Original Research

Analysis of Medication, Cost, and Clinical Outcome of Human and Analogue Insulins of Type 2 Diabetes Mellitus at MMC Hospital 2016-2017

HIJP
Health Information : Jurnal Penelitian

Jayati, Turpuk Mannaria; Anggriani, Yusi; Laksmitawati, Dian Ratih; Waspadji, Sarwono

Turpuk Mannaria Jayati
mannaria.butar4@gmail.com
Pharmacy Program, Faculty of Pharmacy, University of Pancasila, Indonesia
Yusi Anggriani
Pharmacist Profession Program, Faculty of Pharmacy, University of Pancasila, Indonesia
Dian Ratih Laksmitawati
Pharmaceutical Science Program, Faculty of Pharmacy, University of Pancasila, Indonesia
Sarwono Waspadji
Department of Internal Medicine, Faculty of Medicine, University of Indonesia, Indonesia

Health Information: Jurnal Penelitian
Poltekkes Kemenkes Kendari, Indonesia
ISSN: 2085-0840
ISSN-e: 2622-5905
Periodicity: Bianual
vol. 13, no. 2, 2021
jurnaldanhakcipta@poltekkes-kdi.ac.id

Received: 11 April 2021
Accepted: 30 November 2021

URL: http://portal.amelica.org/ameli/journal/504/5042238015/

DOI: https://doi.org/10.36990/hijp.v13i2.273

Funding
Funding source: Nihil.
Corresponding author: mannaria.butar4@gmail.com

Abstract: Human insulin and analog insulin are available at RS.MMC. The use of analog insulin was more prevalent among doctors between 2016 and 2017. The data collection was conducted retrospectively, taking samples of 132 outpatients type 2 DM using insulin, of which 74 were evaluated for their clinical outcome. The study's goal is to provide information for developing insulin usage guidelines. The medication profile data were collected from the medicine administration at the Hospital Pharmacy Installation. The clinical outcome data, such as fasting plasma glucose (FPG), two-hour postprandial plasma glucose (2HPP), and Hemoglobin A1c (HbA1c), were garnered from the patients' medical records. The cost data were collected from the outpatients' payment receipts provided by the Hospital's Financial Department. Kolmogorov Smirnov normality test was applied in this research. Statistical trials of differences in clinical outcomes and costs using the Kruskal-Wallis test, showed there was a significant difference between human insulin and insulin analogues in terms of clinical outcomes of GDP, GDPP, HbA1c, and cost after follow-up testing with Mann Whitney, showed average cost of using human insulin for 30 days was Rp1,597,066, and analogue was Rp2,497,535 shows that human insulin and analogues differ significantly in terms of cost ($p = 0.015$).

Keywords: Medication, Cost, Clinical outcome, Diabetes mellitus, Human insulin.

Ringkasan: Saat ini tersedia insulin manusia dan insulin analog di RS.MMC yang diresepkan dokter untuk terapi pasien DM tipe2. Insulin analog lebih banyak diresepkan oleh dokter periode 2016-2017. Tujuan penelitian adalah untuk memberikan informasi pengambilan kebijakan penggunaan insulin. Subjek penelitian adalah pasien DM tipe2 yang menggunakan insulin. Data dikumpulkan secara retrospektif. Sampel diambil dari 132 pasien, dimana74 dari 132 pasien tersebut diambil untuk evaluasi hasil klinis. Profil pengobatan diperoleh dari penggunaan obat di Instalasi Farmasi. Data luaran klinis diambil dari hasil GDP, GDPP dan HbA1c di rekam medis pasien . Data biaya dikumpulkan dari unit keuangan berupa kuitansi pembayaran pasien. Uji normalitas menggunakan uji Kolmogorov Smirnov. Uji statistik perbedaan outcome klinis dan biaya menggunakan uji Kruskal-Wallis. Hasil menunjukkan ada perbedaan yang signifikan antara insulin manusia dan insulin analog dalam hal hasil klinis GDP, GDPP, HbA1c, dan biaya setelah dilakukan

uji lanjutan dengan Mann Whitney. Hasil penelitian ini juga menyatakan biaya rata-rata penggunaan insulin manusia tunggal selama 30 hari adalah Rp1.597.066, dan analog tunggal adalah Rp2.497.535. Hal ini menunjukkan insulin manusia dan insulin analog berbeda secara signifikan dalam hal biaya (p = 0,015).

Kata kunci: Obat, Biaya, Hasil klinis, Diabetes mellitus, Insulin manusia.

INTRODUCTION

Diabetes Mellitus (DM) is a chronic, complex disease requiring continuous medical attention by applying strategies to reduce multi-factor risks and to control glucose levels in the blood (S. Soelistijo, 2021; Casner et al., 1968). DM was one of the clinical diseases afflicting around 415 million people worldwide. This number is growing predicted to reach 642 million people in 2040 (Edition, 2015)

World Health Organization (WHO) predicted the increase in the number of DM outpatients in Indonesia from 8.4 million in 2000 to 21.3 million in 2030. This prediction showed a growing number of people suffering from DM doubling up to 2-3 times in 2035 (S. A. Soelistijo et al., 2015), International Diabetes Federation (IDF) predicted a growing number of people suffering from DM in Indonesia from 10 million in 2015 to 16.2 million in 2040, thus putting Indonesia in level 6 from previous level 7 as a country with the highest number of DM outpatients worldwide (Edition, 2015).

DM outpatients needed insulin as a long-term therapy, which to some of them eventually became a life-saving therapy. Insulin is considered as an expensive treatment for the country's health system as well as for the outpatients themselves. This is because administering insulin needs other types of equipment, such as syringes, blood glucose meter, as well as non-tangible aspects, such as education, information, and supports from families. Diabetes mellitus may reduce the quality of life and impact huge healthcare financing (Kehlenbrink et al., 2017).

There are two types of insulin, i.e. human and analogue insulins. Eighteen expert committee members on their review on the selection and use of human and analogue insulins for diabetes mellitus treatments stated that analogue insulin offered a little advantage in controlling blood glucose as reflected in the values of HbA1c test, fasting plasma glucose (FPG) test, and two-hour postprandial plasma glucose (2HPP) test. It, moreover, has an advantage in reducing hypoglycemia, especially nocturnal hypoglycemia and severe hypoglycemia (18th Expert Committee on the Selection and Use of Essential Medicines, 2011).

Nevertheless, analogue insulin is more readily available in the market than human insulin. It takes a good consideration when it comes to choosing what insulin it is to be administered to the outpatients to achieve an optimum result with economic values so that DM outpatients can afford the treatment. Patients with chronic diseases and other complications will likely spend more money (Hartman, 2008).

In Indonesia, there was no significant difference in price between human and analogue insulins as offered in e-catalogue. Human insulin is 8% cheaper than analogue one (LKPP, 2016).The data showed that DM outpatients need a considerable amount of money if their disease was exacerbated by other diseases. Good control of blood glucose levels was needed. Insulin therapy was one of the therapies administered by Metropolitan Medical Centre (MMC) Hospital to treat diabetes mellitus outpatients. MMC Hospital was one of the private hospitals which accepted private health insurance, cash payments, as well as outpatients who do not covered by the state healthcare insurance. DM disease was one of the ten major diseases treated by MMC Hospital. It was found that MMC Hospital treated their DM outpatients with analogue insulin rather than human insulin.

One of the quality indicators required outpatients' treatment considered not only the clinical outcome as a quality indicator but also the cost incurred. Related to the cost disparity between human and analogue insulin and the lack of data to prove that analogue insulin was more effective than human one, this research found its rationale to examine the efficacy of human and analogue insulin at MMC Hospital. The research finding can also be used as quality and cost control.

The research was carried out using methods that the requirements code of ethics issued by the University of Indonesia No. KET-614/UN2.F1.ETIK/PPM.00.02/2019.

METHODOLOGY

The research applied a longitudinal/time series approach, meaning that it was conducted in a certain period to examine the changes in the treatment of type-2 DM outpatients in chronological order. The data of medical records and prescription records were collected from the MMC Hospital's pharmacy installation from January 2016 to December 2017. The data were qualitatively and quantitatively analysed. The independent variables in this research were human and analogue insulins, while the dependent variables were the clinical outcomes, medication, and cost profiles as well. The research was a longitudinal/time series in which the data were collected in a certain period from 2016 to 2017.

The population was the type-2 outpatients' medical records treated in Metropolitan Medical Centre Hospital from January 2016 to December 2017. The number of type-2 DM outpatients using insulin treated from January 2017 to December 2018 was 201 people. The sample was taken from the outpatients' medical records which meet the inclusion criteria. Inclusion criteria: outpatients diagnosed with type-2 DM from January 2016 to December 2017 at MMC Hospital Jakarta.

Patients routinely control their DM at MMC Hospital from January 2016 to December 2017. Patients administered type-2 DM therapy. Exclusion criteria: outpatients diagnosed with type-2 DM from January 2016 to December 2017 at MMC Hospital Jakarta having the following criteria: Incomplete laboratory data, Incomplete medication administered data, Incomplete medication cost data Outpatients not receiving type-2 DM therapy.

Krejcie-Morgan formula was applied to obtain the number of patients taken as samples in this research. Out of 210 population of type-2 DM outpatients

treated at MMC Hospital from January 2016 to December 2017, the number of 132 patients were taken as samples. Out of 132 patients, 74 patients had been treated three successive times with the same insulin, while 58 patients had been administered with different insulins.

RESULT AND DISCUSSIONS

Treatment Profile

The average number of medications administered to the patients was 6 items of DM medication and 6 items of non DM medications. A study conducted by Sari & Inayah (2014) found that DM medication administered to patients consisted of 4 or more drugs including 3 items of oral anti-diabetic (OAD) medication in addition to insulin. According to Indonesia Endocrinologists' Association (PERKENI, Perhimpunan Endokrinologi Indonesia) in 2015, if a combination of two oral medications could not control blood glucose, the therapy could be furthered by administering a combination of three oral medications (S. A. Soelistijo et al., 2015).

Table 1
Average Number of Medications Per Patient

Month	Number of Visit	Total DM Drug	Total Non DM Drug	Total of Drug	Average DM Drug	Average Non DM Drug
Jan-16	8	48	41	89	6,0	5,1
Feb-16	13	86	54	140	6,6	4,2
Mar-16	15	73	72	145	4,9	4,8
Apr-16	15	86	80	166	5,7	5,3
May-16	14	88	69	157	6,3	4,9
Jun-16	13	77	73	150	5,9	5,6
Jul-16	9	66	59	125	7,3	6,6
Aug-16	7	49	48	97	7,0	6,9
Sep-16	6	58	51	109	9,7	8,5
Oct-16	10	61	68	129	6,1	6,8
Nov-16	9	75	71	146	8,3	7,9
Dec-16	7	44	51	95	6,3	7,3
Jan-17	4	82	82	164	20,5	20,5
Feb-17	13	85	81	166	6,5	6,2
Mar-17	20	119	98	217	6,0	4,9
Apr-17	19	82	68	150	4,3	3,6
May-17	18	84	75	159	4,7	4,2
Jun-17	11	58	56	114	5,3	5,1
Jul-17	8	52	48	100	6,5	6,0
Aug-17	7	55	58	113	7,9	8,3
Sep-17	12	77	80	157	6,4	6,7
Oct-17	10	81	63	144	8,1	6,3
Nov-17	5	39	41	80	7,8	8,2
Dec-17	3	51	55	106	17,0	18,3
Total	**256**	**1676**	**1542**	**3218**		
Average					**6,5**	**6,0**

The average proportion of DM and non DM medications to the patients was 52.08% for DM medications and 47.92% for non-DM ones. The average proportion of DM medications (insulin and OAD) and non-DM ones within a period of 2016-2017 was 28.37% for insulin, 23.71% for DM medications non-insulin, and 47.92% for non DM medications (Table 1)

Table 2
Average Number of Medications Per Patient

Visit Period	Number of Patients	Type of Drug								Total of Drug	
		Insulin		DM Drug		Total DM Drug		Non-DM Drug			
		Total	%	Total	%	Total	%	Total	%	Total	%
Jan-16	8	28	31.46%	20	22.47%	48	53.93%	41	46.07%	89	100.00%
Feb-16	13	46	32.86%	40	28.57%	86	61.43%	54	38.57%	140	100.00%
Mar-16	15	44	30.34%	29	20.00%	73	50.34%	72	49.66%	145	100.00%
Apr-16	15	50	30.12%	36	21.69%	86	51.81%	80	48.19%	166	100.00%
May 2016	14	45	28.66%	43	27.39%	88	56.05%	69	43.95%	157	100.00%
Jun-16	13	40	26.67%	37	24.67%	77	51.33%	73	48.67%	150	100.00%
Jul-16	9	35	28.00%	31	24.80%	66	52.80%	59	47.20%	125	100.00%
Aug 2016	7	26	26.80%	23	23.71%	49	50.52%	48	49.48%	97	100.00%
Sep-16	6	30	27.52%	28	25.69%	58	53.21%	51	46.79%	109	100.00%
Oct 2016	10	43	33.33%	18	13.95%	61	47.29%	68	52.71%	129	100.00%
Nov 2016	9	39	26.71%	36	24.66%	75	51.37%	71	48.63%	146	100.00%
Dec 2016	7	32	33.68%	12	12.63%	44	46.32%	51	53.68%	95	100.00%
Jan-17	4	44	26.83%	38	23.17%	82	50.00%	82	50.00%	164	100.00%
Feb-17	13	48	28.92%	37	22.29%	85	51.20%	81	48.80%	166	100.00%
Mar-17	20	58	26.73%	61	28.11%	119	54.84%	98	45.16%	217	100.00%
Apr-17	19	37	24.67%	45	30.00%	82	54.67%	68	45.33%	150	100.00%
May 2017	18	47	29.56%	37	23.27%	84	52.83%	75	47.17%	159	100.00%
Jun-17	11	32	28.07%	26	22.81%	58	50.88%	56	49.12%	114	100.00%
Jul-17	8	29	29.00%	23	23.00%	52	52.00%	48	48.00%	100	100.00%
Aug 2017	7	28	24.78%	27	23.89%	55	48.67%	58	51.33%	113	100.00%
Sep-17	12	40	25.48%	37	23.57%	77	49.04%	80	50.96%	157	100.00%
Oct 2017	10	42	29.17%	39	27.08%	81	56.25%	63	43.75%	144	100.00%
Nov 2017	5	24	30.00%	15	18.75%	39	48.75%	41	51.25%	80	100.00%
Dec 2017	3	26	24.53%	25	23.58%	51	48.11%	55	51.89%	106	100.00%
	256	**913**	**28.37%**	**763**	**23.71%**	**1676**	**52.08%**	**1542**	**47.92%**	**3218**	**100%**

OAD medications prescribed for type-2 patients as a single or in combination with insulin were biguanide, DPP-4 inhibitor, biguanide, and DPP-4 inhibitor combinations, sulfonylurea, biguanide, and sulfonylurea combinations, thiazolidinediones, glycosides, SGLT-2 inhibitor. The common OAD medications prescribed were Janumet tablet consisting of Sitagliptin (DPP-4 Inhibitor) and Metformin (biguanide group) (Table 2).

Table 3
Percentage of Types of NonDM Medications

CLASS	BRANDS	GENERIC NAME	PERCENTAGE
Combination of Biguainide + DPP IV Inhibitor	Janumet	Sitagliptin + Metformin	15,53
DPP IV Inhibitor	Galvus	Vidagliptin	10,52
Biguanide	Glucophage	Metformin	10,36
DPP IV Inhibitor	Januvia	Sitagliptin	9,55
Sulfonil Urea	Diamicron	Gliclazid	8,41
Sulfonil Urea	Metrix	Glimepirid	7,44
Sulfonil Urea	Amaryl	Glimepirid	7,28
Combination of Biguanide + Sulfonil Urea	Glucovance	Metformin + Glibenclamid	4,69
Sulfonil Urea	Glurenorm	Gliquidone	4,53
Sulfonil Urea	Glimepirid	Glimepirid	4,21
DPP IV Inhibitor	Onglyza	Saxagliptin	3,72
DPP IV Inhibitor	Ttajenta	Linagliptin	3,40
Biguanide	Metformin	Metformin	2,91
TZD /Tiazolidindione	Actos	Pioglitazone	2,75
Combination of Biguanida + Sulfonil Urea	Amaryl M	Glimepirid + Metformin	1,94
Biguanide	Nevox	Metformin	1,29
α-Glicoside Inhibitor	Glucobay	Acarbose	1,13
Sulfonil Urea	Daonil	Glibenclamid	0,16
SLGT-2 Inhibitor	Forxiga	Dafaglifozin	0,16

The most common non DM medications prescribed were dyslipidemia, antiplatelet, and anti-hypertension. Type 2 DM is a disease that plays an important role in causing macrovascular disease in example : cardiovascular disease/stroke/dyslipidemia, peripheral vascular disease, hypertension (Table 3). In addition, microvascular disease as a co-morbidity (Table 4), in example : nephropathy, retinopathy and neuropathy (Hikmat, 2017).

Table 4
The Proportion of Insulin Use

NO	CLASS OF DRUG	PERCENTAGE
1	Dyslipidemia	32,51
2	Antiplatelet	20,13
3	Antihipertensi	18,57
4	Vitamin	5,93
5	Neuropathy	4,76
6	Gangguan saluran pencernaan	3,91
7	Nephropathy	3,39
8	Hyperurisemia	2,21
9	Hypothyroidisme	1,89
10	Antibiotika	0,72
11	Hyperfostatemia	0,72
12	Cardiovaskular	0,65
13	Serebrovaskular	0,59
14	Analgetika	0,52
15	Alzheimer	0,46
16	Hyperplasia Prostat	0,46
17	Asidosis	0,39
18	Obat Flu	0,39
19	Psikotroika	0,33
20	Obat batuk	0,26
21	Imunosupresan	0,20
22	Mukolitik	0,20
23	Hypokalemia	0,20
24	Antipiretik	0,13
25	Hemoroid	0,13
26	ISK	0,13
27	Antifungi	0,07
28	Asma	0,07
29	Lotion	0,07
30	Paru Paru	0,07

N=number of patients, V=number of visit

The proportion of Insulin Use

From 2016 to 2017, the most insulin type prescribed was analogue insulin. There was an increase in the use of analogue insulin combined with OAD/GLP1 injection (insulin analogue+ OAD/GLP1). There was also an increase in the use of the combination of analogue insulin and analogue insulin with OAD/GLP1 injection (insulin analogue+insulin analogue+OAD/ GLP1). Human insulin use was reportedly decreasing in 2016 in which there was 7 prescription, but in 2017 single human insulin was no longer administered to the patients. There was, however, an increase in the use of the combination of human insulin and OAD/GLP1 injection. The use of human and analogue insulin combination was also reportedly decreasing. The most frequent use of insulin in 2016 was the combination of analogue insulin with OAD drugs or with GLP-1 injection as much as 29.315. In 2017, the most frequent use of insulin was the combination of analogue insulin with OAD drugs or with GLP-1 injection as much as 37.64%. In 2016, the use of a combination of human insulin with analogue insulin was 10.14%, human insulin with oral anti-diabetic drugs 3.29%, and combination

of analogue and human insulin with OAD drugs 6.85%. In 2017, the use of a combination of human insulin with analogue insulin was 1.72%, human insulin with OAD drugs 4.02%, and analogue and human insulin with oral anti-diabetic drugs 3.16%. The use of insulin for both the 2016 and 2017 periods was analog insulin, this is because analog insulin has a fast onset with a long duration of action and has a lower risk of hypoglycemia and nocturnal hypoglycemia compared to human insulin. Additionally, the risk of weight loss by human insulin (Hemkens et al., 2009).

Table 5
The Proportion of Insulin Use

No	Type of Insulin	Year 2016				Year 2017				Year 2016 - 2017			
		N	%	V	%	N	%	V	%	N	%	V	%
1	**Analogues Insulin**	**95**	**49.7%**	**226**	**44.5%**	**96**	**50.3%**	**282**	**55.5%**	**191**	**100.0%**	**508**	**100.0%**
	Single Analogues Insulin	12	54.55%	22	55.00%	10	45.45%	18	45.00%	22	100.00%	40	100.00%
	Analogues Ins + Analogues Ins	30	57.69%	69	53.49%	22	42.31%	60	46.51%	52	100.00%	129	100.00%
	Analogues Ins + ADO/GLP-1 Injection	40	45.98%	107	44.96%	47	54.02%	131	55.04%	87	100.00%	238	100.00%
	Analogues Ins + Analogues Ins + ADO/GLP-1 Injection	13	43.33%	28	27.72%	17	56.67%	73	72.28%	30	100.00%	101	100.00%
2	**Human Insulin**	**9**	**60.0%**	**19**	**57.6%**	**6**	**40.0%**	**14**	**42.4%**	**15**	**100.0%**	**33**	**100.0%**
	Single Human Insulin	3	100.00%	7	100.00%		0.00%		0.00%	3	100.00%	7	100.00%
	Human Ins+ADO/GLP-1 Injection	6	50.00%	12	46.15%	6	50.00%	14	53.85%	12	100.00%	26	100.00%
3	**Combination of Human Insulin and Analogues Insulin**	**29**	**74.4%**	**62**	**78.5%**	**10**	**25.6%**	**17**	**21.5%**	**39**	**100.0%**	**79**	**100.0%**
	Analogues Ins + Human Ins	18	78.26%	37	86.05%	5	21.74%	6	13.95%	23	100.00%	43	100.00%
	Analogues Ins + Human Ins + ADO/GLP-1 Injection	11	68.75%	25	69.44%	5	31.25%	11	30.56%	16	100.00%	36	100.00%

N=number of patients, V=number of visit

Health Information: Jurnal Penelitian, 2021, vol. 13, no. 2, July-December, ISSN: 2085-0840 / 2622-5905

Insulin onset of action could be classified as rapid-acting, short-acting, intermediate-acting, and long-acting. Based on its onset of action, it was found that in 2016 and 2017, the most frequent insulin used was the combination of long-acting analogue insulin with OAD, followed by the combination of rapid-acting and long-acting analogue insulins with OAD. Basal insulin was administered once per day, while prandial insulin was three times after each meal (Table 5). Nevertheless, insulin therapy could be administered according to the patients' convenience as long as it sufficed their physiological needs. Analogue basal insulin was safe to reduce postprandial plasma glucose level (as HbA1c contributor) due to its minimal hypoglycemic effect compared to other insulins. It could reduce HbA1c to 2% (Fahmiyah & Latra, 2016; Gamayanti et al., 2018).

Table 6
Insulin Therapy Based on Onset of Action

No	Insulin Based on Time of Action	Year 2016				Year 2017				Total			
		N	%	V	%	N	%	V	%	N	%	V	%
1	Human ins short acting	3	100.00%	7	100.00%		0.00%		0.00%	3	100.00%	7	100.00%
2	Combination of short acting human insulin and ADO (antidiabetic oral)	2	33.33%	2	22.20%	4	66.67%	7	77.80%	6	100.00%	9	100.00%
3	Combination of intermediate acting human insulin and ADO	3	50.00%	5	38.50%	3	50.00%	8	61.50%	6	100.00%	13	100.00%
4	Combination of intermediate acting human insulin and GLP1	1	100.00%	1	100.00%		0.00%		0.00%	1	100.00%	1	100.00%
5	Single analogues insulin long acting	1	14.29%	1	10.00%	6	85.71%	9	90.00%	7	100.00%	10	100.00%
6	Premixed analogues insulin	2	50.00%	5	50.00%	2	50.00%	5	50.00%	4	100.00%	10	100.00%
7	Single analogues insulin rapid acting	7	70.00%	14	77.80%	3	30.00%	4	22.20%	10	100.00%	18	100.00%
8	Combination rapid acting insulin analogues and long acting analogues insulin	26	52.00%	53	46.10%	24	48.00%	62	53.90%	50	100.00%	115	100.00%
9	Combination long acting analogues ins and rapid acting analog ins and ADO	5	62.50%	9	69.20%	3	37.50%	4	30.80%	8	100.00%	13	100.00%
10	Combination long acting analogues ins and short acting human insulin	18	78.26%	35	85.40%	5	21.74%	6	14.60%	23	100.00%	41	100.00%
11	Combination long acting analogues ins and ADO	36	50.70%	90	48.90%	35	49.30%	94	51.10%	71	100.00%	184	100.00%
12	Combination long acting analogues ins and GLP1	5	83.33%	10	66.70%	1	16.67%	5	33.30%	6	100.00%	15	100.00%
13	Combination long acting analogues ins and premixed analogues ins	2	100.00%	7	100.00%		0.00%		0.00%	2	100.00%	7	100.00%
14	Combination long acting analogues ins and premixed analogues ins and ADO	2	66.67%	5	62.50%	1	33.33%	3	37.50%	3	100.00%	8	100.00%
15	Combination long acting analogues ins and premixed analogues ins and GLP1	1	100.00%	1	100.00%		0.00%		0.00%	1	100.00%	1	100.00%
16	Combination long acting analogues ins and rapid acting analogues ins and GLP1	9	40.91%	18	23.40%	13	59.09%	59	76.60%	22	100.00%	77	100.00%
17	Combination short acting human ins and long acting analogues ins and GLP1	6	66.67%	16	76.20%	3	33.33%	5	23.80%	9	100.00%	21	100.00%
18	Combination short acting human ins and long acting analogues ins and ADO	1	33.33%	1	25.00%	2	66.67%	3	75.00%	3	100.00%	4	100.00%
19	Combination short acting human insulin and GLP1	2	100.00%	5	100.00%		0.00%		0.00%	2	100.00%	5	100.00%
20	Combination premixed human ins and long acting analogues ins and ADO	2	66.67%	6	66.70%	1	33.33%	3	33.30%	3	100.00%	9	100.00%
21	Combination rapid acting analogues insulins and GLP1	1	50.00%	2	66.70%	1	50.00%	1	33.30%	2	100.00%	3	100.00%
22	Combination rapid acting analogues insulins and ADO	2	22.22%	6	27.30%	7	77.78%	16	72.70%	9	100.00%	22	100.00%
23	Combination premixed analogues insulin and ADO	3	27.27%	6	27.30%	8	72.73%	16	72.70%	11	100.00%	22	100.00%
24	Combination long acting analogues ins and intermediate acting human ins and ADO	1	100.00%	1	100.00%		0.00%		0.00%	1	100.00%	1	100.00%
-	-	27	60.00%	57	58.80%	18	40.00%	40	41.20%	45	100.00%	97	100.00%
	Total	**168**	**54.55%**	**363**	**50.90%**	**140**	**45.45%**	**350**	**49.10%**	**308**	**100.00%**	**713**	**100.00%**

Based on commercial brands, in 2016 the most frequently prescribed human insulin was Humulin R (short-acting) produced by Eli Lilly Co. Ltd., Canada. Eli Lilly Canada Humulin R was administered in combination with Levemir (long-acting analogue insulin), a trademark of Novo Nordisk Co. Ltd. Novo Nordisk The most frequently prescribed analogue insulin was Lantus Solostar (long-acting), a trademark of Sanofi Co. Ltd. Sanofi (Table 6).

In 2017, human insulin was no longer prescribed. In 2016, human insulin (Humulin R) combined with analogue insulin (Levemir) was 17.56%. In 2017 its use decreased to 1.77%. The most frequently prescribed analogue insulin was Lantus Solostar both single and combination. Lantus Solostar was a trademark of Sanofi Co. Ltd. Sanofi (Table 7).

Table 7
Percentage of Insulin Use in Patients on Products Brands

NO	BRANDS	YEAR 2016	YEAR 2017	YEAR 2016 - 2017
1	Humulin R + Levemir	17,56	1,77	8,97
2	Lantus Solostar	17,20	29,79	24,36
3	Levemir	15,77	6,74	10,42
4	Levemir + Novorapid	14,34	3,19	9,46
5	Novorapid	5,73	6,38	6,57
6	Apidra + Lantus Solostar	5,38	12,41	8,49
7	Humulin R	4,30	2,48	3,37
8	Novorapid + Lantus Solostar	3,94	6,74	5,13
9	Novomix	3,23	5,32	5,13
10	Levemir + Apidra	2,87	11,35	6,57
11	Levemir + Novomix	2,87	0,00	1,28
12	Humulin N	2,15	2,13	2,24
13	Mixtard + Lantus Solostar	1,79	1,42	1,44
14	Lantus Solostar + Novomix	1,43	1,42	1,28
15	Humulin R + Lantus Solostar	0,72	1,42	0,96
16	Levemir + Humalog	0,36	5,32	3,04
17	Levemir + Humulin N	0,36	0,00	0,16
18	Apidra	0,00	0,35	0,32
19	Lantus Solostar + Humalog	0,00	1,77	0,80

Cost Evaluation

One-month treatment cost was defined as the treatment cost of type-2 DM patients for 30 days or 1 month. The average one-month treatment cost of type-2 DM patients with insulin therapy within the period of 2016-2017 was Rp4,033,930.71. The highest cost occurred in December 2017 and the lowest cost in July 2016. One-month medication cost took the highest portion of the treatment cost with an average proportion of 75.16%. Compared to 2016, there was an increase in the average proportion as much as 5.53% in 2017.

Medication cost consisted of insulin, DM and non-DM drugs. The average cost of type-2 outpatients within the period of 2016-2017 was Rp3,047,419.10, of which the highest cost was insulin taking an average of Rp1,113,779 per month. In 2016, the highest percentage of one-month medication cost was insulin, while in 2017 was non-DM drugs.

DM medication cost consisted of insulin cost, which is the cost incurred due to the use of human and analogue insulins as well as the combination of human insulin with analogue insulin or with OAD/GLP-1. Non-DM medication cost was a cost incurred due to the therapy of DM comorbidities. The average cost of DM medication with the period of 2016-2017 was Rp923,623, while non-DM drugs Rp960,804. The proportion of DM and non-DM medications was not much different only 2%.

In 2016, the lowest treatment cost of type-2 DM patients based on the insulin types use from 2016 to 2017 was the use of single human insulin, while the highest was the combination of analogue insulin and analogue insulin with OAD/GLP-1. Single analogue insulin cost was higher than single human insulin. The combination of human insulin with OAD/GLP-1 cost was lower than the combination of analogue insulin with OAD-GLP-1.

The average cost of single human insulin was lower than other insulin therapies. The average cost of single human insulin was lower than single analogue insulin, although the difference was not much. This was in line with a study conducted by Luh Putu Febryana Larasanty et.al. stating that the treatment cost of type-2 DM outpatients in Denpasar treated with single human insulin was lower than other types of insulin (Gamayanti et al., 2018). Post-Hoc Mann-Whitney Difference Test on the Treatment Cost

The average treatment cost of single human insulin was Rp1,597,066, while single analogue insulin was Rp2,497,535, which was higher than the average treatment cost of single human insulin. The average medication cost of single human insulin incurred to type-2 DM outpatients within the period of 2016-2017 was lower than single analogue insulin. This was in line with a study conducted by Dyah Retnaningrum et.al. stating that the treatment cost of type-2 DM outpatients in RSUD Tarakan treated with single human insulin was lower than other types of insulin (Larasaty et al., 2017), also studies conducted by Jing Luo,MD and Migdalis,IN (Retnaningrum et al., 2021; Luo, 2017)

The combination of single analogue insulin with OAD/GLP-1 was not significantly different from the combination of human insulin with analogue insulin. The average treatment cost of analogue insulin combination was Rp 3,449,352, while the combination of human insulin with analogue insulin was Rp3,429,082.

The group of human insulin with OAD/GLP-1 combination and analogue insulin with OAD/GLP-1 showed an insignificant difference. The medication cost of human insulin with OAD/GLP-1combination was Rp3,372,068. The medication cost of analogue insulin combination was Rp3,449,352.

This study found that there was a significant difference in the medication cost of single human insulin and single analogue insulin. The combination of human insulin with OAD/GLP-1 and the combination of analogue insulin with OAD/GLP-1, however, showed no significant difference. This confirmed the hypothesis that human insulin treatment is cheaper than analogue insulin one.

Clinical outcomes based on the types of insulin. The human insulin clinical outcomes of FPG test resulted in the lowest average value of 103.3 mg/dL or 66.7%. The combination of human insulin and OAD/GLP clinical outcomes of 2HPP test resulted in the lowest average value of 153.5% and 73.3%. Meanwhile, the combination of analogue insulin and OAD/GLP1 clinical outcomes of

HbA1c test resulted in 28.3% with a glucose level of 7.3 mg/dL. The analysis of FPG Clinical Outcomes with Kruskal-Wallis Difference Test.

Kruskal-Wallis test on the FPG clinical outcome resulted in p-value (Sig.) as much as 0.000 (Sig. < 0.05). Because the probability value (p-value) was 0.000 < a = 0.05, null hypothesis (H0) was rejected. It was concluded, therefore, that there was a significant difference between types of insulin (at least there was one pair of a type that was significantly different). There was the best different clinical outcomes between insulin combination of analogue insulin + analogue insulin + OAD/GLP1 injection with a mean rank of 86.02. The best different clinical outcome of non-combination insulin was human insulin with a mean rank of 69.83.

Based on Kruskal-Wallis test to 2HPP clinical outcomes, the p-value (Sig.) was 0.000 (Sig. < 0.05). Because the probability value (p-value) was 0.000 < a = 0.05, null hypothesis (H0) was rejected. It was concluded, therefore, that there was a significant difference between types of insulin (at least there was one pair of type that was significantly different). There was the best different clinical outcomes between insulin combination of human insulin + OAD/GLP1 injection with mean rank of 58.87). The best different clinical outcome of non-combination insulin was analogue insulin with mean rank of 115.86. The result of 2HPP Clinical Outcomes with Kruskal-Wallis Difference Test. Based on Kruskal-Wallis test to HbA1c clinical outcomes, the p-value (Sig.) was 0.000 (Sig. < 0.05). Because the probability value (p-value) was 0.991 > a = 0.05, null hypothesis (H0) was accepted. It was concluded, therefore, that there was no significant difference between all types of insulin based on HbA1c clinical outcomes.

Post-Hoc Test of Clinical Outcomes Difference Using Mann-Whitney U Test. Based on the post-hoc Mann-Whitney test on the clinical outcomes of 28 groups of insulin pairs showed that there were no significant differences in the clinical outcomes of several groups of insulin pairs. The groups showing a significant difference in their clinical outcomes were FPG and 2HPP. Post-hoc Mann-Whitney test on the FPG clinical outcomes showed a significant difference in single human insulin with the combination of analogue and human insulin. Post-hoc Mann-Whitney test on the 2HPP clinical outcomes showed an insignificant difference in single human insulin with the combination of analogue and human insulin. Meanwhile, the post-hoc Mann-Whitney test on the 2HPP clinical outcomes showed a significant difference in single human insulin with the combination of analogue and human insulin. The post-hoc Mann-Whitney test on the HbA1c clinical outcomes showed an insignificant difference between human and analogue insulin.

CONCLUSION

The medication profile of type-2 DM outpatients treated by insulin at MMC Hospital year 2016-2017 showed that analogue insulin was administered more frequently than human insulin. Single analogue insulin was used 81.93%, human analogue 5.33%, and the combination of human and analogue insulin 12,74%. In 2016-2017 the average cost of treatment in outpatient type 2 DM patients who used single insulin was Rp 1,597,066 which was lower than that of single

analogue insulin, which was Rp 2,497,538. There was no significant difference in the clinical outcomes of HbA1c using human and single insulin, but the clinical outcomes of FPG and 2HPP showed a significant difference.

Acknowledgments

The author gratefully acknowledges and thanks the Metropolitan Medical Centre for providing facilities for this research.

REFERENCES

18th Expert Committee on the Selection and Use of Essential Medicines. (2011). Review of the Evidence Comparing Insulin (Human or Animal) With Analogue Insulins. *Analogue Insulins, FEBRUARY*, 1–51.

Casner, S. W., Campbell, D. E., & Early, R. G. (1968). A five-week cardiovascular conditioning program. *Journal of Sports Medicine and Physical Fitness, 8*(4), 236–240.

Edition, S. (2015). *IDF Diabetes Atlas, the Seventh Edition*.

Fahmiyah, I., & Latra, I. N. (2016). Faktor yang Memengaruhi Kadar Gula Darah Diabetes RSUD Dr. Soetomo Surabaya Menggunakan Regresi Probit Biner. *Jurnal Sains Dan Seni ITS, 5*(2), 456–461.

Firni Dwi Sari, Inayah, M. Y. H. (2016). Pola Penggunaan Obat Anti Hiperglikemik Oral Pada Pasien Diabetes Tipe 2 Rawat Inap Di Rumah Sakit X Pekan Baru Tahun 2014. *JOM FK, 3 No 1*, 1–14.

Gamayanti, K. ayu V., Ratnasari, N. L. M. N., & Bhargah, A. (2018). Pola penggunaan insulin pada pasien diabetes mellitus tipe 2 di poli penyakit dalam RSU Negara Periode Juli—Agustus 2018. *Intisari Sains Medis, 9*(3), 68–73. https://doi.org/10.15562/ism.v9i3.306

Hartman, I. (2008). Insulin analogs: Impact on treatment success, satisfaction, quality of life, and adherence. *Clinical Medicine and Research, 6*(2), 54–67. https://doi.org/10.3121/cmr.2008.793

Hemkens, L. G., Grouven, U., Bender, R., Günster, C., Gutschmidt, S., Selke, G. W., & Sawicki, P. T. (2009). Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: A cohort study. *Diabetologia, 52*(9), 1732–1744. https://doi.org/10.1007/s00125-009-1418-4

Hikmat, P. (2017). Komplikasi Kronik dan Penyakit Penyerita pada Diabetes. *Medical Care*, 1–5.

Kehlenbrink, S., Mcdonnell, M. E., Luo, J., & Laing, R. (2017). Review of The Evidence on Insulin and Iys Use In Diabetes. *Health Action International Overtoom, 60*(20), 412–4523.

Larasaty, L. P. F., Dewantara Putra, I. G. N. A., & Sarasmita, M. A. (2017). Total Biaya Terapi Insulin Pada Kasus Diabetes Mellitus Tipe 2 Rawat Jalan Di Kotamadya Denpasar. *JURNAL MANAJEMEN DAN PELAYANAN FARMASI (Journal of Management and Pharmacy Practice), 7*(1), 1. https://doi.org/10.22146/jmpf.361

LKPP. (2016). Kepala Lembaga Kebijakan Pengadaan Barang/Jasa Pemerintah Nomor 6 Tahun 2016 Tentang Katalog Elektronik Dan E-Purchasing. *Jdih.Lkpp.Go.Id, 53*(9), 1689–1699.

Luo, J. (2017). *The Fair Price of Analogue Insulin when Compared against Human Insulin: A Systematic Review of Published Cost Effectiveness Studies and a Mathematic Derivation of a Value-based Formula. September*.

Retnaningrum, D., Anggriani, Y., & Tri Kusumaeni, H. U. R. (2021). Evaluasi Outcome Klinis Penggunaan Insulin Analog dan Insulin Manusia pada Pasien DM Tipe 2 JKN Rawat Jalan Tahun 2015-2016 Di RSUD Tarakan. *Syntax Literate#; Jurnal Ilmiah Indonesia, 6*(3), 1149. https://doi.org/10.36418/syntax-literate.v6i3.2375

Soelistijo, S. (2021). Pedoman Pengelolaan dan Pencegahan Diabetes Melitus Tipe 2 Dewasa di Indonesia 2021. *Global Initiative for Asthma*, 46.

Soelistijo, S. A., Novida, H., Rudijanto, A., Soewondo, P., Suastika, K., Manaf, A., Sanusi, H., Lindarto, D., Shahab, A., Pramono, B., Langi, Y. A., Purnamasari, D., Soetedjo, N. N., Saraswati, M. R., Dwipayana, M. P., Yuwono, A., Sasiarini, L., Sugiarto, Sucipto, K. W., & Zufry, H. (2015). Konsensus Pengendalian dan Pencegahan Diabetes Melitus Tipe 2 di Indonesia 2015. In *Perkeni*. https://doi.org/10.1017/CBO9781107415324.004

Notes

Catatan Penerbit: Poltekkes Kemenkes Kendari menyatakan tetap netral sehubungan denganklaim dari perspektif atau buah pikiran yang diterbitkan dan dari afiliasi institusional manapun.

Pernyataan Konflik Kepentingan: Para penulis menyatakan tidak terdapat konflik kepentingan dengan pihak manapun.

Kontribusi Penulis: Tidak dideklarasikan.

Berbagi Data: Tidak ada data yang dibagikan.

Author notes

mannaria.butar4@gmail.com