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INVESTIGATING HBA1C REDUCTION AND INCIDENTS OF REPORTED HYPOGLYCAEMIA BETWEEN HUMAN INSULINS VERSUS ANALOGUE INSULINS AMONG TYPE 2 DIABETIC MELLITUS PATIENTS - A SINGLE CENTRE, RETROSPECTIVE STUDY

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ABSTRACT
This study aimed to determine the magnitude of difference in terms of HbA1c reduction and exploring the incidents of reported hypoglycaemia among T2DM patients receiving human insulins compared to analogue insulins. This was a retrospective study conducted in one primary public health clinic in Malaysia. All type 2 diabetes patients who fulfilled the inclusion criteria were identified and recruited for analysis. Sugar profiles and incident of reported hypoglycaemia in patients receiving human insulin versus analogue insulin were compared. No significant HbA1c reduction was noted among patients receiving human insulin therapy. Instead, the results showed an increased HbA1c level of 0.11 %, p = 0.347. Meanwhile, for analogue insulin group, a reduction of HbA1c by 0.99 % was observed, p = 0.004. A total of 13 (37.14%) incidents of hypoglycaemia reported among patients receiving human insulin. Meanwhile, 3 (8.57%) incidents of hypoglycaemia were reported in patients receiving analogue insulin. Premixed human insulins and analogue insulins might not perform similarly. Analogue insulin was associated with better HbA1c control and significantly less incidents of reported hypoglycaemia. Optimal control of postprandial blood sugar is equally important.

KEYWORDS: Type 2 Diabetes Mellitus, Human Insulins, Analogue Insulins, HbA1c, Hypoglycaemia.

INTRODUCTION
International Diabetes Federation reported that 10.5 % of world population, which is 536.6 million people worldwide suffered from diabetes in 2021.[1,2] According to the Malaysia National Diabetes Registry Report 2013 to 2019, one in every five adult Malaysians has been diagnosed with diabetes mellitus. Malaysia National Health and Morbidity Survey 2019 also reported that approximately 3.9 million Malaysians are diagnosed with diabetes. The prevalence rate has increased from 13.4 % in 2015 to 18.3 % in 2019.[3] Sun et al. (2022)[2] found out that type 2 diabetes mellitus (T2DM) accounted for over 90 % of the diabetes cases worldwide.[2]

Despite the good safety and efficacy profiles of oral hypoglycaemic agents, exogenous insulins are still often required to achieve target plasma glucose control in T2DM management. Presently, there are increasing number of T2DM patients receiving insulin replacement therapy in addition to oral hypoglycaemic agents.[4] Cahn et al. (2015)[5] suggested the initiation of insulin as the first-line treatment of T2DM for patients who are intolerant to other oral hypoglycaemic drugs and having comorbidities such as chronic renal or hepatic failure or primary beta cell defect. However, the adverse effects and efficacies of insulin products have been varied, therefore insulin products are suggested based on individuals' conditions. According to the World Health Organization guidelines, in low-resource settings, human insulin products, both short-acting regular insulin and intermediate-acting neutral protamine hagedorn (NPH) insulin, are strongly recommended as the insulin of choice; whereas long-acting insulin analogues are reserved for patients with frequent severe hypoglycaemia events following the use of human insulin.[6] Analogue insulin resulted in better blood glucose control (in terms of lowering post-prandial glucose and HbA1c) and lower

rates of hypoglycaemia incidents compared to human insulin, owing to its pharmacokinetics profile.[7]

In fact, postprandial excursion of plasma glucose is an independent risk factor for cardiovascular disease greater than fasting plasma glucose.[8] According to Ketema (2015)[9], decreases in postprandial glucose accounted for the greater decrease in HbA1c than decreases in fasting plasma glucose. Postprandial glucose also showed a better sensitivity, specificity and positive predictive value than fasting plasma glucose. On the contrary, there are studies showing that both human insulins and analogue insulins performed similarly in reducing blood glucose and achieving targeted HbA1c of ≤ 6.5 % without significant changes in the frequency of serious hypoglycemic or hyperglycemic episodes.[10,11,12]

This present study aimed to bridge the gap of knowledge by determining the magnitude of difference in terms of HbA1c reduction and exploring the incidents of reported hypoglycaemia among T2DM patients receiving human insulins compared to analogue insulins.

MATERIALS AND METHODS

Study design and sampling

A retrospective study was conducted at one public health clinic (primary care) in the state of Perak, Malaysia. The source of information was collected from the patients' records in the medical unit of the health clinic. Adult patients with T2DM receiving insulin treatment with a duration of at least 3 months were included in this study, starting from 1st January 2022 to 31st December 2022. Human insulin used was Insugen® 30/70 100 IU/ml whereas analogue insulin utilised was NovoMix-30® 100 IU/ml. The magnitude of difference in HbA1c and the reported hypoglycaemia incidents of both human insulins and analogue insulins was explored. The initial HbA1c and FBG readings were collected in year 2021, serving as the baseline measurements. Second readings were collected in year 2022 and compared with former to check for differences.

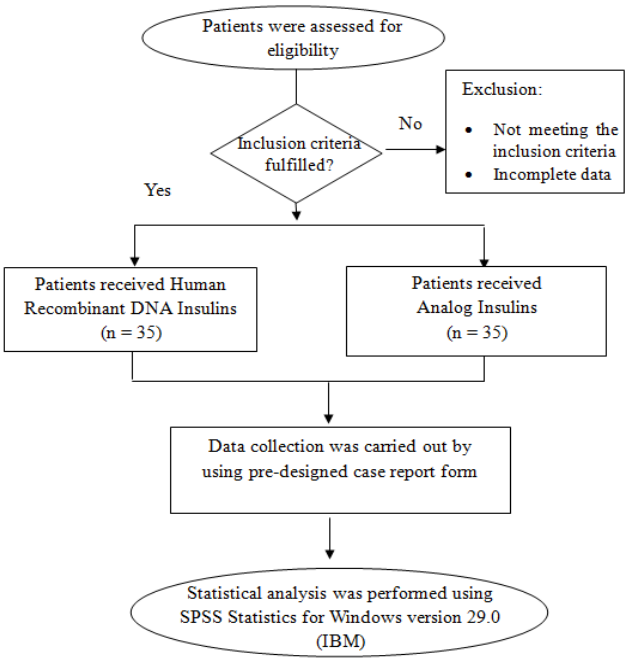

Fig. 1: Methodology Flow Chart.

Sample size calculation

Sample size was calculated using a sample size calculator by Raosoft®, based on the number of patients receiving analogue insulin and human insulin (premixed) registered at the health clinic. In order to achieve a power of 80 % with the confidence interval of 95% and 5% margin error as well as 50% response distribution rate, a minimum sample size of 67 patients was required, and a minimum of 34 patients for each arm.

Ethical considerations

The study was performed in accordance with the principles of the Declaration of Helsinki, as revised in Washington in 2013. This study attained approval from the Medical Research Ethics Committee (MREC), Ministry of Health Malaysia (NMRR ID-23-01929-OK7). Institutional approval was obtained from the district health officer. All data collected were kept strictly confidential, and no identifiable information was collected.

Statistical methods

The statistical analysis was performed by using SPSS Statistics for Windows version 29.0 (IBM). Descriptive statistics was utilized for selected variables. Quantitative data were expressed as mean ± SD or median and interquartile range whereas qualitative data were expressed as frequency and percentages. For those data

which was normally distributed, magnitude of difference of HbA1c was analyzed with an independent T test.

Chi-square test was utilized to determine the difference in the incidents of reported hypoglycaemia between human and analogue insulins treatment groups. Apart from that, binary logistic regression test was used to determine the predictive factors in achieving target HbA1c in T2DM patients receiving either human insulins or analogue insulins. Differences were considered statistically significant if 2-tailed tests estimated at a p-value of less than 0.05 (Lang & Secic, 2006).

RESULTS AND DISCUSSION

Demographic data

A total of 70 T2DM patients were recruited in this retrospective study with 35 patients receiving human insulin and analogue insulin treatment respectively from 1st January 2022 to 31st December 2022. The mean age of the patients receiving human insulin was 61.40 ± 9.74 years old, which was higher than the mean age of patients receiving analogue insulin treatment group (57.31 ± 10.65 years old, p = 0.099). Overall, there were more males (58.5%) than females (41.5%) in this study, however the gender distribution was not significantly different (p=0.145). There were 18 Malay patients, 8 Chinese patients and 9 Indian patients out of 35 patients which stands for 51.43 %, 22.86 % and 25.71 % respectively received human insulins. Meanwhile, for patients receiving analogue insulins, out of 35 patients, 14 Malay patients (40.00 %), 3 Chinese patients (8.57 %) and 18 Indian patients (51.43 %). Based on the results, most of the patients receiving exogenous insulin treatment were Malays (32, 45.7%), followed by Indians (27, 38.6%) and Chinese (11, 15.7%) (p=0.055). The mean duration of T2DM was similar between 2 treatment groups, ranging about 6 years (p=0.33).

Table 1: Demographics of Patients.

Demographic details	Human insulin (*n* = 35) N (%)	Analogue Insulin (*n* = 35) N (%)	p-value
Age (years)	61.40 ± 9.74	57.31 ± 10.65	0.099
Gender Male Female	 17 (48.57) 18 (51.43)	 24 (68.57) 11 (31.43)	0.145
Ethnicity Malay Chinese Indian	 18 (51.43) 8 (22.86) 9 (25.71)	 14 (40.00) 3 (8.57) 18 (51.43)	0.055
Duration of T2DM (years)	6.14 ± 1.69	6.53 ± 1.67	0.330

T2DM = type 2 Diabetes Mellitus

n, number of patients per treatment group. The values were expressed as mean ± standard deviation and counts (percentages over column total). p-values were determined by independent T test.

Magnitude of HbA1c difference

In the human insulin treatment group, the average baseline HbA1c recorded was 9.18 ± 1.97 % whereas the average second HbA1c measured was 9.29 ± 1.93 %. No significant HbA1c reduction among patients receiving human insulin therapy. Instead, the results showed an increased HbA1c level of 0.11 %, p = 0.347. Meanwhile, for analogue insulin group, the mean initial HbA1c level was 9.53 ± 2.25 % and the mean second HbA1c level recorded was 8.54 ± 1.94 %, showing a reduction of 0.99 %, p = 0.004.

In patients receiving human insulin, the average baseline FBG and second FBG observed were 9.33 ± 3.41 mmol/L and 8.01 ± 3.35 mmol/L respectively. For analogue insulin group, the mean baseline FBG and second FBG recorded was 8.89 ± 3.82 mmol/L and 8.51 ± 5.42 mmol/L respectively. Human insulin group had a greater reduction in FBG of 1.32 mmol/L as compared to the reduction of 0.38 mmol/L in analogue insulin group, p > 0.05.

Table 2: Laboratory Data of Recruited Patients between patients receiving Human Insulins and Analogue Insulins.

Laboratory Data	Human insulin (n = 35)	p-value	Analogue Insulin (n = 35)	p-value
Baseline HbA1c (%)	9.18 ± 1.97	0.347	9.53 ± 2.25	0.004
Second HbA1c (%)	9.29 ± 1.93		8.54 ± 1.94	
Baseline FBG (mmol/L)	9.33 ± 3.41	0.123	8.89 ± 3.82	0.634
Second FBG (mmol/L)	8.01 ± 3.35		8.51 ± 5.42	

HbA1c = Haemoglobin A1c; FBG = Fasting Blood Glucose

The values were expressed as mean ± standard deviation and counts (percentages over column total).

P-values were determined by independent T test.

Table 3: Magnitude of difference in terms of HbA1c level and FBG between patients receiving Human Recombinant DNA Insulins and Analog Insulins.

Laboratory Parameters	Magnitude of difference (%)	p-value
Human Recombinant DNA Insulins		
Baseline HbA1c – Second HbA1c	-1.20	0.347
Baseline FBG - Second FBG	14.14	0.123
Analog Insulins		
Baseline HbA1c – Second HbA1c	10.39	0.004
Baseline FBG - Second FBG	4.27	0.634

HbA1c = Haemoglobin A1c; FBG = Fasting Blood Glucose

The values were expressed as mean ± standard deviation. P-values were determined by independent T test. The means with $p < 0.05$ are significantly different and the means with $p > 0.05$ are not statistically significant.

Magnitude of difference of HbA1c is obtained by using the formula of (baseline HbA1c – second HbA1c)/ baseline HbA1c x 100 %.

Magnitude of difference of FBG is obtained by using the formula of (baseline FBG – second FBG)/ baseline FBG x 100 %.

Incidents of reported hypoglycaemia

The incidents and frequency of reported hypoglycaemia between patients receiving human insulins versus analogue insulins were summarised in Table 4. The results showed that 13 patients in the human insulin group (37.14 %) experienced hypoglycaemia. In contrast, in analogue insulins group, there were only 3 patients (8.57 %) encountered hypoglycaemia episodes.

Looking at the frequency of reported hypoglycaemia breakdown among 13 patients who received human insulins, seven patients (20 %) reported 1 episode of hypoglycaemia, three patients (8.57 %) reported 2 hypoglycaemic episodes followed by one patient (2.86 %) experienced 3 hypoglycaemic episodes, one patient (2.86 %) reported 8 episodes of hypoglycaemic attacks and one patient (2.86 %) with 11 episodes of hypoglycaemia. Conversely, out of 3 patients who were receiving analogue insulins and encountered hypoglycaemia, one patient (2.86 %) recorded 1 episode of hypoglycaemia and two patients (5.71 %) recorded 2 episodes of hypoglycaemia, $p = 0.009$. It clearly showed that analogue insulins were associated with fewer reported hypoglycaemia as compared to human insulins.

Table 4: Incidents of reported hypoglycaemia between patients receiving human insulins versus analogue insulins *n*, number of patients per treatment group. The values were expressed whole number and counts (percentages over column total). P-value was determined by chi-square test or fisher exact test (where applicable).

Reported hypoglycaemia	Human insulin (n = 35) N (%)	Analog Insulin (n = 35) N (%)	P-value
Incidents of reported hypoglycaemia			
No (Count)	22 (62.86)	32 (91.43)	
Yes (Count)	13 (37.14)	3 (8.57)	
Frequency of reported hypoglycaemia			
0	22 (62.86)	32 (91.43)	0.009
1	7 (20.00)	1 (2.86)	
2	3 (8.57)	2 (5.71)	
3	1 (2.86)	0 (0)	
8	1 (2.86)	0 (0)	
11	1 (2.86)	0 (0)	

DISCUSSION

Real-world database which included mainly hospital-based clinics found that premixed regimens were the most popular regimen even though basal bolus was also commonly used in Malaysia.[13] This was supported by Karla et al. (2017)[14], in which the preferred type of insulin in Southeast Asian region was premixed insulin. It served as the initial insulin of choice in 75% of T2DM patients. A study conducted by Polinski et al. (2017)[15] found out that the flexibility provided by analogue insulins, allowing for easier integration into daily life and routine activities.

Principal Findings

Results from this study revealed that T2DM patients treated with premixed human insulin did not show statistical significance in reducing HbA1c with a p-value of 0.123. Referring to table 2 and table 3, the magnitude of difference in terms of HbA1c among patients who received human insulins recorded a notable deviation from the expected outcome. Instead of experiencing a reduction in HbA1c, these patients exhibited a 1.20 % increase in HbA1c. The failure of HbA1c reduction could be due to the pharmacology profile of premixed human insulin. Human insulin is monomeric at physiological concentrations in the circulation with 1

nmol/l, but it produces dimers followed by hexamers at greater concentrations which are unable to penetrate the capillary walls. The delayed dissociation of a subcutaneous depot of hexameric human insulin into monomers and dimers results in insufficient plasma concentrations of human insulin to completely establish the normal prandial glucose loadings.[16] This is further supported by the systematic review and meta-analysis conducted by Ketema et al. (2015)[9] which showed that postprandial glucose has a stronger association with HbA1c than FBG. Hence, it is believed that the increased HbA1c in patients receiving premixed human insulin may be due to the sub-optimal control of postprandial plasma glucose. Since around 50% of the day is spent in the post-prandial state, the contribution of post-prandial glucose to HbA1c is significant on top of fasting blood glucose. Monnier at al (2003)[17] reported that post prandial glucose contributed up to approximately 70% of glucose load. Glycaemic targets are more likely to achieved when treating both fasting and post-prandial glucose.

This study showed that the patients who received premixed analogue insulin showed a statistically significance in HbA1c reduction by 10.39%, p = 0.004. This indicated that the premixed analogue insulins achieved better HbA1c control as compared to premixed human insulins. Our findings were in line with the randomized study in Japan by Yamada et al. (2007)[18] which reported that reduction between baseline and endpoint HbA1c was statistically significant greater in premixed insulin analogues compared to premixed human insulin treatment group. In addition, a multicentre, prospective study conducted by Home et al. (2011)[19] demonstrated improved HbA1c control resulted from switching premixed human insulin 30/70 (PHI) to analogue insulin (BIAsp 30). Similarly, IMPROVE observational study by Shah et al. (2009)[20] found that transition from a human premixed insulin to premixed analogues resulted in mean HbA1c reduction of 20 % after 6 months of treatment.

Aligned with the results demonstrated in the previous studies, this study showed that premixed analogue insulins treatment was associated with lower risk of hypoglycaemia as compared to human insulins (p = 0.009). Thirteen patients (37.14 %) who were on premixed human insulins reported hypoglycaemia events whereas only 3 patients (37.14 %) who were on premixed analogue insulins reported hypoglycaemia episodes. The significant lower risk of hypoglycaemia in analogue insulin treatment could be explained by its less glycaemic fluctuation which resulted in a reduced risk of hypoglycaemia as its efficacy profile fitted better with the physiology of insulin secretion.[21]

Comparisons with other studies

In contrast to the present results, other studies reported that analogue insulin achieved similar HbA1c reduction as human insulin. Based on PROGENS BENEFIT observational study in Poland by Nabrdalik et al. (2018)[22], it showed that both premixed human insulin and analogue insulin were equally effective in reducing HbA1c. Similar result was reported in a meta-analysis conducted by Home et al. (2015).[23] Besides, according to Grzeszczak et al. (2010)[24], the survey study concluded that there was no significant difference in terms of HbA1c among T2DM patients treated with premixed human insulin (Gensulin M30) and premixed insulin aspart (NovoMix 30). The differences observed in this study could be explained by several factors. Premixed insulin with rapid-acting insulin analogues should improve glycaemic control in East Asian patients with diabetes because, theoretically, a larger proportion of insulin analogues would be more effective for higher glycaemic-index foods. Since East Asians prefer foods with a higher glycaemic index, like rice than the Western population, this should be beneficial.[18] In addition, Venn (2010)[25] reported that the mean difference in AUC was 29% (95%CI 10, 51) and 63% (95%CI 32, 102) higher in the Asian compared with the Caucasian group following the glucose beverage and cereal, respectively. The glycaemic index (GI) of the cereal was 77(95%CI 66, 90) in the Asian group and 61 (95% CI 55, 67) in the Caucasian group; the values were different (P = 0.01).

FBG reduction was not statistically significant for both premixed human insulin and analogue insulin therapy. There was no significant improvement in FBG reduction among patients who were on premixed human insulin with magnitude difference of 14.14 %, p = 0.123. In the same way, FBG reduction shown no statistically significant among patients who received premixed analogue insulins with magnitude difference of 4.27 %, p = 0.634. A systematic review by Qayyum et al. (2008)[26] found that premixed analogue insulin reduced FBG similarly to premixed human insulin. The study conducted by Grzeszczak et al. (2010)[24] also demonstrated that there was no significant difference in terms of FBG between the study groups using premixed human and analogue insulins. The underlying factor that resulted in the insignificant reduction in FBG could be due to incorrect practice of fasting routine before FBG measurement was taken. Additionally, a single individual's daily fasting glucose readings might fluctuate greatly. Thus, HbA1c remained as the golden standard and served as a reliable indicator in T2DM as advocated by Clinical Practice Guideline instead of FBG measurement.

In line with the results demonstrated in the previous studies, this study showed that premixed analogue insulins treatment was associated with lower risk of hypoglycaemia as compared to human insulins, p = 0.009. It was found that 13 patients (37.14 %) who were on premixed human insulins reported hypoglycaemia events whereas 3 patients (37.14 %) who were on premixed analogue insulins reported hypoglycaemia episodes. The significant lower risk of hypoglycaemia in

analogue insulin treatment could be explained by several well-established advantages of using analogue insulins, including less glycaemic fluctuation which result in a reduced risk of hypoglycaemia due to the better fit with the physiology of insulin secretion.[21]

Majority of the patients experienced 1 to 3 episodes of hypoglycaemia events. However, there were two patients on human insulins encountered 8 and 11 episodes of hypoglycaemia during year 2022. Based on the global HAT study, it was reported that insulin-treated T2DM patients were at risk of experiencing hypoglycaemia in which the annual rate of hypoglycaemia was approximately 2.5 occurrences in each patient.[26] It could be obviously observed that 8 and 11 episodes of hypoglycaemia were the outliers of the results. This could be due to irregular mealtime or practice of skipping meal. This was supported by a cross-sectional analysis by Agrawal et al. (2022)[27] which stated that the habit of irregular meal and skipping a meal disrupted the equilibrium between insulin production and food intake. The blood glucose level began to reduce when a meal was missed and this eventually resulted in a decrease in blood sugar levels in which the risk of hypoglycaemia was increased among the diabetics who were reliant on insulin.[27]

Limitations

Retrospective study relies heavily on accuracy of written record and record keeping. Some important data may not be available or missing leading to excluding a huge number of potential subjects. In addition, this study has a small sample size.

Recommendation

Prospective study with larger sample size and to include measurements of post-prandial blood glucose is highly recommended in future studies.

CONCLUSION

Premixed human insulins and analogue insulins might not perform similarly in terms of reducing HbA1c (efficacy) and incidents of hypoglycaemia (safety). Analogue insulin was associated with better HbA1c control and significantly less incidents of reported hypoglycaemia. It is important to reinstate that the primary goal of treating diabetes is to prevent its long term microvascular and macrovascular complications and to prevent premature death secondary to macrovascular complications. With the growing evidences that postprandial plasma glucose excursion as independent risk factor for cardiovascular disease, optimal control of postprandial plasma glucose is as important as fasting plasma glucose and HbA1c. Controlling postprandial insulin by using human insulin heavily relies on its time of administration and the time of food intake. The unique pharmacokinetics profile of analogue insulins (close mimic to physiological insulin) should be the insulin of choice in treating diabetes.

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