyses of direct treatment comparisons, we used indirect comparisons to evaluate the relative efficacy between insulin analogues. Indirect treatment comparisons in meta-analyses can be analyzed by various methods according to the different networks applied, including star, ladder, closed-loop and partially closed-loop designs (Wells, 2009). We used the star design, as described by Bucher *et al*. (Bucher; Guyatt; Griffith Le; Walter, 1997), and adjusted the relative efficacy by the level of response to a common denominator (NPH or regular insulin).

Statistical analyses were conducted using the software Review Manager V.5.0 for Windows (Copenhagen - Denmark: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011) and the Indirect Treatment Comparison Software Application by the ADDIS (Aggregate Data Drug Information System) V.1.6 (Groningen – Netherlands: University of Groningen, 2012). A p value less than 0.05 was considered to be statistically significant.

RESULTS AND DISCUSSION

Systematic review of the literature

We initially identified 635 citations for glargine vs. NPH, 416 citations for detemir vs. NPH and 187 citations for glargine and detemir, of which 601, 397 and 183, respectively, were excluded on the basis of the title or abstract. Two independent reviewers evaluated the remaining articles (see Figure 1).

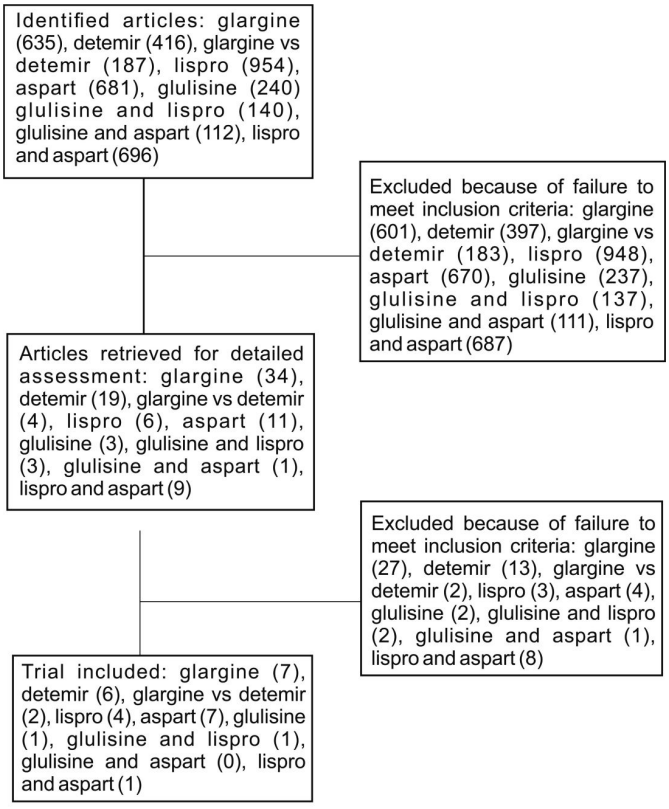

FIGURE 1 - Flowchart of the selection of randomized controlled trials included in our systematic review of long- and short-acting insulin analogues.

The remaining 16 articles for long-acting insulin analogues (glargine vs. NPH, 7; detemir vs. NPH, 7; glargine vs detemir, 2) were included in our meta-analysis

(Garg *et al.*, 1995; Anderson Jr. *et al.*, 1997; Ciofetta *et al.*, 1999; Home, 2000; Raskin, Guthrie*, et al.*, 2000; Raskin, Klaff *et al.*, 2000; Ratner *et al.*, 2000; Rosenstock *et al.*, 2000; Bode, Strange, 2001; Tamas *et al.*, 2001; Bode *et al.*, 2002; Devries *et al.*, 2003; Vague *et al.*, 2003; Hermansen *et al.*, 2004; Porcellati *et al.*, 2004; Russell-Jones *et al.*, 2004; Home *et al.*, 2004; De Leeuw *et al.*, 2005; Fulcher *et al.*, 2005; Home *et al.*, 2005; Pieber *et al.*, 2005; Home *et al.*, 2006; Pieber *et al.*, 2007; Bartley *et al.*, 2008; Heller *et al.*, 2009; Bolli *et al.*, 2009 b).

When we combined all of the studies, we counted 5,733 patients who received a short-acting insulin analog (aspart, lispro or glulisine). For lispro vs. regular, there were 954 patients; aspart vs. regular, 681; glulisine vs. regular, 240; glulisine vs. lispro, 140; glulisine vs. aspart, 112; lispro vs. aspart, 696. For all of the participants, the mean age was 39.2 years, and the mean body mass index (BMI) was 24.8. The number of patients in each study ranged from 57 to 747. The durations of the trials ranged from 7 to 64 weeks. The studies that examined the effects of long-acting insulin included 4,771 patients who received long-acting or NPH insulin. For the participants in these studies, the mean BMI was 24.9. The number of patients in each study ranged from 57 to 747. The trials included in the current meta-analysis had a mean duration of treatment of 26 weeks for glargine and 25 weeks for detemir. The durations of the trials ranged from 4 weeks to 12 months.

Efficacy of long- and short-acting insulin analogues

Forest plots showing the mean difference (MD) based on the change in HbA1c values at the end of the studies in adults with type 1 diabetes receiving glargine or detemir versus NPH or aspart, lispro or glulisine versus regular insulin are represented in Figure 2.

Compared with NPH insulin, the use of insulin glargine did not result in significant differences in HbA1c values (MD: -0.04% [95% CI: -0.12 to 0.05]; p = 0.39). There was a moderate degree of heterogeneity (43%). Primary data for detemir, compared with NPH insulin, were pooled into two subgroups based on the treatment regimen of once- or twice-daily treatment. For the once-a-day regimen, no statistically significant differences were found that favored one particular treatment (MD: -0.11% [95% CI: -0.32 to 0.11]; p = 0.34), but the results were inconsistent (I^2 = 71%) because of the low number of studies. For the twice-a-day regimen, the difference in HbA1c values favored detemir (MD: -0.14% [95% CI: -0.21 to -0.01]; p<0.0001; I^2 = 0%). The overall result of the meta-analysis favored detemir because of the low heterogeneity values. We found no significant differences in the mean change in HbA1c values when we directly compared glargine and detemir (2 studies). The MD, independent of the detemir treatment regimen, was -0.07% (95% CI: -0.19 to 0.06; p = 0.31; I^2 = 0%). It was not possible to perform a meta-analysis separately comparing once-daily or twice-daily glargine and detemir. A mixed treatment comparison of glargine and detemir (once- or twice-daily), adjusted for the level of response to NPH insulin, showed no significant difference in the mean change in the HbA1c value. The MD observed for both detemir regimens was -0.12% [95% CI: -0.03 to 0.20]. We found that aspart is more effective than regular insulin (MD: -0.13 [95% CI: -0.17 to -0.09]; p < 0.00001%), with little variability between studies, as demonstrated by a heterogeneity value of 0%. While inpatients treated with insulin lispro did not differ significantly (p = 0.36, MD: -0.08 [95% CI: -0.24 to 0.8]), the absence of heterogeneity

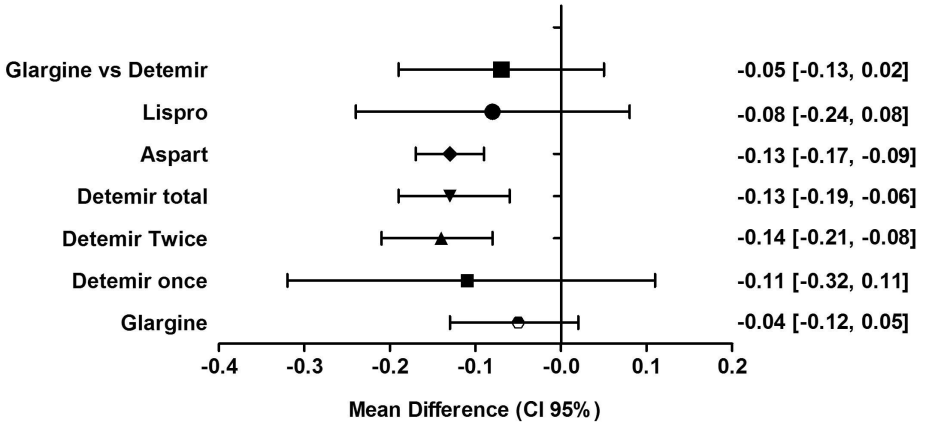

FIGURE 2 - Forest plots showing the MD based on the HbA1c changes at the end of the studies in adults with type 1 diabetes using the inverse variance method (random effect model).

(0%) was demonstrated by the sensitivity, robustness and regularity among the studies. The network of evidence surrounding comparisons of glargine, detemir and NPH insulin showed that there were no significant differences among treatments (glargine vs. NPH [-0.07 (-0.16; 0.03)], detemir vs. NPH [-0.07 (-0.16; 0.02)] and glargine vs. detemir [-0.00 (-0.11; 0.11)]). The rank of probability to choose long-acting insulin shows that NPH is first (87%), detemir is second (53%) and glargine is third (46%). The potential reduction scale factor was 1, and these results are consistent.

In our systematic review, we only found one article comparing insulin glulisine versus regular insulin and one clinical trial comparing insulin aspart, glulisine and lispro. Therefore, we could not perform a meta-analysis of these comparisons. The results for HbA1c reductions in these studies are presented in Table I.

We found small differences between treatments when we searched the various studies, and direct meta-analyses were performed to contribute to the analysis of this outcome.

HbA1C reductions were analyzed using the ADDIS software, which performs network meta-analyses and portrays results graphically, as shown in Figures 3 A and B.

Among human rapid-acting insulin options, regular insulin is most likely to be the first choice for the treatment of type 1 DM, followed by the insulin analog glulisine, then lispro and finally aspart. Our results, which show small differences in the ability of similar rapid-acting insulin analogues and regular human insulin to lower

TABLE I - HbA1C reductions, SD and p values for the following comparisons: glulisine vs. regular insulin, glulisine vs. lispro and aspart vs. lispro

Comparison	Author/year	Reduction HbA1C±SD	p value	
Glulisine vs. Regular	Garg, 2005	Glulisine	Regular	P=0.670
		*AM		
		-0.26±0.65	-0.13±0.66	
		**BM		
		-0.11±0.65	-0.13±0.66	
Glulisine vs. Lispro	Kawamori, 2009	Glulisine	Regular	NA
		0.10±0,71	0.03±0.58	
Aspart vs. Lispro	Bode, 2002	Aspart	Lispro	NA
		0.00±0.51	0.18±0.84	

* AF: after meal; ** BM: before meal; NA: not available

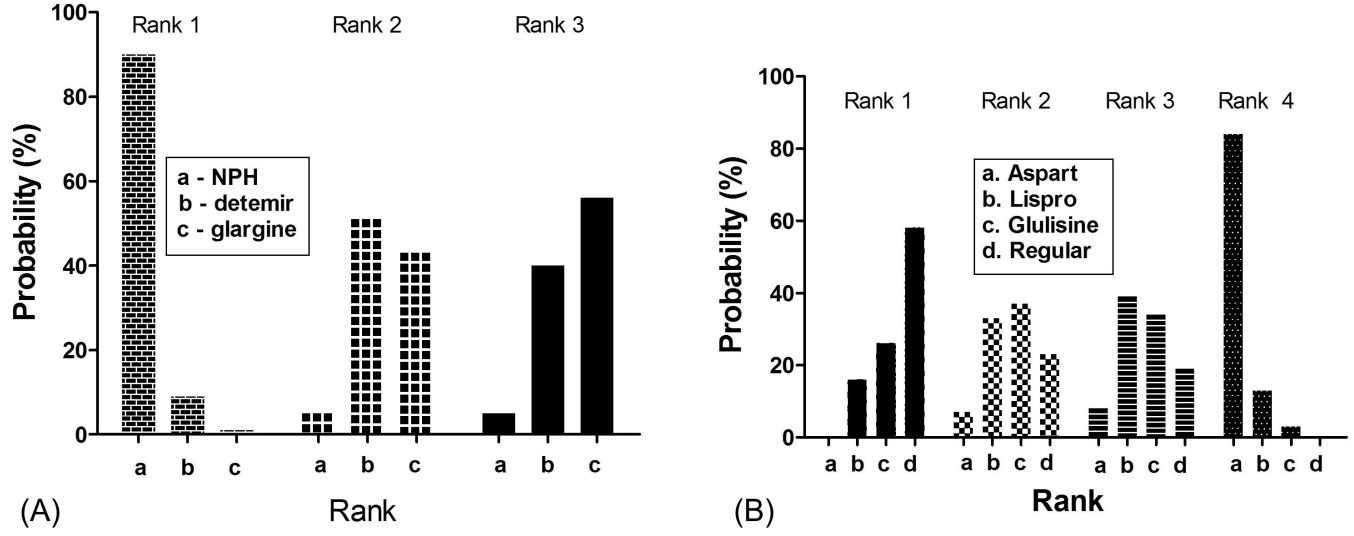

FIGURE 3 – The probability that long- (A) or rapid-acting (B) insulin analogues are the best choice for patients with type 1 diabetes mellitus. Rank 1 represents the insulin analog most likely to be the first choice for treatment of type 1 diabetes mellitus.

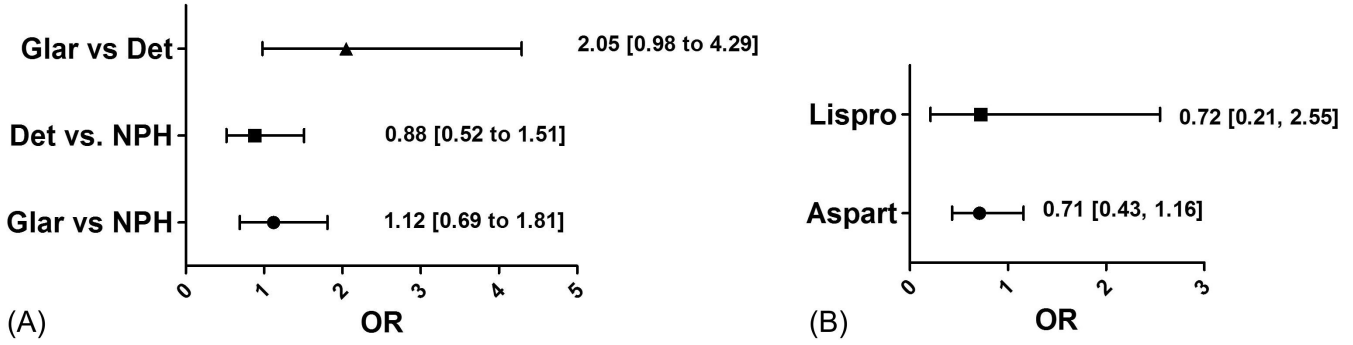

FIGURE 4 - Odds ratio for hypoglycemia (patients with any episode during the study) with insulin analogues, where A contains the meta-analysis of the safety of long-acting insulins and B contains the meta-analysis of the safety of short-acting insulin analogues. Legend: Glar, glargine; Det, Detemir; NPH, Human Insulin NPH.

HbA1C values, are in agreement with those that have been found by other authors (Jansson *et al.*, 1998; Siebenhofer *et al.*, 2004; Plank *et al.*, 2005; Forst, Pfützner, 2007).

The results of the long- and short-acting insulin analogues are consistent, and direct and indirect comparisons did not reveal significant differences among human insulin and insulin analogues with regard to their ability to reduce HbA1C values. Therefore, although there is a ranking system that can be used to choose the best option for insulin therapy, the differences in efficacy between them are small. These data are consistent with direct measurements that have already been published.

Safety of long-acting insulin analogues

The results detailing the safety of glargine, detemir and NPH insulin are shown in Figure 4 A. Figure 4 B shows the safety results of short-acting (lispro, aspart and regular) insulin types.

The hypoglycemia results were inconsistent for both insulin analogues (high I^2). For glargine and NPH, the mean percentages of participants reporting any hypoglycemia episode (74.4 vs. 74.1%) were not different. The hypothetical exclusion of any trial did not change the outcomes. For detemir and NPH, we found similar results; the mean percentages of participants reporting any hypoglycemia episode were 79.2 and 81.5%, respectively. The exclusion of one study (39) reduced the heterogeneity to 52% without significant changes to the results. This difference likely results from the high doses of detemir (0.83 UI/kg/day) and NPH insulin (0.44 UI/kg/day) in the study by Vague *et al.* in relation to the doses used in the other studies (0.31 to 0.44 UI/kg/day for detemir and 0.32 to 0.36 UI/kg/day for NPH). Safety, as measured by the number of patients with at least one hypoglycemic episode per month, was analyzed for short-acting insulin analogues. We observed no significant differences between insulin aspart and regular insulin, and the heterogeneity was 0%. The same result was found when we compared insulin lispro with regular insulin; however, the clinical trial by Ciofetta *et al.* (Ciofetta *et al.*, 1999) included only a small number of patients (n = 8) in both groups, thereby causing greater variability in the results. This variability resulted in moderate heterogeneity (38%). Insulin glulisine compared with regular insulin was also not significantly different; however, for insulin glulisine, the meta-analysis was not performed because only one clinical trial was found with the correct inclusion criteria. A similar situation occurred when we compared insulin lispro with glulisine (3.93 vs. 3.86; p = 0.1642). In the only instance where both insulin aspart and lispro were compared, the authors (Bode *et al.*, 2002) confirmed that hypoglycemic episodes per month were not significantly different between the treatments; however, there was less of these episodes for the group treated with insulin aspart (3.9 ± 4.2) compared with insulin lispro (4.4 ± 5.6) or regular insulin (4.9 ± 4.6).

CONCLUSIONS

Long- and short-acting insulins are used to compensate for a lack of insulin secretion in patients with type 1 diabetes. These patients use multiple daily injections or continuous subcutaneous insulin infusions to mimic the mealtime rapid-acting or basal insulin normally secreted by the pancreas (Bolli *et al.*, 2009 a).

There were no significant differences in the changes in HbA1c values for glargine and detemir (once-daily) compared with NPH insulin and glargine versus detemir. Moreover, for the twice-daily detemir regimen, the differences in HbA1c values favor detemir over NPH insulin. With regard to indirect comparisons of detemir and glargine, the two primary studies combined the efficacy

data of once- or twice-daily detemir regimens and thus did not allow a separate meta-analysis of both regimens. In these cases, mixed treatment comparisons indicated no significant differences in the efficacy of once- or twice-daily detemir compared with once-daily glargine. Aspart is more effective when compared with regular insulin, but lispro and glulisine, which are also short-acting insulin analogues, are not more effective than human short-acting insulin.

Safety data based on clinical trials comparing glargine and detemir were similar with regard to patients with any hypoglycemia episode (56.1% vs. 37.8%; p = 0.06, respectively), without significant differences calculated by the risk ratio. There were no statistically significant differences among short-acting insulin treatments. In summary, these results indicate that there are only small differences in glycemic control and safety among human and insulin analogues (long- and short-acting).

CONFLICTS OF INTEREST

All authors declare that they do not have any conflicts of interest.

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