

**A RETROSPECTIVE COHORT STUDY ON THE
EFFECT OF INTENSIFICATION FROM HUMAN
TO ANALOGUE INSULIN ON GLYCAEMIC
CONTROL AND INSULIN COST IN PATIENTS
WITH TYPE 2 DIABETES MELLITUS IN
HOSPITAL UNIVERSITI SAINS MALAYSIA**

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LIST OF ABBREVIATIONS

HUSM	Hospital Universiti Sains Malaysia
T1DM	Type 1 Diabetes mellitus
T2DM	Type 2 Diabetes mellitus
CPG	Clinical Practice Guideline
HTA	Health Technology Assessment
HbA1c	Hemoglobin A1c
FBS	Fasting Blood Sugar

ABSTRAK (BAHASA MALAYSIA)

Latar belakang:

Kebanyakan diabetes mellitus jenis 2 adalah disebabkan oleh kerintangan serta kekurangan hormon insulin. Penyakit ini dimanifestasi sebagai keadaan hiperglisemia kronik serta gangguan metabolic yang lain. Insulin analog dikaitkan dengan pematuhan yang lebih baik dengan episod hipoglisemik yang lebih rendah, walau bagaimanapun harganya lebih mahal. Matlamat kajian ini adalah untuk menilai keberkesanan intensifikasi daripada insulin manusia kepada insulin analog dan kos tambahannya.

Kaedah:

Kajian retrospektif ini telah dijalankan di klinik pesakit luar di Hospital Universiti Sains Malaysia (HUSM). Pesakit T2DM yang menggunakan insulin analog dikenal pasti daripada pangkalan data farmasi pesakit luar dari 2010 hingga 2020. Pesakit yang menjalani intensifikasi selama sekurang-kurangnya tiga bulan daripada insulin manusia kepada analog dimasukkan dalam kajian. Rekod perubatan pesakit dan keputusan penyiasatan (HbA1c dan FBS) diambil daripada Sistem Preskripsi Dalam Talian (POLS), nota discaj dalam talian dan Sistem Maklumat Makmal (LIS). Jumlah kos pra dan pasca intensifikasi insulin dikira menggunakan harga insulin yang diperoleh daripada farmasi menggunakan Sistem Pengurusan Inventori Farmasi Ubat (SPIFU). Hemoglobin A1c (HbA1c), gula darah puasa (FBS), dan jumlah kos insulin sebelum dan selepas intensifikasi pesakit yang memenuhi kriteria dianalisis menggunakan ujian-t berpasangan.

Keputusan:

Sejumlah 163 pesakit diabetes mellitus jenis 2 yang mengalami intensifikasi insulin manusia kepada analog di HUSM telah dimasukkan dalam kajian ini, yang terdiri daripada 80 (49.1%) lelaki dan 83 (50.9%) perempuan. Umur pesakit adalah antara 27 hingga 75 tahun dengan umur purata 57.87 ± 10.20 tahun. 51 (31.3%) daripada mereka menggunakan insulin basal, 72 (44.2%) menggunakan insulin pracampuran, 16 (9.8%) menggunakan insulin bolus basal dan 24 (14.7%) menggunakan insulin bolus. Kedua-dua tahap HbA1c dan gula darah puasa adalah jauh lebih rendah dalam insulin analog berbanding insulin manusia ($p < 0.05$) masing-masing, namun tidak signifikan secara klinikal kerana pengurangan purata HbA1c adalah kurang daripada 0.5%. Jumlah kos insulin analog selama tiga bulan secara statistik lebih tinggi berbanding insulin manusia (397.55 ± 242.10 vs. 104.70 ± 71.29 ; $p < 0.001$), dengan perbezaan min Ringgit Malaysia 292.85 (95% CI: 265.79, 319.91).

Kesimpulan:

Kesimpulannya, tiada peningkatan yang ketara secara klinikal dalam pesakit HbA1c dan gula darah puasa selepas intensifikasi daripada insulin manusia kepada analog, walaupun kos tambahan yang tinggi dibelanjakan, tidak mengambil kira faktor lain seperti episod hipoglisemia dan pengurangan dalam kemasukan ke hospital dan kadar kematian berkaitan diabetes. Oleh itu, adalah penting bagi doktor untuk memilih kumpulan pesakit yang betul untuk menerima analog insulin untuk memaksimumkan faedahnya, tetapi pada perbelanjaan kos yang paling optimum.

Kata kunci: T2DM, insulin analog, insulin manusia, HbA1c, FBS, perbezaan kos insulin.

ABSTRACT (ENGLISH)

Background:

Type 2 diabetes mellitus (T2DM) is primarily due to insulin resistance and deficiency. It is manifested by a chronic hyperglycaemic state and other metabolic derangements. Uncontrolled T2DM will lead to multiorgan complications, hence the importance of achieving good glycaemic control. Analogue insulins are associated with better adherence with lower hypoglycaemic episodes; however more expensive. This study aims to evaluate the efficacy of intensification from human to analogue insulin and the added cost.

Methods:

This retrospective study was conducted at the medical outpatient clinic at Hospital Universiti Sains Malaysia (HUSM). Patients with T2DM who were on analogue insulin were identified from the outpatient pharmacy database from 2010 to 2020. From this database, patients who underwent intensification for at least three months from human to analogue insulin were included in the study. The patient's medical records and investigation results (HbA1c and FBS) were retrieved from Prescription On – Line System (POLS), online discharge summary and Laboratory Information System (LIS). The total cost pre and post intensification of insulin were calculated using insulin price obtained from the pharmacy using Drug Pharmacy Inventory Management System (SPIFU). Hemoglobin A1c (HbA1c), fasting blood sugar (FBS), and total insulin cost pre and post intensification of patients who fulfilled the criteria were analysed using paired t-test.

Result:

A total of 163 patients with T2DM who had intensification from human to analogue insulin at HUSM were included in this study, which consisted of 80 (49.1%) males and 83 (50.9%) females. The age of the patients ranged between 27 to 75 years old, with a mean age of 57.87 ± 10.20 years old. 51 (31.3%) of them had basal insulin, 72 (44.2%) had premixed insulin, 16 (9.8%) had basal bolus insulin, and 24 (14.7%) had bolus insulin. Both HbA1c and FBS levels were significantly lower in analogue insulin compared to human insulin ($p < 0.05$), respectively, however not clinically significant as the mean reduction of HbA1c is less than 0.5%. Total costs of analogue insulin for three months were statistically higher compared to human insulin (397.55 ± 242.10 vs. 104.70 ± 71.29 ; $p < 0.001$), with a mean difference of Ringgit Malaysia 292.85 (95% CI: 265.79, 319.91).

Conclusion:

In conclusion, there were no clinically significant improvements in patients' HbA1c and FBS after intensification from human to analogue insulin, despite the extra cost spent, not considering other factors such as hypoglycaemic episodes and reduction in hospitalisation and diabetes-related mortality rate. Hence, it is vital that physicians choose the right group of patients to receive insulin analogue to maximise its benefit but at the most optimal cost.

Keywords: T2DM, analogue insulin, human insulin, HbA1c, FBS, insulin cost difference.

CHAPTER 1: INTRODUCTION

Diabetes mellitus (DM) remains one of the most significant causes of morbidity and mortality worldwide, and its global impact is likely to accelerate over the coming decades. DM has several categories. However, the main subtypes are Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM), which result from defective insulin secretion in T1DM or action in T2DM. The pathogenesis for both T1DM and T2DM is substantially different; therefore, each type has different aetiologies, clinical presentations, and treatment approaches (Sapra, 2022).

Worldwide, around 463 million people lived with diabetes in 2019. In Malaysia, it is estimated that 3.9 million (18.3%) of the adult population had raised blood sugar in the same year, and these numbers are expected to increase over the years. Based on National Diabetes Registry Report (2013 – 2019), it was found that the overall trend was also increasing for DM comorbidities, including hypertension and dyslipidemia.

Locally, the prevalence of DM in Kelantan has been reported to be high at 10.5% in 1999 (Mafauzy *et al.*, 1999) and increased to 11.7% in 2010 (Sukminingrum & Radjeni, 2013). In 2011, this state recorded the highest number of diabetic patients compared to other states in Malaysia (Najib *et al.*, 2014). The high number of diabetes cases reported in Kelantan might be due to the sugar-laden local delicacies (Letchuman *et al.*, 2010).

Malaysian Ministry of Health Clinical Practice Guidelines (CPG) on the management of T2DM (6th edition) 2020 recommended that therapy for most patients with T2DM should be targeted to achieve a Hemoglobin A1c (HbA1c) of less than 7%. HbA1c $\leq 6.5\%$ is only for patients with a shorter duration of T2DM, no evidence of significant cardiovascular disease, and longer life expectancy, with a low risk of hypoglycaemia. The goal of treatment is to achieve good glucose control, avoid multiorgan complications and prevent hypoglycaemic episodes in everyday life, as well as minimal weight gain, and this can be done by mimicking, as closely as possible, the serum level of insulin produced in a healthy person (Colquitt, Royle & Waugh, 2003).

Analysis of HbA1c in the blood reflects a patient's average blood sugar levels during the past two to three months, which is equivalent to the predicted half-life of red blood cells. It provides a reliable measure of chronic hyperglycaemia and correlates well with the risk of multiorgan diabetes complications. After initiation of treatment, a reduction of HbA1c of more than 0.5% is deemed clinically significant to gain benefit in terms of reducing long-term diabetic complications National Institute for Health and Care Excellence (NICE Guideline, 2015). Previous guidelines suggested that HbA1c levels be monitored at least every three months. Thus, the cost-effectiveness of insulin intensification can be measured after three months of insulin intensification.

Based on two large scales studies, the UK Prospective Diabetes Study (1998) in T2DM and the Diabetes Control and Complications Trial (1993) in T1DM, reduction HbA1c by 1%, associated with a significant reduction of microvascular complications by 37%. A clinically significant HbA1c decrease is defined as a difference of $\geq 0.5\%$ compared to baseline. This is based on the National Institute for Health and Care Excellence (NICE) guideline in 2015, according to an analysis by Tyndall *et al.* 2019. This is in keeping with another study done in the United States by Maureen J. Lage & Kristina S. Boye (2020). This study revealed that patients with T2DM with a 1% reduction in HbA1c were associated with a 2% reduction in all-cause total healthcare costs and a 13% reduction in diabetes-related healthcare costs ($p < 0.0001$).

In reality, it is difficult to obtain and maintain near-normal concentrations of HbA1c in patients with T2DM. This can be achieved via treatment intensification by adding insulin to improve glucose control. The success of insulin management depends on how closely it can mimic normal physiologic insulin release patterns (Colquitt, Royle & Waugh, 2003).

Human insulin is synthetic insulin created by growing insulin proteins within *Escherichia coli* to mimic insulin in humans created in the laboratory. It is claimed that conventional human insulin cannot provide optimal therapy due to a few limitations, such as weight gain and hypoglycaemic episodes.

Analogue insulin has been designed to mimic physiologic insulin patterns more closely through improved pharmacokinetic characteristics that result in either more rapid or prolonged pharmacodynamics. Rapid-acting analogue insulin, also known as short-acting, can offer a more rapid onset of action and a shorter duration of activity. It can be administered right before eating, producing a rapid and short-lived insulin spike to cater to postprandial glucose rise. This is significantly more convenient for patients than human insulin, which is recommended to be administered roughly 30 minutes before a meal. The long-acting basal insulin analogues have been designed to approach the ideal characteristics of basal insulin by having a relatively flat, 24- hour basal insulin supply with less variability in action.

Over the last decade, the use of human insulin has declined from being the only type of insulin used. In low-income countries, human insulin still comprises over 94% of all insulin. In Malaysia, the use of insulin analogues in public hospitals ranges from 2% to 3%, mainly because of the price- insulin analogues are significantly more expensive (up to three to five times) than human insulin. Healthcare resources are limited in our country, hence the importance of cost analysis to determine whether insulin analogues are justified for all or some diabetic patients (Malaysian Health Technology Assessment Section, 2012).

Based on a study by Shafie and Ng (2020), it was shown that in Malaysia, the total cost for the year 2015 for using NPH insulin, insulin Detemir and insulin Glargine was Ringgit Malaysia 33,182 (US\$ 7887), Ringgit Malaysia 39,209 (US\$9320) and Ringgit Malaysia 38,051 (US\$ 9045) respectively. The cost of analogue insulin is higher than human insulin by Ringgit Malaysia 6,027 for NPH insulin VS Determir,

and Ringgit Malaysia 4869 for NPH VS Glargine, even though the utilisation of insulin in Malaysia is lower than in Australia, based on this study.

This study aims to evaluate the efficacy of intensification from human insulin to analogue insulin and the added cost. No similar study had been done in Malaysia before, where the glycaemic control and cost implication of insulin intensification from human insulin to analogue insulin was evaluated for three months duration. This study will evaluate the practice of insulin use in HUSM specifically, and hopefully, the data will help clinicians to effectively utilise insulin analogue for the management of T2DM patients. This study will give both practical and financial implications regarding hospital costs for future improvements where the resources are finite.

CHAPTER 2: OBJECTIVES OF THE STUDY

2.1 GENERAL OBJECTIVE

To evaluate the change in glycaemic control (HbA1c and FBS) in patients with T2DM who had intensification from human insulin to analogue insulin in HUSM.

2.2 SPECIFIC OBJECTIVES

- i) To evaluate the mean change in glycaemic control (HbA1c and FBS) after intensification from human insulin to analogue insulin.
- ii) To describe the mean change in glycaemic control (HbA1c and FBS) in patients on four different insulin regimes (basal, premixed, basal bolus, bolus) after intensification from human insulin to analogue insulin.
- iii) To describe the change in insulin cost after insulin intensification from human insulin to analogue insulin.

2.3 RESEARCH HYPOTHESIS

Null hypothesis: There is no significant mean difference in glycaemic control after intensification from human to analogue insulin.

Alternative hypothesis: There is significant mean difference in glycaemic control after intensification from human to analogue insulin.

2.4 OPERATIONAL DEFINITION

Type 1 Diabetes mellitus:	characterized by autoimmune destruction of insulin-producing beta cells in the islets of the pancreas. As a result, there is an absolute deficiency of insulin.
Type 2 Diabetes mellitus:	characterised as a diminished response to insulin, defined as insulin resistance.
Fasting Blood Sugar:	glucose level in the serum after an overnight fast. The patient is considered prediabetes if the FBS is between 6.1- 6.9 mmol/L and diabetes if the FBS is ≥ 7.0 mmol/L.
Haemoglobin A1c:	glycated haemoglobin, which identifies average plasma glucose concentration over the period of eight to 12 weeks. The patient is considered prediabetes if the HbA1c is between 5.7 – 6.2% and diabetes if the HbA1c is $\geq 6.3\%$.
Significant HbA1c reduction:	reduction of more than 0.5% from baseline.
Basal insulin:	long acting type of insulin.
Basal bolus insulin:	a combination of long-acting insulin with short/ rapid-acting insulin at mealtimes in different injections.
Bolus:	short/ rapid acting insulin.
Premixed insulin:	fixed component formulations of rapid or short-acting and intermediate or long-acting insulin.

CHAPTER 3: MANUSCRIPT

JOURNAL: Malaysian Journal of Medical Sciences

TITLE: A retrospective cohort study on the effect of intensification from human to analogue insulin on glycaemic control and insulin cost in patients with Type 2 Diabetes in HUSM

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3.1 ABSTRACT

Background:

Type 2 diabetes mellitus (T2DM) is primarily due to insulin resistance and deficiency. It is manifested by a chronic hyperglycaemic state and other metabolic derangements. Uncontrolled T2DM will lead to multiorgan complications, hence the importance of achieving good glycaemic control. Analogue insulins are associated with better adherence with lower hypoglycaemic episodes; however more expensive. This study aims to evaluate the efficacy of intensification from human to analogue insulin and the added cost.

Methods:

This retrospective study was conducted at the medical outpatient clinic at Hospital Universiti Sains Malaysia (HUSM). Patients with T2DM who were on analogue insulin were identified from the outpatient pharmacy database from 2010 to 2020. From this database, patients who underwent intensification for at least three months from human to analogue insulin were included in the study. The patient's medical records and investigation results (HbA1c and FBS) were retrieved from Prescription On – Line System (POLS), online discharge summary and Laboratory Information System (LIS). The total cost pre and post intensification of insulin were calculated using insulin price obtained from the pharmacy using Drug Pharmacy Inventory Management System (SPIFU). Hemoglobin A1c (HbA1c), fasting blood sugar (FBS), and total insulin cost pre and post intensification of patients who fulfilled the criteria were analysed using paired t-test.

Result:

A total of 163 patients with T2DM who had intensification from human to analogue insulin at HUSM were included in this study, which consisted of 80 (49.1%) males and 83 (50.9%) females. The age of the patients ranged between 27 to 75 years old, with a mean age of 57.87 ± 10.20 years old. 51 (31.3%) of them had basal insulin, 72 (44.2%) had premixed insulin, 16 (9.8%) had basal bolus insulin, and 24 (14.7%) had bolus insulin. Both HbA1c and FBS levels were significantly lower in analogue insulin compared to human insulin ($p < 0.05$), respectively, however not clinically significant as the mean reduction of HbA1c is less than 0.5%. Total costs of analogue insulin for three months were statistically higher compared to human insulin (397.55 ± 242.10 vs. 104.70 ± 71.29 ; $p < 0.001$), with a mean difference of Ringgit Malaysia 292.85 (95% CI: 265.79, 319.91).

Conclusion:

In conclusion, there were no clinically significant improvements in patients' HbA1c and FBS after intensification from human to analogue insulin, despite the extra cost spent, not considering other factors such as hypoglycaemic episodes and reduction in hospitalisation and diabetes-related mortality rate. Hence, it is vital that physicians choose the right group of patients to receive insulin analogue to maximise its benefit but at the most optimal cost.

Keywords: T2DM, analogue insulin, human insulin, HbA1c, FBS, insulin cost difference.

3.2 INTRODUCTION

Diabetes mellitus (DM) causes significant morbidity and mortality worldwide, and its impact is likely to increase over the years. Type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) are different; thus, the approaches for treatment are different (1). In Malaysia, it is estimated that 3.9 million (18.3%) of the adult population had raised blood sugar in 2019, which is expected to increase over the years (2). In 2011, Kelantan state recorded the highest number of diabetic patients as compared to other states in Malaysia (5), and this is attributable to the sugar-laden local delicacies (6)

Analysis of Hemoglobin A1c (HbA1c) provides a reliable measure of chronic hyperglycaemia and correlates well with the risk of multiorgan diabetes complications. After initiation of treatment, a reduction of HbA1c of more than 0.5% is deemed clinically significant. Target HbA1c of less than 7% is recommended by the Malaysian Ministry of Health Clinical Practice Guidelines (CPG) on the management of T2DM (6th edition) 2020 (7). The goal of treatment is to achieve good glucose control, avoid multiorgan complications and prevent hypoglycaemic episodes in everyday life. This can be done by mimicking, as closely as possible, the serum level of insulin produced in a healthy person (8).

In low-income countries, human insulin still comprises over 94% of all insulin. In Malaysia, the use of insulin analogues in public hospitals ranges from 2% to 3%, mainly because of the price- insulin analogues are significantly more expensive (up to three to five times) than human insulin. Healthcare resources are limited in our country, hence the importance of cost analysis to determine whether insulin analogues are justified for all or some diabetic patients (17).

Based on a study by Shafie and Ng (2020), it was shown that in Malaysia, the total cost for the year 2015 for using NPH insulin, insulin Detemir and insulin Glargine was Ringgit Malaysia 33,182 (US\$ 7887), Ringgit Malaysia 39,209 (US\$9320) and Ringgit Malaysia 38,051 (US\$ 9045) respectively. The cost of analogue insulin is higher than human insulin by Ringgit Malaysia 6,027 for NPH insulin VS Determir, and Ringgit Malaysia 4869 for NPH VS Glargine, even though the utilisation of insulin in Malaysia is lower than in Australia, based on this study (29).

Based on two large scales studies, reduction HbA1c by 1%, associated with a significant reduction of microvascular complications by 37% (12, 13). A clinically significant HbA1c decrease is defined as a difference of $\geq 0.5\%$ compared to baseline. This is based on the National Institute for Health and Care Excellence (NICE) guideline in 2015, according to an analysis by Tyndall *et al.* 2019 (10, 11). Another study also revealed that patients with T2DM with a 1% reduction in HbA1c were associated with a 2% reduction in all-cause total healthcare costs and a 13% reduction in diabetes-related healthcare costs (39).

Analogue insulin has been designed to mimic physiologic insulin patterns more closely through improved pharmacokinetic characteristics that result in either more rapid or prolonged pharmacodynamics. Rapid-acting analogue insulin can be administered right before eating, producing a rapid and short-lived insulin spike to cater to postprandial glucose rise. This is significantly more convenient for patients relative to human insulin. The long-acting basal insulin analogues have been designed to approach the ideal characteristics of basal insulin by having a relatively flat, 24-hour basal insulin supply with less variability in action (8). The usage of analogue insulin in Malaysia is still limited, mainly due to its price. Healthcare resources are limited in our country, hence the importance of cost analysis to determine whether insulin analogues are justified for all or some diabetic patients (9).

No similar study had been done in Malaysia before, where the glycaemic control and cost implication of insulin intensification from human insulin to analogue insulin was evaluated for three months duration. This study will evaluate the past practice of insulin use in Hospital Universiti Sains Malaysia (HUSM) specifically. Hopefully, the data will help clinicians to effectively utilise insulin analogue for the management of T2DM patients. This study will give both practical and financial implications regarding hospital costs for future improvements where the resources are finite.

3.3 METHODOLOGY

Study population and study design

This retrospective study was conducted at the medical outpatient clinic at Hospital Universiti Sains Malaysia (HUSM). Patients with T2DM who were on analogue insulin were identified from the outpatient pharmacy database from 2010 to 2020. From this database, patients who underwent intensification for at least three months from human to analogue insulin were included in the study. The patient's medical records and investigation results (HbA1c and FBS) were retrieved from Prescription On – Line System (POLS), online discharge summary and Laboratory Information System (LIS). The total cost pre and post intensification of insulin were calculated using insulin price obtained from the pharmacy using Drug Pharmacy Inventory Management System (SPIFU).

The inclusion criteria were those aged 18 years old and above, who previously was on human insulin for at least three months, then switched to analogue insulin for at least three months, diagnosed with T2DM at least one year before inclusion to the study, conversion from human insulin to analogue insulin within the same regime (basal, premixed, basal-bolus, bolus), and also on stable other diabetic medications after intensification to analogue insulin. The exclusion criteria were any emergency hospitalisation episode six months before and after the change of insulin and significant changes in physical activity, dietary habits, and insulin compliance.

The change of Hemoglobin A1c (HbA1c) after intensification of human insulin to analogue insulin were analysed, and the results were categorised based on different insulin regime. A clinically significant change in HbA1c value was defined as a reduction of at least 0.5% from baseline, and the FBS value is targeted to be within a normal range (4.4 – 7 mmol/L). The cost of human and analogue insulin was calculated for three months for each patient, based on the insulin price per unit and total insulin dosage used per day.

1818 T2DM patients on human insulin, then intensified to analogue insulin from 2010 to 2020 in HUSM, were screened. Out of that, 1025 patients were excluded due to incomplete data on glycaemic control (HbA1c and/or FBS). 163 patients fulfilled the inclusion and exclusion criteria.

Statistical analysis

Categorical variables were presented as frequency and percentage, whereas numerical variables were presented as mean and standard deviation for normally distributed variables. To compare mean HbA1c, FBS value, and the three months total cost change pre and post intensification from human insulin to analogue insulin, paired t-tests were used. The statistical significance level was set as p-value values of < 0.05 were reported. All statistical analyses were performed with IBM Statistic Program for Social Sciences (SPSS version 26) software.

Sample size calculation

A priori power analysis was conducted using G*Power 3.1.9.7 (Faul et al. 2007) to determine the minimum sample size required to test the study hypothesis. The result indicated the required sample size to achieve 80% power with an effect size of 0.2, and an α value of 0.05 was 156 patients. 10% drop out was expected thus a total of 172 patients were needed. Paired t-test was used as statistical analysis to reject the null hypothesis that there is no significant mean difference in glycaemic control (HbA1c and FBS) after intensification from human to analogue insulin, thus the obtained 163 patients were adequate to test the study hypothesis.

Ethical issue

Ethical approval was obtained from Jawatankuasa Etika Penyelidikan (Manusia) – JEPeM, Universiti Sains Malaysia on the 13th of March 2022 with study protocol code USM/JEPeM/21120773.

3.4 RESULTS

Socio-demographic data of the patients

A total of 163 patients with T2DM who had intensification from human insulin to analogue insulin at HUSM were included in this study, as shown in Table 3.8.1. This consisted of 80 (49.1%) males and 83 (50.9%) females. The age of the patients ranged between 27 to 75 years old, with a mean age of 57.87 ± 10.20 years old. The majority of the patients were aged 41 – 80 (95%) (Table 3.8.1). Out of 163 patients, 51 (31.3%) of them had basal insulin regime, 72 (44.2%) had premixed insulin regime, 16 (9.8%) had basal bolus insulin regime, and 24 (14.7%) had bolus insulin regime.

Differences in glycaemic control (HbA1c and FBS) before and after the intensification of insulin treatment from human insulin to analogue insulin.

Table 3.8.2 shows the differences in glycaemic controls for both HbA1c and FBS before and after intensification from human insulin to analogue insulin. The results showed statistically significant differences in glycaemic control between human insulin and analogue insulin ($p < 0.05$). Both HbA1c and FBS levels were significantly lower in analogue insulin compared to human insulin, with $p < 0.001$ and $p = 0.004$, respectively.

Differences in glycaemic control for four different insulin regimes before and after intensification from human insulin to analogue insulin.

Table 3.8.3 and Table 3.8.4 showed the differences in HbA1c and FBS for four different insulin regimes (basal, premixed, basal bolus, and bolus) before and after intensification from human insulin to analogue insulin. Only the premixed insulin regimen and bolus insulin regimen had significantly lower HbA1c in analogue insulin compared to human insulin ($p < 0.05$). Meanwhile, there was no significant difference in HbA1c observed in the basal insulin regimen and basal bolus insulin regimen between human insulin and analogue insulin ($p > 0.05$) (Table 3.8.3).

Only the basal insulin regimen showed significantly lower fasting FBS in analogue insulin compared to human insulin (8.81 ± 3.58 vs. 10.23 ± 3.67 ; $p = 0.016$) (Table 3.8.4). Meanwhile, FBS in premixed insulin regimen, basal bolus insulin regimen, and bolus insulin regimen were similar between analogue insulin and human insulin ($p > 0.05$).

Differences in cost between human insulin and analogue insulin for three months.

Table 3.8.5 shows there was a statistically significant difference in mean cost for three months between human insulin and analogue insulin ($p < 0.05$). Costs of using analogue insulin for three months were statistically higher compared to the cost of human insulin (397.55 ± 242.10 vs. 104.70 ± 71.29 ; $p < 0.001$), with a mean difference of 292.85 (95% CI: 265.79, 319.91).

3.5 DISCUSSION

Socio-demographic data of the patients

In this study, the majority of the patients were aged 41 and above, as this study included only T2DM patients (95%). In terms of gender, the proportion of male and female patients was almost similar, as reported in NDR 2013 to 2019 (2). Most of the patients included in this study were on a premixed insulin regime, where the majority of them were switched from biphasic isophane insulin to novomix insulin (44.2%).

Differences in glycaemic control (HbA1c and FBS) before and after the intensification of insulin treatment from human insulin to analogue insulin.

A clinically significant HbA1c decrease is defined as a difference of $\geq 0.5\%$ from the baseline. This is based on the National Institute for Health and Care Excellence (NICE) guideline in 2015, according to an analysis by Tyndall *et al.* 2019 (10, 11). A reduction of HbA1c by 1% is associated with a significant reduction of microvascular complications by 37%, based on two large scales studies, the UK Prospective Diabetes Study 1998 (12) in T2DM and the Diabetes Control and Complications Trial 1993 (13) in T1DM. The target of HbA1c should be individualised based on patients' profiles, where the majority of patients are targeted for HbA1c of less than 7%, as suggested by the 6th edition Clinical Practice Guideline (CPG) 2020 (7).

The mean HbA1c post intensification was still above target HbA1c (9.67%), meaning that patients are still prone to get microvascular and macrovascular complications of T2DM. This study showed a mean HbA1c reduction of 0.45% (p-value <0.05) after intensification to analogue insulin. This reduction does not meet the standard criteria suggested in multiple guidelines to reduce the risk of DM-related complications despite the significant cost difference between human and analogue insulin. The result is consistent with other studies in the past, which measure the mean difference of HbA1c. This might be due to other confounding factors such as poor injection technique, medication adherence, and intolerance towards the intensification of insulin treatment.

In terms of mean change in FBS, there was a statistically significant drop after intensification from human insulin to analogue insulin. Based on our 6th edition CPG 2020 (7), the target FBS for patients on treatment should be between 4.4 to 7 mmol/L. Our results have shown that despite a decrease in FBS level, the mean value was far from our target (9.25 mmol/L)

Differences in glycaemic control of four different insulin regimes before and after intensification from human insulin to analogue insulin

When we further evaluate the mean change of HbA1c and FBS for four different regimes, we can see that only the premixed insulin regimen and bolus insulin regimen had significantly lower HbA1c in analogue insulin compared to human insulin ($p < 0.05$). This result is in contrast to previous studies, as stated by a systemic review by Qayyum *et al.* 2008 (14), where premixed insulin analogues appeared to be similar in lowering HbA1c. The findings of two other randomised controlled trials, by Gao *et al.* 2008 and Li *et al.* 2009 (15, 16), showed that HbA1c control was the same in both human and analogue insulin for the premixed regime. For short-acting insulin, Health Technology Assessment (HTA) report by Barnajee *et al.* 2007 (17) reported no statistically significant differences between insulin lispro and regular human insulin treatments. Likewise, Singh *et al.* 2010 (18) reported that the HbA1c from a pooled analysis of 11 trials involving 3,093 patients was only -0.03% (-0.12 to 0.06%) for insulin lispro. Insulin aspart also did not result in a significant reduction in HbA1c level compared with human insulin, as demonstrated by a pooled analysis of studies based on three systematic reviews by Barnajee *et al.* 2007, Rys P *et al.* 2011, Singh *et al.* 2010 (17 – 19). This difference could be explained by the difference in our study population demography compared to the previous studies and also due to our small sample size.

Based on this small study, it was found that there was no significant difference in HbA1c observed in the basal insulin regimen and basal bolus insulin regimen between human insulin and analogue insulin ($p>0.05$). This is in keeping with many previous studies that were done in the past. Warren *et al.* 2004 (20) showed that there was no evidence that insulin glargine was more effective than NPH insulin in reducing either FBS or HbA1c and some evidence that both insulins were as effective as each other in both FBS and HbA1c control. Mattia *et al.* 2009 (21) conducted a randomised, open-label, two-way cross-over study among T2DM patients treated with insulin glargine versus NPH insulin, and it was reported that both insulin glargine and NPH insulin provided similar improvements in terms of glycaemic control. Two HTA reports by Tran *et al.* 2007 and Waugh *et al.* 2010 (22, 23) and two systematic reviews by Singh *et al.* 2007 and Horvath *et al.* 2009 (18, 24) reported similar HbA1c values for T2DM patients treated with insulin detemir in comparison with NPH insulin.

Differences in cost between human insulin and analogue insulin for three months.

From this study, it was evident that there was a statistically significant difference in mean cost for three months between human insulin and analogue insulin ($p < 0.05$), with a mean difference of RM 292.85 (95% CI: 265.79, 319.91).

A noteworthy finding from this small study was the dramatic increase in terms of insulin cost after intensification from human insulin to analogue insulin for minimal change in HbA1c and FBS. The mean value for both HbA1c and FBS was also far from the optimal value or the target value needed to ensure a significant reduction of microvascular and macrovascular complications of T2DM. However, this is a crude or a simple cost change calculation for three months of use and not an extensive cost analysis, where costs for hospitalisation for episodes of hypoglycaemia, and T2DM-related complications were not included in this study. No similar study had been done in Malaysia before, where the glycaemic control and cost implication of insulin intensification from human insulin to analogue insulin were evaluated for three months duration. However, the ability to avoid hypoglycaemia and better adherence to insulin treatment that have been associated with insulin analogues represent a significant value consideration, probably beyond price. This is based on modelling for cost-effectiveness analyses and also the willingness to pay threshold of each country.

Insulin detemir could be considered as cost-effective in Sweden, the UK, and the USA, but not in Canada (25 – 28). Insulin glargine could also be considered cost-effective in Switzerland and the UK but not in Canada (30, 31). A study done in Malaysia by Shafie and Ng 2020 showed that insulin glargine and insulin detemir were cost-effective (29). However, this study is different from ours, where the aim was to measure the cost effectiveness of long-acting insulin analogue vs NPH insulin in insulin naïve T2DM patients, and the UKPDS-Outcome Model version 2.0 (UKPDS-OM2) was used to evaluate the cost and consequence of diabetes-related complication.

Novomix 30 could be considered cost-effective in the USA, China, and South Korea, while insulin Aspart could be considered cost-effective in Canada, Sweden, Spain, and Italy but not Poland (32 – 35). Insulin lispro was found to be dominant in the UK and was associated with reductions in annual costs of diabetes in Spain by reducing the frequency of severe hypoglycaemia (36, 37).

The drug costs were higher in the insulin analogues group than the conventional human insulin, but this was partly offset by reduced complication costs. However, another study was done to compare the other way round- the effect of changing from analogue insulin back to human insulin. Luo *et al.* in 2019 has found that encouraging diabetes patients to switch from analogue to human insulin was associated with a small increase in population-level HbA1c but with a dramatic reduction in expenditure for insulin cost. The intervention was not associated with changes in rates of serious hypoglycemia or hyperglycemia, based on the report by Luo *et al.* 2019 (38).