



The Cost-effectiveness of Analogue Insulin Pens in Comparison with Human Insulin Pens for Controlling Type 1, Type 2, and Gestational Diabetes: A Systematic Review Article

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Abstract

Context: For many years, the classical (traditional) insulin injection methods have been used. The first insulin pen was made in the 1980s. These types of pens are divided into two categories, namely analogue and vial-human. Analogue insulin pens are similar to human insulin pens in molecular structure and can lead to differences in pharmacokinetic and pharmacodynamic properties.

Methods: This was a systematic review conducted by searching Web of Science PubMed, SID, Embase, Scopus, and Magiran databases for articles published from the beginning of 2007 to June 2017. The related studies in the field of health technology and economic assessment were investigated.

Results: Twenty studies were included; these studies indicated that there is no reason for the higher risk of rapid-acting insulin analogue pens in comparison with vial (human) and that analogue insulin pens significantly reduce the risk of hypoglycemia. Analogue insulin was compared to other existing insulins and was not found cost effectiveness (ICER: 642994\$QALY), (ICER: 130865 \$ QALY), (ICER: 87932\$ QALY), but due to the increased quality of life and patient satisfaction compared to vial insulin pens, this type of pen has been used. Some studies have shown that aspart 30 insulin pens are more cost-effective than other analogues (ICER: 22488\$QALY).

Conclusions: Although the use of analogue insulin is more expensive for diabetic patients, it is more effective than vial insulin. Thus, insurance companies are recommended to develop special plans for the three vulnerable groups of seniors, children, and pregnant women to provide them with analogue insulin.

Keywords: Analogue Insulin, Vial Insulin (Regular), Type 1 Diabetes, Type 2 Diabetes, Pregnancy Diabetes, Cost-Effectiveness

1. Context

Personal and public health is undoubtedly the most crucial aspect of life, and humans have been trying to maintain it since the prehistoric era (1). Diabetes is a complex metabolic disease that in addition to inheritance, environmental conditions, lifestyle, weight, tension, food pattern, and awareness of people play a decisive role in its development. Diabetes is a chronic disease caused by metabolic disorders and is the 50 cause of mortality in the Western world. Ten percent of the whole emergency care has been dedicated to this disease (2).

Type 1 diabetes is a chronic inflammatory disease that

leads to the destruction of beta cells. During the last few decades, the incidence rate of type 1 diabetes, an autoimmune disorder, has increased notably in children and in the developing countries. Type 2 diabetes is a type of metabolic disorder. In 1995, about 135 million people were suffering from this disease, and this number is expected to rise to 300 million by the year 2025. It seems that glycosylation and oxidative stress are effective in the process of developing diabetic complications and many other illnesses (3).

Gestational diabetes can be defined as carbohydrate intolerance with various intensities that happens during pregnancy for the first time (4). Despite the developments

in pregnancy outcomes in recent years, women with gestational diabetes are at higher risk for pregnancy complications (5). Complications of gestational diabetes include retinopathy, neuropathy, nephropathy, and cardiovascular complications that can lead to myocardial infarction and cerebrovascular accident. Along with these complications, diabetes promotes the risk of urinary tract infections (6). Diabetes reduces the quality of life in almost all aspects of life (7). Over the past few decades, the disease burden has increased the need for new ways to improve and manage this disease. Several factors, including genetics, lifestyle, environmental, and nutritional status, play an important role in diabetes (8).

For many years, traditional ways have been used for insulin injection (9). Almost 60% of diabetic patients use insulin pens, although there are different statistics in different countries, for instance, in Japan, China, and Australia, 95% of people with diabetes use insulin pens. However, approximately 20% of diabetic patients in America use injectable insulin (10). In the 1930s, the first long-acting insulin, protamine zinc insulin, was developed to decrease the number of injections needed. In the early 1980s, pure pig insulin and then recombinant human insulin resulted in the elimination of insulin sensitivity and immune-mediated lipoatrophy. In recent decades, analogue insulin has been developed with the aim of overcoming some disadvantages of vial insulin. All types of analogue insulins are produced via recombinant technology. These types of insulin include glargine, aspart, detrim, and lispro (11). Given the fact that there are various ways to treat diabetes, this systematic review was conducted on the cost-effectiveness of analogue insulin pens versus vial pens in order to put it at the disposal of politicians who can decide on the relevant laws.

2. Objectives

This review was intended to compare the cost-effectiveness of analogue insulin and vial insulin for patients with diabetes.

3. Methods

The most reliable and important databases including PubMed, Scopus, Embase, Web of Science, Magiran were searched for the related articles published from the beginning of June 2007 to June 2017. In addition to retrieving the electronic articles and scrutinizing their references, a manual search was conducted, and if necessary, we contacted the experts in the field. To search appropriately, the following keywords were used: “analogue insulin”, “vial insulin”,

“diabetes type 1”, “diabetes type 2”, “gestational diabetes”, and “cost-effective” (MeSH, Free text).

3.1. Inclusion and Exclusion Criteria

All the health technology assessment studies and economic assessment studies that compared analogue and vial insulin pens (i.e., NovoMix, detemir, degludec, glargine, biphasic, basal, reguar, NPH, Lantus, aspart, lispro, and detrim) were included in the study. Studies that focused only on the outcome or cost-effectiveness of the two types of insulin pens and studies that only worked on new insulin pens or just traditional insulin pens were excluded from the study. Moreover, due to limited resources and time, only English and Persian-language articles were used.

3.2. Study Selection

PRISMA principles were followed, that is, at the beginning, titles and abstracts of all the retrieved articles were screened. Then, the full texts of the articles were studied. In all the stages of study selection, two researchers were used, and if there was a disagreement over an issue, it was resolved through discussion, and in cases where a consensus could be reached, a third researcher was included.

3.3. Data Extraction

A researcher-made data extraction form was completed separately to extract data from each included study. The extracted information included author(s) name, year of publication, therapeutic interventions, investigated outcomes, the ratio of cost-effectiveness, and costs.

3.4. Quality Assessment

Quality assessment of the studies was performed based on consensus on health economics criteria checklist (CHEC), which contains 20 questions that scrutinize population descriptors, economic studies, validation of the methods and models, cost equity with the physical unit, the studies' results, cost-effectiveness, follow-up, and ethics. The score of each study ranges from 1 to 12 according to the questions. Based on the criteria set, a score was assigned to each study, which signified the quality of the study (12).

3.5. Data Analysis

Regarding the heterogeneity in the results of the studies and the methods of economic evaluation, there was no possibility of meta-analysis. Therefore, the qualitative method was used to analyze the data.

4. Results

4.1. Study Selection

A systematic review was performed in the mentioned databases based on the inclusion and exclusion criteria, which yielded 1,726 studies. After excluding duplicates, 1516 articles were categorized based on their titles, and then 210 papers were excluded. At this stage, 155 studies were entered into the abstract-screening phase to determine the final studies, the full text of these articles was searched by the first researcher for the inclusion and exclusion criteria. In case of ambiguity, the second researcher intervened. Eventually, 20 papers were entered into the final phase of the study. The process of study selection was conducted based on the PRISMA protocol (Figure 1).

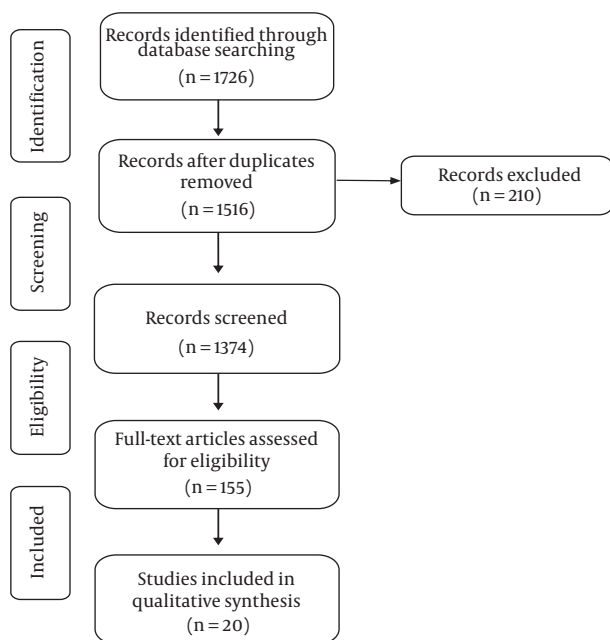


Figure 1. The flowchart of study selection based on the PRISMA standard

4.2. Data Extraction

Six studies out of the 20 included studies were performed within the past four years. Ten studies were on diabetes type 2, 6 on diabetes type 1, and 3 studies on diabetes types 1 and 2 and gestational diabetes. In all the studies, quality adjusted life years (QALY) outcomes, and in six studies (30%), side effects were reported. The features of the included studies are reported in Table 1.

4.3. Quality Control

CHEC was utilized to assess the quality of the included studies. Based on this checklist, four, eight, seven, and one of the studies obtained the scores of 9, 10, 11, and 12, respectively (Table 2).

4.4. Data Analysis

Cameron and Bennett (13) claimed the cost-effectiveness of analogue insulin (i.e., aspart, lispro, detemir insulin) compared to vial insulin pens (i.e., regular and NPH). In this regard, other studies performed over the past four years in different countries indicated that detemir insulin pen compared to NPH insulin pen was more effective and increased the quality of life (in type 1 diabetes with incremental cost-effectiveness ratio (ICER) = 7682\$ QALY and in type 2 diabetes with ICER = 15,009\$ QALY) (13-15, 26, 28-31). The results of various studies on the comparison of insulin pens in type 1 diabetes (insulin-dependent), type 2 (non-insulin-dependent diabetes), and gestational diabetes have shown that glargine insulin pen compared to NPH insulin with ICER = 57,002\$ QALY had a more dramatic effect on patients' quality of life and reducing costs (17-19, 21, 22, 24, 27).

Other studies concluded that a biphasic pen compared to an NPH pen with ICER = 17859\$ QALY improved the quality of life and disease burden (20, 23). In the study of Belanger and Cameron in Canada, it was indicated that the aspart pen was more effective than the regular insulin pen (25). In addition, the comparison of the aspart pen with regular human insulin with ICER = 22,488\$ QALY also confirmed the greater cost-effectiveness and quality of aspart (32). Another study carried out in 2015 also confirmed the cost-effectiveness of rapid-acting analogue insulin (-RAAI) relative to regular insulin pens (16). Overall, studies have shown that the cost of vial insulin pens is higher than analogue insulin pens, but the efficacy of analogue insulin pens is higher than vial insulin pens. However, the ratio of the estimated cost-effectiveness suggests that the analogue insulin pen is more cost-effective than the vial insulin pen.

5. Discussion

The current research contributes to the evaluation of health technology aimed at investigating the efficiency of the use of analogue injection insulin pens and vial insulin pens in patients with type 1, 2 and gestational diabetes. To compare the above-mentioned studies, a systematic review was carried out using the cost-effectiveness criterion as the measurement benchmark. Due to the variety of analogue insulin pens and the competitiveness among

Table 1. The Entered Studies' Features Considering the Determined Inclusion and Exclusion Criteria

Reference	Insulin Type	Consequences	Cost-effectiveness (ICER)
Cameron and Bennett (13)	Insulin aspart, Insulin lispro, Insulin glargine, Insulin detemir vs. NPH	QALY	T1DM
			Insulin lispro: 28996\$ QALY
			Insulin glargine: 87932\$ QALY
			Insulin detemir: 387729\$ QALY
			T2DM
			Insulin aspart: 22488\$ QALY
			Insulin lispro: 130865\$ QALY
Insulin glargine: 642994\$ QALY			
Morales et al. (14)	Insulin detemir vs. NPH insulin	QALY adverse effect	T1DM: 7682\$ QALY T2DM: 15,009\$ QALY
Ramirez et al. (15)	Insulin detemir vs. NPH insulin	QALY	T1DM: 244.03\$ QALY T2DM: 16,381.18\$ QALY
Saunders et al. (16)	(RAAI) vs. (RHI)	QALY	RAAI: 3,473\$ QALY RHI: 5,103\$ QALY
Hagenmeyer et al. (17)	Insulin glargine vs. NPH insulin	QALY	57,002\$ QALY
McEwan et al. (18)	Insulin glargine vs. NPH insulin	QALY	2695\$ QALY
Greiner et al. (19)	Insulin glargine vs. NPH insulin	QALY	51,100\$ QALY
Farshchi et al. (20)	Biphasic insulin vs. NPH insulin AND regular human insulin	QALY adverse effect	930.55 ± 81.43\$ QALY Insulin NPH 1101.24 ± 165.49\$ QALY Regular human insulin
Brandle et al. (21)	Insulin glargine vs. NPH insulin	QALY adverse effect	5,711\$ QALY
Pfohl et al. (22)	Insulin glargine vs. NPH insulin	QALY	9576\$ QALY
Aagren et al. (23)	Biphasic insulin vs. NPH Insulin	QALY adverse effect	17,859\$ QALY
Alvares et al. (24)	Glargine insulin vs. NPH insulin	QALY	1,006.03\$ QALY
Belanger and Cameron (25)	(RAIA) vs. (RHI)	QALY	Type I: 28,996\$ QALY
			Type II: 22,488\$ QALY
Ramirez et al. (26)	Insulin detemir vs. NPH insulin	QALY	2,286.67\$ QALY
Brandle et al. (27)	Insulin glargine vs. NPH insulin	QALY	51,100\$ QALY
Ridderstrale et al. (28)	Insulin detemir vs. NPH insulin	QALY adverse effect	Denmark: 170,852\$ QALY
			Norway: 169,789\$ QALY
			Sweden: 226,622\$ QALY
Smith-Palmer et al. (29)	Insulin detemir vs. NPH insulin	QALY adverse effect	384,216\$ QALY
Valentine et al. (30)	Insulin detemir vs. NPH	QALY	49,757\$ QALY
Valentine et al. (31)	Insulin detemir vs. NPH insulin	QALY	Denmark: 12,612\$ QALY
			Sweden: 12,612 \$ QALY
			Finland: 16,568\$ QALY
			The Netherlands: 12,216 \$QALY
Lloyd et al. (32)	Insulin aspart vs. NPH insulin	QALY adverse effect	5,000 \$ QALY

Abbreviations: ICER, incremental cost-effectiveness ratio; NPH, neutral protamine hagedorn insulin; QALY, quality adjusted life years; RAAI, rapid-acting analogue insulin; RAIA, rapid-acting insulin analogue; RHI, regular human insulin.

these pens, numerous studies have been performed in this regard. Cazarim et al.'s (33) study entitled as "cost-effectiveness in the Brazilian health system" compared different types of analogue insulin pens and NPH insulin pens. The results indicated that regular insulin pens can be a better alternative to NPH insulin pens.

Overall, based on the cost and sensitivity analyses, the aspart and detemir pens can be the best choices. Also, based on QALY indicator, aspart insulin pen is the most

cost-effective analogue insulin pen to control HbA1c (33).

The limitations caused by diabetes have attracted much of researchers' attention. In this regard, Morales et al. (14) conducted a study to compare the cost-effectiveness of NPH pen with that of detemir insulin pen and concluded that the quality of life of type 1 diabetes patients using NPH pen is less than the quality of life of those using a detemir pen, which is also the case for type 2 and gestational diabetes patients. With regards to the cost-effectiveness

Table 2. Quality Analysis of the Included Studies

Q	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
1	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
3	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
4	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
5	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
6	N	Y	N	N	N	N	Y	Y	N	Y	Y	N	N	N	N	N	Y	N	N	N
7	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
8	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
9	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
10	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
11	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
12	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
13	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
14	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
15	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N
16	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
17	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
18	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
19	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
20	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Total	17	18	17	17	17	17	18	19	17	18	18	17	17	17	17	17	18	17	17	17

Abbreviations: N, no; Q, question; Y, yes.

of detemir pens in type 1 diabetes, the increasing cost-effectiveness ratio of this intervention was more than NPH insulin pen (ICER = 7682\$ QALY in comparison with ICER = 1910\$ QALY), and for type 2 diabetes, detemir insulin pen had a higher cost-effectiveness ratio than NPH insulin (ICER = 2522\$ QALY compared to CER = 15,009\$ QALY). In the same vein, it can be stated that detemir insulin is more cost-effective (14). However, in a systematic review, Rys et al. (34) by reviewing clinical trials on the effectiveness insulin pen demonstrated that using glargine insulin pen versus NPH insulin pen decreases HbA1c with no significant reduction in blood glucose.

The extent of the side effects of analogue insulin pen and vial insulin pen was also taken into consideration in a study by Farshchi et al. in 2014 in order to study the cost-effectiveness of the biphasic insulin pen and NPH pen in type 2 diabetic patients. This study revealed that among the biphasic, NPH, and regular human insulin pens, none affects HbA1c. However, biphasic insulin, based on the quality of life expectancy index and the ICER (ICER = 930.55 ± 81.43\$ QALY for NPH insulin, and ICER = 1101.24 ± 165.49\$

QALY for regular human insulin) had a more significant effect on type 2 diabetes compared to NPH insulin pens. Besides, biphasic insulin pens were more cost-effective (20). With the increasing importance of analogue insulin pens and the expanding need for this type of treatment, the cost-effectiveness and efficacy of these interventions have been studied. In this regard, a series of studies, including a systematic review by Hagenmeyer et al. (17), was carried out for economic evaluation of glargine insulin pens versus NPH insulin pens. The results indicated that glargine is 4 to 6 times more cost-effective than NPH insulin pen. Moreover, its cost-effectiveness had increased from ICER = 3.859\$ QALY to ICER = 57.002\$ QALY. He concluded glargine insulin pen as a brand-new analogue insulin can be more efficient and cost-effective. The results of Monami et al. (35) study on the long-term effects of detemir pen in comparison with NPH pen indicated that detemir pen causes less weight gain and that this kind of insulin pen poses less risk of reducing blood glucose levels. In a systematic review by Horvath et al. (36), the long-term performance of analogue insulin pen compared to NPH insulin was examined. He

concluded that analogue insulin pen was not superior to vial insulin pen in this regard. However, in a clinical trial on 2,293 patients, it was recognized that analogue insulin causes less increased heartbeat. The current study's results confirmed the findings obtained by other studies in that analogue insulin pens outperform vial insulin pens with regards to quality of life and cost-effectiveness ratio in type 1, type 2, and gestational diabetes.

The present study has some limitations. One of the limitations of this study is that the results were limited to English and Persian-language studies. Another limitation of the study is that the obtained results are not based on actual intervention(s) and collection of new empirical data. Moreover, the results of this study are based on modelling and assumed costs and effectiveness, as a result, researcher bias may have influenced these findings. All the results of the study were based on modelling, where the inputs were drawn from published datasets, existing literature, or experts' advice. Therefore, the study is based profoundly on modelling and there is a need for evaluating the effectiveness of new interventions in the field by using more robust study designs and parallel economic evaluations.

5.1. Conclusions

According to the conducted systematic review study, the results indicated that among the variety of insulin analogues (rapid-acting and long-acting) used in the treatment of type 2 diabetes, aspart 30 can be more cost-effective compared to Glargine insulin pen and human biphasic insulin pen.

For type 1 diabetes, aspart 30 insulin pen is more effective and less costly than NPH insulin.

In women with gestational diabetes, aspart insulin pen is more cost-effective than NPH insulin pen. Therefore, considering the sensitivity of care for the elderly, children and pregnant women, this technology should be provided for these three groups by governmental resources.

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