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ORIGINAL RESEARCH

Artificial Pancreas as an Effective and Safe Alternative in Patients with Type 1 Diabetes Mellitus: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Insulin injection is the main treatment in patients with type 1 diabetes mellitus (T1DM). Even though continuous glucose monitoring has significantly improved the conditions of these patients, limitations still exist. To further enhance glucose control in patients with T1DM, an artificial pancreas has been developed. We aimed to systematically compare artificial pancreas with its control group during a 24-h basis in patients with T1DM.

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Methods: Electronic databases were carefully searched for English publications comparing artificial pancreas with its control group. Overall daytime and nighttime glucose parameters were considered as the endpoints. Data were evaluated by means of weighted mean differences (WMDs) and 95% confidence intervals (CIs) generated by RevMan 5.3 software.
Results: A total number of 354 patients were included. Artificial pancreas significantly maintained a better mean concentration of glucose (WMD -1.03, 95% CI -1.32 to -0.75; $P = 0.00001$). Time spent in the hypoglycemic phase was also significantly lower (WMD -1.23, 95% CI -1.56 to -0.91; $P = 0.00001$). Daily insulin requirement also significantly favored artificial pancreas (WMD -3.43, 95% CI -4.27 to -2.59; $P = 0.00001$). Time spent outside the euglycemic phase and hyperglycemia phase (glucose > 10.0 mmol/L) also significantly favored artificial pancreas. Also, the numbers of hypoglycemic events were not significantly different.
Conclusion: Artificial pancreas might be considered an effective and safe alternative to be used during a 24-h basis in patients with T1DM.

Keywords: Artificial pancreas; Glucose control; Type 1 diabetes mellitus

Abbreviations
T1DM Type 1 diabetes mellitus
WMD   Weight mean difference
CIs   Confidence intervals

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is still a major concern in this new era. This chronic disorder occurs when beta cells of the pancreas are destroyed by autoimmune antibodies at a younger age (childhood) or it can even develop in adults, during their late 30s or 40s [1]. Insulin injection has been the main treatment in these patients with T1DM [2]. However, despite concerted efforts of patients and physicians/caregivers, control of blood glucose has often been difficult to achieve [3].

With the development of new techniques and devices in clinical medicine, continuous glucose monitoring has significantly improved conditions of patients with T1DM [4]. To further enhance glucose control in these patients, an artificial pancreas has recently been developed [5].

Even though this artificial pancreas has already been approved for use by the US Food and Drug Administration (FDA) [5], the existence and benefits of this "expected to be" effective device are not well known to the general population.

In this analysis, we aimed to systematically compare artificial pancreas with its control group in terms of effectiveness and safety, during a 24-h treatment of patients with T1DM.

METHODS

Searched Databases

The Medline database of medical publications, the Cochrane library of randomized controlled trials, and EMBASE database were carefully searched by the five authors for English publications comparing artificial pancreas with its control group (any control group). Reference lists of selective publications (most relevant ones) were also carefully reviewed for appropriate articles. In addition, official websites of specific journals such as *Lancet Diabetes and Endocrinology*, *Diabetes Care*, and *Cardiovascular Diabetology* were also searched for any relevant publication.

Search Strategies

During this process, we searched for the terms "artificial pancreas", "bionic pancreas", "closed loop glucose control", "type 1 diabetes mellitus", "diabetes mellitus", "glucose control", and "glucose monitoring", one at a time and in combination. Publications comparing artificial pancreas with its control group were considered relevant to this analysis.

Inclusion Criteria

Studies were included if they compared artificial pancreas with its control group (any relevant control group); they reported glucose control parameters or other outcomes related to glucose monitoring (during daytime and overnight/24-h basis); they involved patients with T1DM.

Exclusion Criteria

Studies were excluded if they did not compare artificial pancreas with its control group; they did not report glucose monitoring parameters as their endpoints or they reported only daytime or overnight measurement, but not both in combination; they involved patients with type 2 diabetes mellitus instead of patients with T1DM; they were duplicates.

Type of Participants, Endpoints, and Follow-Up Periods

This analysis included patients with T1DM.

The endpoints (during daytime and nighttime) which were analyzed included:
(a) Mean and median glucose concentration.
(b) Time spent outside the euglycemic phase (outside the glucose range 3.90 to 8.0 mmol/L).
(c) Time spent in the hypoglycemia phase (blood glucose < 3.9 mmol/L).
(d) Insulin required/delivered per day.
(e) Time spent in the hyperglycemia phase (blood glucose > 10.0 mmol/L).
(f) Number of hypoglycemic events.

The follow-up period ranged from less than 1 week to 2 months.

Data Extraction, Review, and Statistical Analysis

After the search process, which was conducted in accordance with the PRISMA guideline [6], the same reviewers assessed the titles and abstracts and independently selected the most suitable articles which satisfied the inclusion and exclusion criteria of this analysis and then data were extracted. The studies which were included in this analysis were judged as having low to moderate risk of bias [7].

This is a meta-analysis and therefore inconsistency across the studies was evident [8]. Hence, heterogeneity was assessed by two statistical methods:

(a) The Q statistic test, whereby a P value less or equal to 0.05 was considered statistically significant.

(b) The I^2 statistic test; a high percentage value indicated high heterogeneity (whereby a random effects model was used) and low percentage value denoted low heterogeneity (whereby a fixed effects model was used).

Since continuous data was used in this analysis, i.e., mean and standard deviation (SD), data were evaluated by means of weighted mean differences (WMDs) and 95% confidence intervals (CIs). In case the SD value was not provided, but a p value was given, SD was calculated using the formula SD = $\sqrt{n \times p \times (1 - p)}$. The analysis was carried out by RevMan 5.3 software.

Publication bias was assessed by visually observing funnel plots.

Compliance with Ethics Guidelines

This meta-analysis is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

RESULTS

Search Outcomes, Main and Baseline Features of the Studies

Eight studies [9–16] were selected to be used in this analysis as shown in Fig. 1.

Table 1 summarizes the main features of the studies included in this analysis. As per the criteria of this analysis which required an experimental and a control group, a total of 354 patients were included (177 patients in each group) as shown in Table 1.

The baseline features are reported in Table 2.

Analysis Results

Results of this current analysis showed artificial pancreas to significantly maintain a better mean concentration of glucose with WMD − 1.03, 95% CI − 1.32 to − 0.75; P = 0.00001, I^2 = 46% compared to the control group during a 24-h basis. The median glucose concentration was similar in both groups with WMD − 0.30, 95% CI − 1.03 to 0.44; P = 0.43, I^2 = 0% as shown in Fig. 2.

In addition, the time spent in the hypoglycemic phase (glucose < 3.9 mmol/L) also significantly favored artificial pancreas with
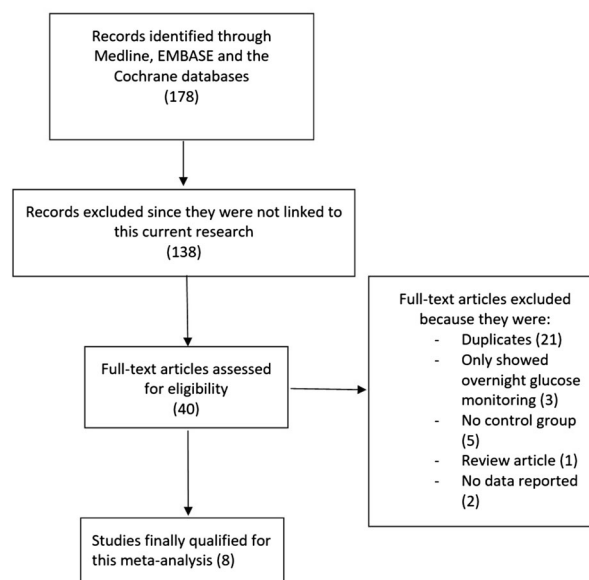
Fig. 1 Flow diagram representing the study selection

Table 1 Main features of the studies included

Studies	Type of study	Patients with AP (*n*)	Patients in control group (*n*)	Total patients (*n*)
Blauw [9]	Randomized crossover	5	5	10
Kropff [10]	Randomized crossover trial	32	32	64
Renard [11]	Single-arm non-randomized extension	20	20	40
Thabit [12]	Randomized crossover	24	24	48
Kovatchev [13]	Randomized crossover	18	18	36
El-Khatib [14]	Randomized crossover trial	39	39	78
Russell [15]	Randomized crossover	20	20	40
Russell [16]	Randomized crossover trial	19	19	38
Total patients (*n*)		177	177	354

AP artificial pancreas

Table 2 Baseline features of the patients in the studies included

Studies	Mean age (years) AP/C	Male (%) AP/C	HBA1c (%) AP/C	BMI (kg/m^2) AP/C	DM duration (years) AP/C
Blauw [9]	–	–	–	–	–
Kropff [10]	47.0/47.0	56.0/56.0	8.2/8.2	25.1/25.1	28.6/28.6
Renard [11]	46.3/46.3	45.0/45.0	8.2/8.2	24.9/24.9	28.9/28.9
Thabit [12]	43.0/43.0	54.2/54.2	8.1/8.1	26.0/26.0	29.0/29.0
Kovatchev [13]	–	–	–	–	–
El-Khatib [14]	33.3/33.3	46.0/46.0	7.7/7.7	25.9/25.9	16.9/16.9
Russell [15]	40.0/40.0	40.0/40.0	7.1/7.1	25.0/25.0	24.0/24.0
Russell [16]	9.80/9.80	32.0/32.0	7.8/7.8	17.8/17.8	5.00/5.00

AP artificial pancreas, *C* control group, *HBA1c* glycosylated hemoglobin, *BMI* body mass index, *DM* diabetes mellitus

WMD − 1.23, 95% CI − 1.56 to − 0.91; $P = 0.00001$, $I^2 = 19\%$ meaning the patients experienced less time in the hypoglycemia phase with this artificial pancreas as compared to the control group (Fig. 2).

Daily insulin required (24-h basis) also significantly favored artificial pancreas with WMD − 3.43, 95% CI − 4.27 to − 2.59; $P = 0.00001$, $I^2 = 0\%$ compared to the control group, indicating that good glucose control was continuously maintained without requiring an excess of insulin (Fig. 2).

Also, the numbers of hypoglycemic events were not significantly different with WMD − 0.83, 95% CI − 1.76 to 0.10; $P = 0.08$, $I^2 = 0\%$ (Fig. 2).

Study or Subgroup	Artificial pancreas			Control			Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total			
1.1.1 Mean glucose concentration									
Blauw2016	7.4	0.53	5	8.1	0.53	5	8.9%	-0.70 [-1.36, -0.04]	
El-Khatib2016	7.8	0.6	39	9	1.6	39	13.3%	-1.20 [-1.74, -0.66]	
Russell2014	7.38	0.72	20	8.82	1.69	20	5.9%	-1.44 [-2.25, -0.63]	
Russell2016	7.6	0.6	19	9.3	1.7	19	5.8%	-1.70 [-2.51, -0.89]	
Thabit2014	8.7	0.8	24	9.3	1.1	24	12.9%	-0.60 [-1.14, -0.06]	
Subtotal (95% CI)			**107**			**107**	**46.8%**	**-1.03 [-1.32, -0.75]**	
Heterogeneity: Chi² = 7.37, df = 4 (P = 0.12); I² = 46%									
Test for overall effect: Z = 7.08 (P < 0.00001)									
1.1.2 Median glucose concentration									
Blauw2016	7.3	0.73	5	7.7	0.73	5	4.7%	-0.40 [-1.30, 0.50]	
Renard2016	8.9	2.03	20	9	2.03	20	2.4%	-0.10 [-1.36, 1.16]	
Subtotal (95% CI)			**25**			**25**	**7.1%**	**-0.30 [-1.03, 0.44]**	
Heterogeneity: Chi² = 0.14, df = 1 (P = 0.70); I² = 0%									
Test for overall effect: Z = 0.79 (P = 0.43)									
1.1.3 Time spent in Hypoglycemia (< 3.9mmol/L)									
Blauw2016	1.3	0.77	5	2.4	0.77	5	4.2%	-1.10 [-2.05, -0.15]	
El-Khatib2016	0.6	0.6	39	1.9	1.7	39	12.0%	-1.30 [-1.87, -0.73]	
Kropff2015	2.6	1.4	32	3.6	2	32	5.4%	-1.00 [-1.85, -0.15]	
Renard2016	1.9	1.1	20	3.2	1.8	20	4.5%	-1.30 [-2.22, -0.38]	
Russell2014	4.1	3.5	20	7.3	4.7	20	0.6%	-3.20 [-5.77, -0.63]	
Russell2016	1.2	1.1	19	2.8	1.2	19	7.1%	-1.60 [-2.33, -0.87]	
Thabit2014	1.7	2.2	24	1.7	2.2	24	2.5%	0.00 [-1.24, 1.24]	
Subtotal (95% CI)			**159**			**159**	**36.2%**	**-1.23 [-1.56, -0.91]**	
Heterogeneity: Chi² = 7.43, df = 6 (P = 0.28); I² = 19%									
Test for overall effect: Z = 7.43 (P < 0.00001)									
1.1.4 Number of hypoglycemic events									
Kropff2015	5.7	2.1	32	6.3	2.4	32	3.1%	-0.60 [-1.70, 0.50]	
Renard2016	5	2.4	20	6.4	3.1	20	1.3%	-1.40 [-3.12, 0.32]	
Subtotal (95% CI)			**52**			**52**	**4.4%**	**-0.83 [-1.76, 0.10]**	
Heterogeneity: Chi² = 0.59, df = 1 (P = 0.44); I² = 0%									
Test for overall effect: Z = 1.76 (P = 0.08)									
1.1.5 Insulin needed/delivered/used per day									
Kovatchev2014	59.2	1.3	18	62.6	1.3	18	5.3%	-3.40 [-4.25, -2.55]	
Kropff2015	36.7	11.7	32	43.2	16.3	32	0.1%	-6.50 [-13.45, 0.45]	
Renard2016	40.3	15.2	20	42.3	15.5	20	0.0%	-2.00 [-11.51, 7.51]	
Subtotal (95% CI)			**70**			**70**	**5.4%**	**-3.43 [-4.27, -2.59]**	
Heterogeneity: Chi² = 0.84, df = 2 (P = 0.66); I² = 0%									
Test for overall effect: Z = 8.02 (P < 0.00001)									
Total (95% CI)			**413**			**413**	**100.0%**	**-1.17 [-1.37, -0.98]**	
Heterogeneity: Chi² = 51.26, df = 18 (P < 0.0001); I² = 65%									
Test for overall effect: Z = 11.76 (P < 0.00001)									
Test for subgroup differences: Chi² = 34.88, df = 4 (P < 0.00001), I² = 88.5%									

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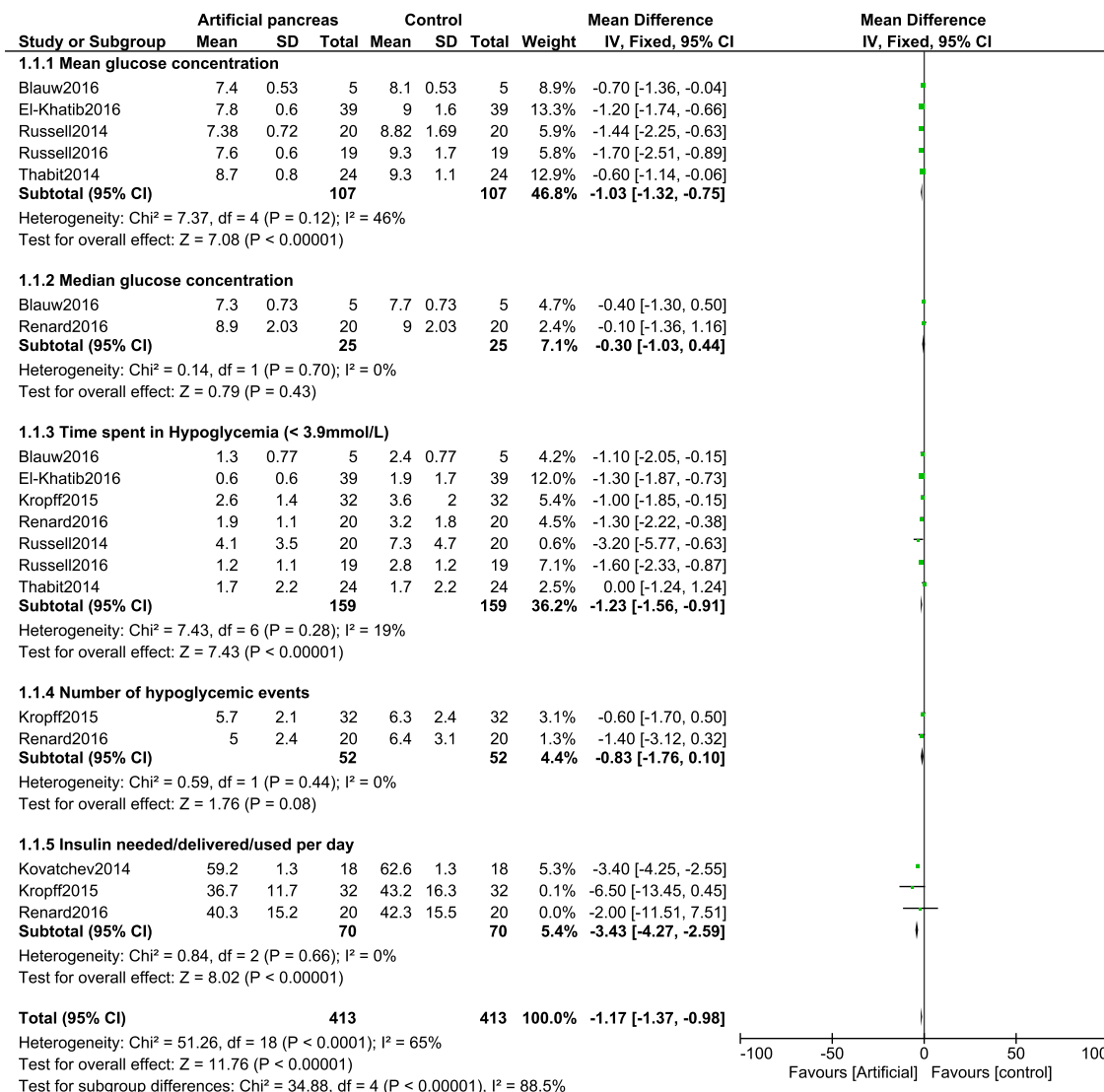Favours [Artificial] Favours [control]

Fig. 2 Comparing artificial pancreas with the control group (part 1)

Time spent outside the euglycemic phase (24 h-basis) also significantly favored artificial pancreas with WMD − 6.28, 95% CI − 10.67 to − 1.88; P = 0.005. This meant that most of the time, patients using artificial pancreas were in the euglycemic phase (neither experiencing hypoglycemia nor hyperglycemia) as shown in Fig. 3. However, the results were moderately heterogeneous.
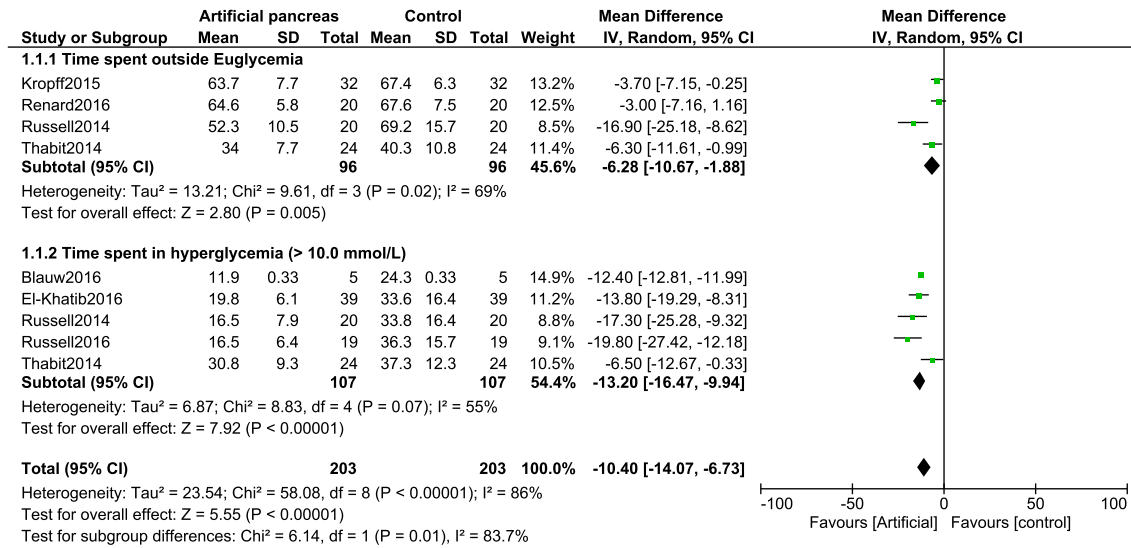
Moreover, the time spent in the hyperglycemia phase (glucose > 10.0 mmol/L) also significantly favored artificial pancreas with WMD − 13.20, 95% CI − 16.47 to − 9.94;

P = 0.00001 meaning that patients using artificial pancreas hardly suffered any hyperglycemic stage as shown in Fig. 3. However, this result was also moderately heterogeneous.

DISCUSSION

The use of a fully integrated artificial pancreas in patients with T1DM was previously demonstrated [17].

The current results showed artificial pancreas to be significantly more effective compared to its control group in terms of glucose

Study or Subgroup	Artificial pancreas			Control			Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total			
1.1.1 Time spent outside Euglycemia									
Kropff2015	63.7	7.7	32	67.4	6.3	32	13.2%	-3.70 [-7.15, -0.25]	
Renard2016	64.6	5.8	20	67.6	7.5	20	12.5%	-3.00 [-7.16, 1.16]	
Russell2014	52.3	10.5	20	69.2	15.7	20	8.5%	-16.90 [-25.18, -8.62]	
Thabit2014	34	7.7	24	40.3	10.8	24	11.4%	-6.30 [-11.61, -0.99]	
Subtotal (95% CI)			**96**			**96**	**45.6%**	**-6.28 [-10.67, -1.88]**	
Heterogeneity: Tau² = 13.21; Chi² = 9.61, df = 3 (P = 0.02); I² = 69%									
Test for overall effect: Z = 2.80 (P = 0.005)									
1.1.2 Time spent in hyperglycemia (> 10.0 mmol/L)									
Blauw2016	11.9	0.33	5	24.3	0.33	5	14.9%	-12.40 [-12.81, -11.99]	
El-Khatib2016	19.8	6.1	39	33.6	16.4	39	11.2%	-13.80 [-19.29, -8.31]	
Russell2014	16.5	7.9	20	33.8	16.4	20	8.8%	-17.30 [-25.28, -9.32]	
Russell2016	16.5	6.4	19	36.3	15.7	19	9.1%	-19.80 [-27.42, -12.18]	
Thabit2014	30.8	9.3	24	37.3	12.3	24	10.5%	-6.50 [-12.67, -0.33]	
Subtotal (95% CI)			**107**			**107**	**54.4%**	**-13.20 [-16.47, -9.94]**	
Heterogeneity: Tau² = 6.87; Chi² = 8.83, df = 4 (P = 0.07); I² = 55%									
Test for overall effect: Z = 7.92 (P < 0.00001)									
Total (95% CI)			**203**			**203**	**100.0%**	**-10.40 [-14.07, -6.73]**	
Heterogeneity: Tau² = 23.54; Chi² = 58.08, df = 8 (P < 0.00001); I² = 86%									
Test for overall effect: Z = 5.55 (P < 0.00001)									
Test for subgroup differences: Chi² = 6.14, df = 1 (P = 0.01), I² = 83.7%									

-100   -50   0   50   100
Favours [Artificial]   Favours [control]

Fig. 3 Comparing artificial pancreas with the control group (part 2)

concentration, time spent in the hypoglycemic phase, and insulin delivery during a 24-h period. Artificial pancreas was also safer to use owing to its association with a significantly lower time period in the hyperglycemia phase, its significant maintenance of a longer euglycemic period, and its lack of association with any significantly higher episode of hypoglycemic event compared to its control.

Similarly, Hovorka et al. showed that artificial pancreas improved overnight control of glucose level and decreased the rate of nocturnal hypoglycemia in patients with T1DM within a study time period of 3 months [18]. Another multicenter study showed this artificial pancreas to be very effective and safe to use in patients with T1DM [19]. Similarly, through a multicenter 6-month trial of 24/7 automated insulin delivery in 2014, Kovatchev et al. recently showed closed-loop control technology to have matured and to appear safe for long-term use in patients with T1DM [20].

This new device was even considered effective in pediatric participants. Weinzimer et al. recently demonstrated fully automated closed-loop insulin delivery versus semi-automated hybrid control in pediatric candidates with T1DM [21]. Insulin delivery using artificial pancreas was further illustrated in the Virginia experience, wherein the participants were studied twice, once using their personal open-loop technique, and then a second time using the closed-loop (artificial) system [22]. Other research further complemented the closed-loop insulin delivery technique [23, 24].

Further improvement is being considered in relation to this artificial pancreas [25]. Also, useful tools have already been devised to improve the assessment of glycemic variability in patients with artificial pancreas [26].

LIMITATIONS

This analysis also has limitations: (a) The number of participants was extremely limited; however, when compared to other previously published studies, this analysis included a large number of patients. (b) The different follow-up time periods could have had an impact on the results obtained. (c) The range of the euglycemic phase was supposed to be a glucose level ranging between 3.9 and 8.0 mmol/L; however, a few studies recorded a glucose level varying between 4.4 and 8.0 mmol/L or 3.9 to 10.0 mmol/L which might have contributed to the moderate level of heterogeneity in this particular subgroup. (d) The inclusion of one non-randomized study might have introduced bias, contributing to the limitations in this analysis. (e) The control groups were not similar

in all the studies, which might be another limitation of this analysis. (f) Utilizing sensor augmented pump as the control group is the current clinical golden standard which artificial pancreas needs to be able to outperform if clinically relevant. So, another limitation of this study might be the lack of an analysis strictly dealing with studies comparing artificial pancreas and sensor-augmented pump. However, the number of studies reporting this control was too small.

CONCLUSION

According to the results of this analysis, artificial pancreas might be considered an effective and safe alternative to be used during a 24-h basis in patients with T1DM. Several benefits of the artificial pancreas in maintaining and improving glucose levels were observed in comparison to its control. Nevertheless, a major shortcoming of this analysis is the extremely limited number of patients analyzed.

ACKNOWLEDGEMENTS

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