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COMPARATIVE EFFECTIVENESS AND SAFETY OF METHODS OF INSULIN DELIVERY AND GLUCOSE MONITORING FOR DIABETES MELLITUS: A SYSTEMATIC REVIEW

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Abstract

Introduction: *Achieving glycemic control remains difficult for patients with type 1 diabetes. We compared the efficacy of day-and-night hybrid closed-loop insulin delivery to sensor-augmented pump therapy in individuals 6 years and older with suboptimally controlled type 1 diabetes.*

The aim: *This article compared effectiveness and safety of methods of insulin delivery and glucose monitoring for diabetes mellitus.*

Methods: *By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2013 and 2023 were taken into account. Several different online reference sources, like Pubmed and SagePub, were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.*

Result: *In the PubMed database, the results of our search brought up 166 articles, whereas the results of our search on SagePub brought up 143 articles. The results of the search conducted for the last year of 2013 yielded a total 116 articles for PubMed and 89 articles for SagePub. In the end, we compiled a total of 23 papers, 15 of which came from PubMed and eight of which came from SagePub. We included six research that met the criteria.*

Conclusion: *The use of a hybrid closed-loop insulin delivery system in free-living conditions for a period of twelve weeks led to clinically relevant improvements in glycaemic control while simultaneously reducing the risk of hypoglycemia in suboptimally controlled type 1 diabetes in adults, adolescents, and children aged six years and older.*

Keyword: *Diabetes mellitus; Insulin; Glucose; Monitoring*

INTRODUCTION

Diabetes Mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various glands, especially the eyes, kidneys, nerves, heart, and blood vessels.[1] Symptoms of DM are characterized by hyperglycemia with polyuria, polydipsia, weight loss, sometimes with polyphagia, and blurred vision. Impaired growth and susceptibility to certain infections may also accompany chronic hyperglycemia.[2]

Type 1 diabetes is a chronic disease characterized by the body's inability to produce insulin due to the autoimmune destruction of beta cells in the pancreas. Although onset often occurs in childhood, the disease can also develop in adults.[3] Unlike people with type 2 DM, those with type 1 DM are usually not obese and usually present with diabetic ketoacidosis (DKA).[4] The characteristic that distinguishes patients with type 1 DM is that if the insulin is stopped, ketosis and ketoacidosis will occur. Hence, these patients are dependent on exogenous insulin. Treatment of type 1 DM using insulin therapy for life.[5]

There is a high relative risk of type 1 diabetes among siblings due to the complexity of the disease's genetic components and the large number of genes involved. At the age of 40 years, the concordance rate for type 1 diabetes in monozygotic twins will be greater than 50%, whereas the rate for type 1 diabetes in dizygotic twins ranges from 5% to 6%. There is also a contribution from extragenetic variables. Viruses (such as enterovirus, mumps, rubella, and coxsackievirus B4), toxic chemicals, exposure to cow's milk while an infant is young, and exposure to cytotoxins are all potential triggers for the immunological death of beta cells.[4]

Type 2 diabetes mellitus is a paracrinopathy that has a reciprocal relationship between glucagon-secreting alpha cells and insulin-secreting beta cells. Loss of this ability can lead to hyperglucagonemia and hence hyperglycemia. Resistance and insulin secretion are not the root cause of type 2 DM.[6] Based on the criteria of the American Diabetes Association in 2012, approximately 10.2 million people in the United States suffer from DM. Meanwhile, in Indonesia the prevalence of DM is 1.5-2.3% of the population aged >15 years, even in the Manado area the prevalence of DM is 6.1%. The incidence of Type 2 DM in women is higher than men.[5,7]

Because women are more likely to gain weight, they are more likely to get diabetes. In 2018, Basic Health Research found 57% of Indonesians had DM. In 2012, 371 million people worldwide had diabetes mellitus, with 95% of them having type 2. 5% have type 1 diabetes.[2,7] Diabetes mellitus consists of multiple dysfunctions characterized by hyperglycemia and resulting from a combination of resistance to insulin action, inadequate insulin secretion, and excessive or inappropriate glucagon secretion. Uncontrolled type 2 diabetes is associated with various microvascular, macrovascular and neuropathic complications.[8]

Microvascular and macrovascular complications of diabetes are reduced with intensive insulin therapy and tight glycemic control. Innovations in insulin delivery and glucose monitoring aim to enhance glycemic control and quality of life (QOL) while minimizing adverse effects such as hypoglycemia and weight gain.[9] Continuous subcutaneous insulin infusion (CSII) and continuous glucose monitoring in real time (rt-CGM) are examples of these developments. Insulin therapy requires glucose monitoring so patients can change their doses and behavior. MDI and CSII use self-monitoring of blood glucose (SMBG).[10–12]

In the last 10 years, a lot of work has been made on closed-loop insulin delivery systems, also called "artificial pancreases." These systems combine continuous glucose monitoring with algorithm-driven insulin pump delivery.[13,14] Hybrid closed-loop devices are set up so that insulin is delivered automatically, except when the user gives insulin boosts before meals. Based on a key safety non-randomized, single-arm trial of a hybrid closed-loop system in people with type 1 diabetes, the first hybrid closed-loop system was put into practical use in 2017.[15,16]
This article compared effectiveness and safety of methods of insulin delivery and glucose monitoring for diabetes mellitus.

METHODS

Following Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines, the author of this study ensured that it adhered to the standards. This is done to ensure the accuracy of the investigation's findings. The purpose of this literature review was to compare the efficacy and safety of methods of insulin delivery and glucose monitoring for diabetes. As the primary objective of this piece of writing, relevance of the identified challenges will be demonstrated throughout.
To participate in the study, researchers were required to fulfill the following criteria: 1) The paper must be written in English and will compare the efficacy and safety of insulin delivery and glucose monitoring methods for diabetes. To be considered for publication, the manuscript must meet both of these requirements. 2) A number of the examined articles were published after 2013, but before the time period deemed relevant by this systematic review. Not permitted are editorials, submissions without a DOI, previously published review articles, and entries that are essentially identical to previously published journal articles.
We used “effectiveness”; “safety”; “insulin delivery”; “glucose monitoring”; and ”diabetes mellitus” as keywords.The search for studies to be included in the systematic review was carried out from August, 7th 2023 using the PubMed and SagePub databases by inputting the words: *((“effect”[All Fields] OR "effecting"[All Fields] OR "effective"[All Fields] OR*

"effectively"[All Fields] OR "effectiveness"[All Fields] OR "effectivenesses"[All Fields] OR "effectives"[All Fields] OR "effectivities"[All Fields] OR "effectivity"[All Fields] OR "effects"[All Fields]) AND ("safety"[MeSH Terms] OR "safety"[All Fields] OR "safeties"[All Fields]) AND ("insulin"[Supplementary Concept] OR "insulin"[All Fields] OR "insulin"[MeSH Terms] OR "insulin s"[All Fields] OR "insuline"[All Fields] OR "insulinic"[All Fields] OR "insulinization"[All Fields] OR "insulinized"[All Fields] OR "insulins"[MeSH Terms] OR "insulins"[All Fields]) AND ("deliveries"[All Fields] OR "delivery, obstetric"[MeSH Terms] OR ("delivery"[All Fields] AND "obstetric"[All Fields]) OR "obstetric delivery"[All Fields] OR "delivery"[All Fields]) AND ("glucose"[Supplementary Concept] OR "glucose"[All Fields] OR "glucose"[MeSH Terms] OR "glucoses"[All Fields] OR "glucose s"[All Fields]) AND ("monitor"[All Fields] OR "monitor s"[All Fields] OR "monitorable"[All Fields] OR "monitored"[All Fields] OR "monitoring"[All Fields] OR "monitoring s"[All Fields] OR "monitorings"[All Fields] OR "monitorization"[All Fields] OR "monitorize"[All Fields] OR "monitorized"[All Fields] OR "monitors"[All Fields]) AND ("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields])) AND ((y_10[Filter]) AND (clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter])) used in searching the literature.

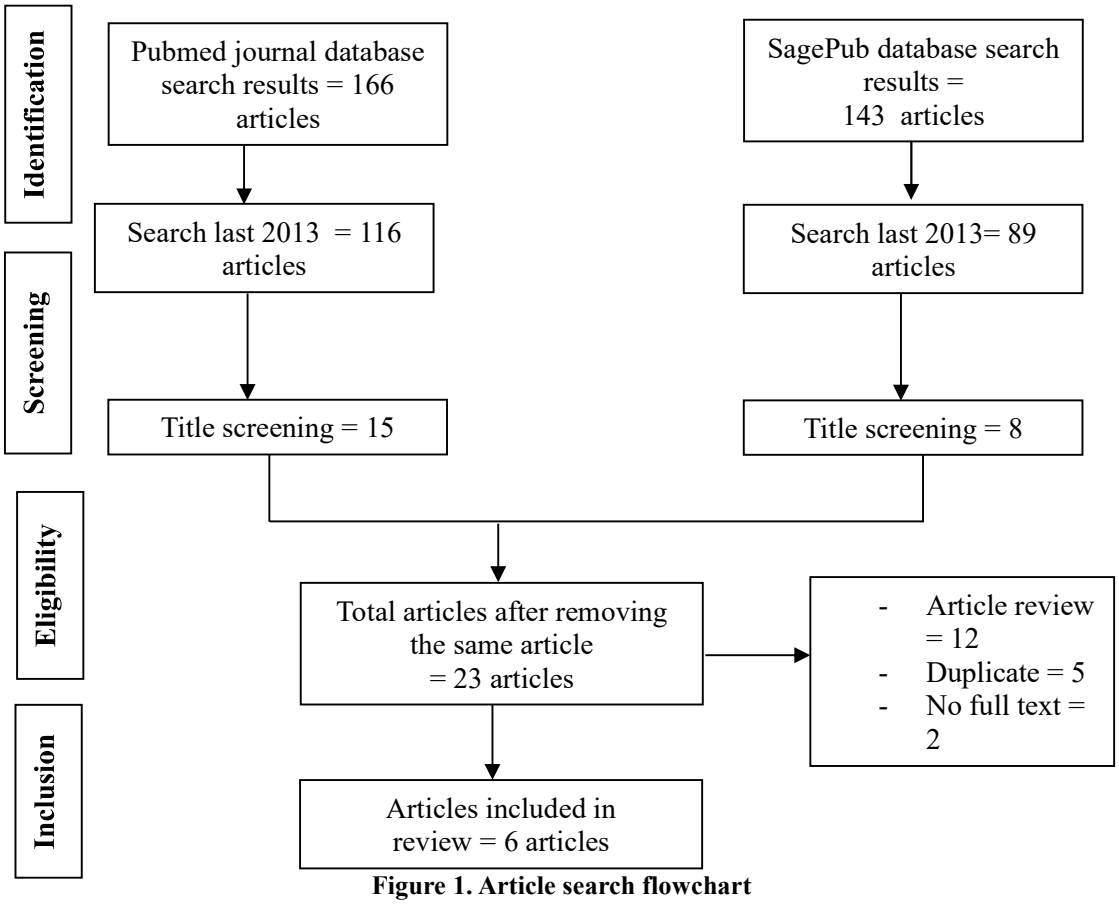

Figure 1. Article search flowchart

After reviewing the abstract and title of each study, the authors determined whether or not it met the inclusion criteria. The authors then determined which prior studies would serve as the article's sources and selected those studies. Examining a variety of studies that all appeared to indicate the same trend led to this conclusion. All submissions must be written in English and have never been published before. Only publications that satisfied all inclusion criteria were considered for the systematic review. This restricts the search results to those which are germane to your query. We do not consider the results of any study that does not meet our criteria. The research findings will then be thoroughly analyzed. The following information was uncovered as a result of the research conducted for this study: names, authors, publication dates, location, study activities, and parameters.

Before deciding which publications to investigate further, each author conducted independent research on the research included in the publication's title and abstract. The subsequent step is to evaluate all of the articles that satisfy the inclusion criteria for the review. Then, we will choose which articles to include in the review based on the findings. This criterion is employed to select documents for additional evaluation. To facilitate as much as possible the selection of papers for evaluation. This section discusses which prior studies were conducted and what aspects of those studies made their inclusion in the review appropriate.

RESULT

In the PubMed database, the results of our search brought up 166 articles, whereas the results of our search on SagePub brought up 143 articles. The results of the search conducted for the last year of 2013 yielded a total 116 articles for PubMed

and 89 articles for SagePub. In the end, we compiled a total of 23 papers, 15 of which came from PubMed and eight of which came from SagePub. We included six research that met the criteria.

Tauschmann, et al (2018) showed proportion of time that glucose concentration was within the target range was significantly higher in the closed-loop group (65%) compared with the control (54%; mean difference [MD] in change 10.8 percentage points, 95% confidence interval [CI] = 8.2-13·5; p <0.001). In the closed-loop group, the HbA1c screening value was reduced from 8.3% to 8.0% after the 4-week run-in period and to 7.4% after the 12-week intervention. In the control group, HbA1c values were 8.2% at screening, 7.8% after run-in, and 7.7% after intervention; HbA1c percentage reductions in the closed-loop group were significantly greater than in the control group (MD in change 0.36%, 95% CI = 0.19-0.53; p <0.001).

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Technique	Result
Tauschmann, 2018[14]	United Kingdom	Open-label, multicentre, multinational, single-period, parallel randomised controlled trial	86 patients with suboptimally controlled type 1 diabetes	Hybrid closed-loop insulin delivery system	In individuals with type 1 diabetes who are not managing their condition as well as they could, hybrid closed-loop insulin delivery can improve glucose management while simultaneously lowering the risk of hypoglycemia across a wide age range.
Garg, 2017[15]	United State of America; Israel	Open-label, multicentre, multinational, single-period, parallel randomised controlled trial	Adolescents (n = 30, ages 14-21 years) and adults (n = 94, ages 22-75 years) with type 1 diabetes	Hybrid closed-loop insulin delivery system	The hybrid closed-loop (HCL) therapy was safe for usage at home by both adolescents and adults, and the trial phase indicated an enhanced time in target, as well as reductions in HbA1c, hyperglycemia, and hypoglycemia, when compared to the baseline values.
Taleb, 2016[17]	Canada	Open-label randomised crossover study	17 adults with type 1 diabetes	Dual-hormone (insulin + glucagon) artificial pancreas reduces hypoglycaemia compared with the single-hormone (insulin alone) artificial pancreas	When it came to managing glucose levels in persons with type 1 diabetes who were about to engage in activity, the dual-hormone artificial pancreas performed significantly better than the single-hormone artificial pancreas.
Castle, 2016[18]	USA	Open-label randomised crossover study	20 adults with type 1 diabetes	Dual-hormone (insulin + glucagon) artificial pancreas reduces hypoglycaemia compared with the single-hormone (insulin alone) artificial pancreas	Adults with type 1 diabetes who engage in physical activity and use a closed-loop system with automated exercise detection experience less hypoglycemia as a result of the combination of these two factors.
Thabit, 2015[13]	United Kingdom	Multicenter, crossover, randomized, controlled studies	33 adults and 25 children – adolescents	Hybrid closed-loop insulin delivery system	In patients with type 1 diabetes, using a closed-loop system for 12 weeks resulted in better glucose control, reduced instances of hypoglycemia, and, in adults, a lower level of glycated hemoglobin when compared to using a sensor-augmented pump. This was the case when comparing the two therapies.
Kropff, 2015[19]	Italy, France, and Netherland	Multicenter, open-label, randomized, controlled studies	17 adults with type 1 DM	Hybrid closed-loop insulin delivery system	This study findings provide evidence that administering artificial pancreas (AP) at home is a viable treatment option that is both safe and advantageous for people with type 1 diabetes. The preliminary results for HbA1c are encouraging, but they are only that.

The time spent with glucose concentrations below 3.9 mmol/L (MD in change -0.83 percentage points, -1.40 to -0.16; p = 0.0013) and above 10.0 mmol/L (MD in change -10.3 percentage points, -13.2 to -7.5; p<0·0001) was shorter in the closed-loop group than the control group. The coefficient of variation of glucose sensor measurements did not differ between treatments (MD in change = -0.4%, 95% CI = -1.4% to 0.7%; p = 0.50). Similarly, neither the total daily insulin dose nor the bodyweight varied. There was no severe hypoglycemia.[14]

Garg, et al (2017)[15] showed adolescent and adult HbA1c levels decreased from 7.7% ± 0.8% to 7.1% ± 0.6% (P <0.001) and from 7.3% ± 0.9% to 6.8% ± 0.6% (P < 0.001, Wilcoxon signed-rank test), respectively. The proportion of overall in-target (71-180 mg/dL) sensor glucose (SG) values increased from 60.4% ± 10.9% to 67.2% ± 8.2% (P < 0.001) in adolescents and from 68.8% ± 11.9% to 73.8% ± 8.4% (P < 0.001) in adults. During the hotel stay, the proportion of in-target i-STAT® blood glucose values was 67.4% ± 27.7% compared to SG values of 72.0% ± 11.6% for adolescents and 74.2% ± 17.5% compared to 76.9% ± 8.3% for adults. There were no severe hypoglycemic or diabetic ketoacidosis events in either cohort.

Taleb, et al (2016)[17] showed exercise-induced hypoglycaemia (plasma glucose <3.3 mmol/l with symptoms or <3.0 mmol/l regardless of symptoms) was observed in four (23.5%) vs two (11.8%) interventions for continuous exercise and in six (40%) vs one (6.25%) for interval exercise. For the pooled study (single vs dual hormone), the median (interquartile range) percentage time spent at glucose levels below 4.0 mmol/l was 11% (0.0-46.7%) vs 0% (0-0%; p = 0.0001) and between 4.0 and 10.0 was 71.4% (53.2-100%) vs 100% (100-100%; p = 0.003). Continuous activity required 0.126 ± 0.057 mg of glucagon, while interval exercise required 0.093 ± 0.068 mg (p = 0.03), with no side effects.

Castle, et al (2016)[18] showed the mean time (SD) in low blood sugar was the shortest with dual-hormone: 3.4% (4.5) vs. 8.3% (12.6) single hormone (P = 0.009) vs. 7.6% (8.0) predictive low glucose suspend (P <0.001) vs. 4.3% (6.8) current care where insulin changes were allowed before exercise (P = 0.49). During the whole 4-day study, time in hypoglycemia was shortest with dual-hormone: 1.3% (1.0) vs. 2.8% (1.7) for single-hormone, 2.0% (1.5) for predicted low glucose suspend, and 3.1% (3.2) for current care (P = 0.007). The single-hormone group spent the most time in range during the whole study: 74.3% (8.0) vs. 72.0% (10.8) for the dual-hormone group (P = 0.44).

Thabit, et al (2015)[13] showed the proportion of time that the glucose level was in the target range was 11.0 percentage points (95% CI = 8.1=13.8) greater with the use of the closed-loop system day and night than with control therapy (P <0.001). The mean glucose level was lower during the closed-loop phase than during the control phase (difference = −11 mg/dL; 95% CI = −17 to −6; P<0.001), as were the area under the curve for the period when the glucose level was less than 63 mg per deciliter (39% lower; 95% CI = 24-51; P<0.001) and the mean glycated hemoglobin level (difference = −0.3%; 95% CI = −0.5 to −0.1; P = 0.002).

Among children and adolescents, the proportion of time with the nighttime glucose level in the target range was higher during the closed-loop phase than during the control phase (by 24.7% points; 95% CI = 20.6-28.7; P <0.001), and the mean nighttime glucose level was lower (difference = −29 mg/dL; 95% CI = −39 to −20; P <0.001). The area under the curve for the period in which the day-and-night glucose levels were less than 63 mg/dL was lower by 42% (95% CI = 4 to 65; P = 0.03). Three severe hypoglycemic episodes occurred during the closed-loop phase when the closed-loop system was not in use.[13]

Kropff, et al (2015)[19] the mean time spent during 2000-0800 h in the target range was higher with AP than with SAP use: 66.7% versus 58.1% (paired difference 8.6% [95% CI = 5.8-11.4], p <0.001), through a reduction in both mean time spent in hyperglycaemia (glucose concentration >10.0 mmol/L; 31.6% vs 38.5%; -6.9% [-9.8% to -3.9], p<0.001) and in hypoglycaemia (glucose concentration <3.9 mmol/L; 1.7% vs 3.0%; -1.6% [-2.3 to -1.0], p<0.001). Taking into account the period effect (p = 0.0034), the decrease in mean HbA1c during the AP period was substantially greater than during the control period (-0.3% vs -0.2%; paired difference -0.2 [95% CI = -0.4 to 0.0], p = 0.047). During this investigation, there were no serious adverse events, and none of the mild-to-moderate adverse events were related to the study intervention.

DISCUSSION

In a multinational, multicenter, open-label, randomised trial, 12-week use of a day-and-night hybrid closed-loop insulin delivery system compared with sensor-augmented insulin pump therapy improved glucose control and reduced hypoglycaemia risk in suboptimally controlled type 1 diabetes in children, adolescents, and adults. Daily life was safe with the hybrid closed-loop system. Study observed a lower amount of bolus insulin and a higher amount of basal insulin in the closed-loop group than in the sensor-augmented pump therapy group. Lower bolus insulin requirements in the closed-loop group than in the sensor-augmented pump therapy group could be explained by lower glucose concentrations in this group during closed-loop use, lessening the need for correction boluses.[14,15,20]

When compared with sensor-augmented pump therapy, the use of hybrid closed-loop therapy resulted in a moderate but clinically significant reduction of 0.36 percentage points in HbA1c. This reduction was additive to that which was found during the run-in period, the latter of which can be attributed to observer bias and the commencement of continuous glucose monitoring. The drop in HbA1c that was found during closed-loop use was slightly more than that which was

observed in two randomized studies that had been run long enough to assess changes in HbA1c, and both of these trials used sensor-augmented pump therapy as a comparison.[13,19]

Kropff and colleagues reported a drop of 0.2% for evening-and-night closed-loop application, while Thabit and colleagues demonstrated a mean reduction in HbA1c of 0.3% with day-and-night hybrid closed-loop therapy. Thabit and colleagues used day-and-night hybrid closed-loop therapy. The size of these two trials was rather low, with roughly 30 participants participating in each experiment, and the closed-loop application was only available to adults. In contrast, the current study allocated individuals at random to 86 persons, and the age range covered a wider spectrum. In this particular trial, improvements in HbA1c were observed across the board for all age categories.[13,19]

In the current trial, the proportion of patients who had an episode of hypoglycemia was minimal, and it was comparable to the proportions seen in other outpatient closed-loop investigations. The use of closed-loop therapy resulted in a statistically significant reduction in the proportion of time spent in hypoglycemia below 3.9 mmol/L. However, the reduction of time spent in hypoglycemia below 3.5 mmol/L and 2.8 mmol/L did not achieve statistical significance.[13,15] Due to the fact that neither group had severe hypoglycemia, it is currently unknown how closed-loop therapy would affect severe hypoglycemia if it were to occur. During physical activity in particular, the incorporation of glucagon into bihormonal closed-loop systems has the potential to provide an even greater reduction in the risk of hypoglycemia.[17,18]

CONCLUSION

The use of a hybrid closed-loop insulin delivery system in free-living conditions for a period of twelve weeks led to clinically relevant improvements in glycaemic control while simultaneously reducing the risk of hypoglycemia in suboptimally controlled type 1 diabetes in adults, adolescents, and children aged six years and older.

REFERENCES

[1]. Jameson J, Fauci A, Kasper D, Hauser S, Longo D, Loscalzo J. Harrison's Principles of Internal Medicine 20th ed. New York NY, McGraw Hill Educ. 2018;
[2]. International Diabetes Federation. Diabetes. Brussels: IDF; 2017.
[3]. Aathira R, Jain V. Advances in management of type 1 diabetes mellitus. World J Diabetes. 2014;15(5):689–96.
[4]. Kliegman R. M; et al. Nelson Textbook of Pediatrics. Philadelphia: Elsevier Saunder; 2016.
[5]. American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 2016;62–9.
[6]. Unger RH, Orci L. Paracrinology of islets and the paracrinopathy of diabetes. Proc Natl Acad Sci U S A. 2010;107(37):16009–12.
[7]. Kementerian Kesehatan Republik Indonesia. Riset Kesehatan Dasar [Internet]. Jakarta; 2018. Available from: http://www.depkes.go.id/resources/download/infoterkini/materi_rakorpop_2018/Hasil Riskesdas 2018.pdf
[8]. Soelistijo SA, Lindarto D, Decroli E, et al. Pedoman Pengelolaan dan Pencegahan Diabetes Melitus Tipe 2 Dewasa di Indonesia. Jakarta: PB Perkeni; 2021.
[9]. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359(15):1577–89.
[10]. Association AD. Standards of medical care in diabetes—2011. Diabetes Care. 2011;34(Supplement_1):S11–61.
[11]. Association AD. 6. Glycemic Targets: Standards of Medical Care in Diabetes—2018. Diabetes Care [Internet]. 2017 Nov 24;41(Supplement_1):S55–64. Available from: https://doi.org/10.2337/dc18-S006
[12]. Monami M, Lamanna C, Marchionni N, Mannucci E. Continuous subcutaneous insulin infusion versus multiple daily insulin injections in type 1 diabetes: a meta-analysis. Acta Diabetol. 2010;47:77–81.
[13]. Thabit H, Tauschmann M, Allen JM, Leelarathna L, Hartnell S, Wilinska ME, et al. Home Use of an Artificial Beta Cell in Type 1 Diabetes. N Engl J Med. 2015 Nov;373(22):2129–40.
[14]. Tauschmann M, Thabit H, Bally L, Allen JM, Hartnell S, Wilinska ME, et al. Closed-loop insulin delivery in suboptimally controlled type 1 diabetes: a multicentre, 12-week randomised trial. Lancet (London, England). 2018 Oct;392(10155):1321–9.
[15]. Garg SK, Weinzimer SA, Tamborlane W V, Buckingham BA, Bode BW, Bailey TS, et al. Glucose Outcomes with the In-Home Use of a Hybrid Closed-Loop Insulin Delivery System in Adolescents and Adults with Type 1 Diabetes. Diabetes Technol Ther. 2017 Mar;19(3):155–63.
[16]. Bergenstal RM, Garg S, Weinzimer SA, Buckingham BA, Bode BW, Tamborlane W V, et al. Safety of a Hybrid Closed-Loop Insulin Delivery System in Patients With Type 1 Diabetes. JAMA. 2016 Oct;316(13):1407–8.
[17]. Taleb N, Emami A, Suppere C, Messier V, Legault L, Ladouceur M, et al. Efficacy of single-hormone and dual-hormone artificial pancreas during continuous and interval exercise in adult patients with type 1 diabetes: randomised controlled crossover trial. Diabetologia. 2016 Dec;59(12):2561–71.
[18]. Castle JR, El Youssef J, Wilson LM, Reddy R, Resalat N, Branigan D, et al. Randomized Outpatient Trial of Single- and Dual-Hormone Closed-Loop Systems That Adapt to Exercise Using Wearable Sensors. Diabetes Care. 2018 Jul;41(7):1471–7.
[19]. Kropff J, Del Favero S, Place J, Toffanin C, Visentin R, Monaro M, et al. 2 month evening and night closed-loop glucose control in patients with type 1 diabetes under free-living conditions: a randomised crossover trial. lancet Diabetes Endocrinol. 2015 Dec;3(12):939–47.
[20]. Yaribeygi H, Farrokhi FR, Butler AE, Sahebkar A. Insulin resistance: Review of the underlying molecular mechanisms. J Cell Physiol. 2019 Jun;234(6):8152–61.