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# A Retrospective Analysis of Insulin Dose in Relation to Body Weight and Glycaemic Control Among Patients with Type 2 Diabetes Mellitus

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**ABSTRACT**

**Purpose**: The progressive nature of Type 2 diabetes mellitus (T2DM) due to declining pancreatic β-cell function frequently requires insulin dose optimization and intensification, resulting in high total daily doses (TDD) of insulin in clinical practice. However, evidence evaluating the relationship between TDD, body weight, and glycaemic control remains limited.
**Methods**: A retrospective cohort study was conducted among adults with T2DM receiving insulin therapy at two primary health clinics between 2020 and 2023 (N=90). Patients were categorised into standard-dose insulin (SDI, n=44) and high-dose (HDI, n=46) insulin groups. The outcomes measured were changes in body weight and follow-up HbA1c. An independent-samples t test was performed to compare outcomes between dose groups and multivariable analyses was conducted to identify factors associated with body weight change and HbA1c.
**Results**: Patients in the SDI group had a smaller mean body weight change than those in the HDI group (3.07±4.90 vs 5.57±6.69kg; mean difference −2.50 kg, 95% CI −4.95 to −0.05; p = 0.045). Mean follow-up HbA1c was higher in the HDI group (10.39±1.86%) compared with the SDI group (9.55±1.95%), with a between-group difference of −0.84% (95% CI −1.64 to −0.04; p = 0.040). TDD and pre-insulin body weight showed statistically significant associations with body weight change. Age, use of metformin and dipeptidyl peptidase-4 (DPP-4) inhibitors, insulin analogue, and mixed human/analogue regimens showed statistically significant associations with HbA1c.
**Conclusion**: Higher insulin doses were associated with greater body weight change and higher HbA1c. However, prospective studies are needed to clarify temporal relationships and to formulate insulin optimization strategies.

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**Introduction**

Diabetes is well known to be a global epidemic with a healthcare cost of USD 966 billion. In 2021, the International Diabetes Federation reported that 537 million people are living with diabetes worldwide. The total prevalence of diabetes is expected to increase to 1.31 billion by 2050. Out of this number, 49.6% is contributed by obesity.[1] The significant incline is largely due to Type 2 Diabetes Mellitus (T2DM).[2] which comprises of approximately 96% of all diabetes cases. T2DM has a strong genetic predisposition and a linkage with obesity and sedentary lifestyle. High body mass index (BMI) is the main risk factor for T2DM globally.[1]

In Malaysia, an estimated 3.9 million adults aged 18 years and above were living with diabetes in 2019, corresponding to approximately one in five Malaysians. This burden is expected to increase in parallel with global trends.[3] Data from the National Diabetes Registry Report 2019 indicate that T2DM accounts for 99.3% of all diabetes cases in the country.[4] Concurrently, the prevalence of overweight and obesity has risen substantially, with findings from the National Health and Morbidity Survey 2023 reporting that 54.4% of Malaysians are overweight or obese, representing a 10% rise in prevalence of overweight, obesity, and abdominal obesity between 2011 and 2023.[5] The coexistence of T2DM and obesity poses a major challenge for long-term disease management.

The management of T2DM involves a stepwise approach that includes lifestyle modification, oral glucose-lowering drugs (OGLDs), and injectable therapies. According to the American Diabetes Association and local clinical practice guidelines, insulin therapy is indicated when glycaemic targets are not achieved despite maximal tolerated doses of OGLDs, in the presence of symptomatic hyperglycaemia, markedly elevated HbA1c levels (>10%), or fasting plasma glucose (FPG) exceeding 13 mmol/L. Following initiation, insulin doses are titrated based on self-monitoring of blood glucose (SMBG).Further treatment intensification such as the addition of prandial insulin or switching to premixed insulin regimens is recommended when glycaemic targets remain unmet.[6,7] These strategies often result in progressive increment in the total daily dose (TDD) of insulin.

While insulin remains an effective therapy for glycaemic control, high insulin doses and sustained hyperinsulinemia are gradually recognised as clinical concerns that warrant careful evaluation.[6] Insulin is an anabolic hormone that promotes energy storage by facilitating glucose uptake, stimulating lipogenesis, and inhibiting lipolysis in adipose and muscle tissues.[8,9] Insulin-associated weight gain (IAWG) has been reported more frequently with non-physiological insulin exposure, particularly at higher systemic doses, which may disrupt normal metabolic regulation.[6,10] Observational evidence suggests that individuals receiving insulin therapy experience greater weight gain and consume higher calories compared with those treated with OGLDs alone.[11] Additionally, higher TDDs have been associated with higher BMI.[12]

Moreover, hypoglycaemia, an important adverse effect of insulin therapy, may also complicate weight management. Episodes of hypoglycaemia often lead to compensatory caloric intake and may contribute to weight gain over time. In studies reflecting contemporary insulin optimisation and intensification practices, severe hypoglycaemic episodes have been reported among patients receiving intensive insulin regimens. Such events have been associated with weight gain despite improvements in HbA1c at follow-up.[13] Furthermore, some studies have observed that a higher proportion of patients treated with insulin experienced concurrent weight gain and worsening glycaemic control compared with those receiving OGLDs alone, although findings have been inconsistent and not uniformly statistically significant.[11] These mixed results highlight the complexity of balancing glycaemic control against unintended metabolic consequences.

In resource-limited settings, where access to newer glucose-lowering agents may be restricted, insulin dose escalation is often relied upon to achieve glycaemic targets. This underscores the need to better understand the relationship between insulin dosing, body weight change, and glycaemic control in real-world clinical practice. Therefore, this study aimed to compare body weight changes and glycaemic control between HDI and SDI groups among individuals with T2DM.

**Methods**

This was a retrospective cohort study that was conducted in Klinik Kesihatan Merlimau and Klinik Kesihatan Umbai, Melaka. Klinik Kesihatan Merlimau is a primary healthcare clinic with the largest number of active T2DM patients yearly in the state of Melaka. Klinik Kesihatan Umbai was selected as our next study site since it is geographically close to Klinik Kesihatan Merlimau with the second largest number of active T2DM patients at the time of study. The index date was defined as the clinic visit during the study period at which the patient met eligibility criteria and had complete baseline data. The clinical study timeline and operational definitions have been summarized in Figure S1.

A list of patients prescribed with insulin from 2020 to 2023 was generated through electronic pharmacy records. Individuals with T2DM aged 18 years old and above who were on insulin therapy with or without the use of concurrent OGLDs were recruited in this study. Patients were excluded if they fulfilled any of the following criteria: prescribed with medications causing weight gain, had clinical evidence of low hemoglobin count, malignancy, gestational diabetes, unable to be weighed (for example: wheelchair bound), incomplete medical records or defaulted follow-ups. Patients were categorized into SDI or HDI if the TDD of insulin is <1.5u/kg/day or ≥1.5u/kg/day respectively in accordance with our Malaysian Clinical Practice Guidelines for management of T2DM.[6] The TDD of insulin threshold was selected as 1.5 units/kg/day based on recommendations from our local practice guidelines which highlight high insulin dose requirements exceeding 1.5units/kg/day as warranting assessment for underlying causes or secondary problems.[6]

Demographic and relevant clinical data were extracted to assess clinical outcomes. Baseline body weight was defined as the body weight prior to insulin initiation. Glycemic control parameters such as HbA1c, FPG, RBS were extracted at baseline (closest measurement within ±3 months of the index date) and at follow-up (closest measurement within 6–12 months after baseline, or the nearest available within a pre-specified window). Changes in body weight were calculated as follow-up minus baseline. Follow-up HbA1c is defined as the closest measurement 3 months after the index date.

**Sample Size Calculation**

The primary outcome of this study was comparing the mean change of body weight and follow-up HbA1c between SDI and HDI. Adapting from previous literature that investigated the trend of high dose insulin usage among diabetes patients in the UK, the mean body weight for standard dose and high dose insulin users are 89.2 ± 20.6 and 106.2 ± 23.6 respectively.[14] To achieve 80% power at a two-sided significance level of 0.05 using a two-sample independent test, a minimum sample size of 27 per group was required. To account for missing data, the sample size was increased to a total of 100 patients. Sample size was calculated utilizing the equation from Kim HY 2015.[15]

**Statistical Analysis**

Data analysis was conducted with the IBM® Statistical Package for the Social Sciences (SPSS) version 23.0 (IBM Corp., Chicago, IL, USA). The principles of the Declaration of Helsinki and the Malaysian Good Clinical Practice Guidelines were adhered by researchers. Descriptive statistics were used to summarise patients'

baseline characteristics. Inspection of histograms revealed that body weight change and follow-up HbA1c were normally distributed for both SDI and HDI groups. Thus, independent-samples t test was employed to compare mean changes in body weight and follow-up HbA1c between both groups. The assumption of homogeneity of variances was evaluated using Levene's test. Welch's t-test was adjusted and reported since the variances were unequal for mean body weight change.

Data completeness was systematically evaluated for all variables. The pattern of missing data was determined using the Little's Missing Completely at Random (MCAR) test. In order to prevent bias and sample attrition, multiple imputation (MI) via using Fully Conditional Specification (FCS) was conducted. Consequently, five imputed datasets (m=5) were produced across 10 iterations per model. Continuous and categorical variables were imputed by linear and binary logistic regression models respectively. In addition, to preserve parameter covariance, auxiliary demographic and clinical covariates were entered into the imputation model. Pooled parameter estimates were obtained across all imputed datasets in agreement with Rubin's rules.

Univariate linear regression analyses were conducted to examine the association between each potential predictor with body weight change and follow-up HbA1c. Variables with p-values of ≤0.25 and potential clinical covariates were subsequently entered into multivariable linear regression (MLR) models. An enter selection method was applied to derive the final models. Insulin dose classification was omitted from the final MLR to prevent multicollinearity with TDD. Pooled model fit was evaluated using the coefficient of determination ($R^2$ and adjusted $R^2$) and overall model significance (F test).

The assumptions for MLR models were tested. Multicollinearity was assessed using the Variance Inflation Factor (VIF) and tolerance. Durbin-Watson statistics was employed to verify residual independence. Normality and homoscedasticity were inspected visually using standardized residual histograms, normal P-P plots, and residual scatterplots. The model was evaluated for influential outliers by employing Cook's distance. Variables with p-values of <0.05 in the MLR model were considered statistically significant. Furthermore, sensitivity analyses using continuous measurement of in TDD (u/day and u/kg/day) and alternative thresholds of (1.0u/kg/day, 1.25u/kg/day, 1.75u/kg/day, 2.0u/kg/day) were conducted to determine the robustness of both models as represented in Table S1 and S2.

**Results**

At completion, a total of 90 patients was included in this study. Table 1 represents the baseline characteristics of these patients according to the dose classification of insulin. Variables such as FBS, number of T2DM medications, combination of insulin, and TDD were found to be significantly different between the SDI and HDI groups ($p < 0.05$). The mean duration of insulin treatment was longer in the HDI group than in the SDI group (10.30 years versus 8.91 years), although this difference was not statistically significant ($p = 0.070$). Patients in the HDI group had a higher median number of T2DM medications compared to the SDI group ($p < 0.001$).

**Table 1** Baseline characteristics according to Dose Classification of Insulin

| Variables | SDI (n=44) | HDI (n=46) | P value |
|---|---|---|---|
| Age | | | |
| Mean age, y (SD) | 59.61 (10.74) | 56.26 (11.19) | 0.15[a] |
| Gender | | | |
| Male | 19 (43.2) | 12 (26.1) | 0.088[b] |
| Female | 25 (56.8) | 34 (73.9) | |
| Ethnicity | | | |
| Malay | 39 (88.6) | 43 (93.5) | 0.514[c] |
| Chinese | 2 (4.5) | 0 (0.0) | |
| Indian | 3 (6.8) | 3 (6.5) | |
| Duration of T2DM | | | |
| Mean duration of T2DM, y (SD) | 16.52 (4.57) | 17.26 (5.90) | 0.510[a] |
| ≤10 | 4 (9.1) | 5 (10.9) | >0.999[c] |
| >10 | 40 (90.9) | 41 (89.1) | |
| Medical conditions (n) | | | |
| Mean number of medical conditions, n (SD) | 2.36 (1.31) | 2.00 (1.01) | 0.146[a] |
| Combination of OGLD | | | |
| Metformin only | 32 (72.7) | 35 (76.1) | 0.085[c] |
| Metformin + SGLT2i | 3 (6.8) | 0 (0.0) | |
| Metformin + DPP4i | 1 (2.3) | 4 (8.7) | |
| Metformin + SGLT2i + DPP4i | 0 (0.0) | 1 (2.2) | |
| Not on any OGLD | 8 (18.2) | 4 (8.7) | |
| Monotherapy SGLT2i or DPP4i | 0 (0.0) | 2 (4.3) | |
| Number of T2DM medications (n) | | | |
| Median number of T2DM medications, n (IQR) | 2.00 (1.00) | 3.00 (0.00) | **<0.001**[d] |
| Combination of insulin | | | |
| Human | 40 (90.9) | 32 (69.6) | **<0.001**[c] |
| Analogue | 4 (9.1) | 1 (2.2) | |
| Combination Human+Analogue | 0 (0.0) | 13 (28.3) | |
| TDD | | | |
| Mean TDD, units/day (SD) | 81.95 (23.99) | 137.52 (25.91) | **<0.001**[a] |
| Median TDD, units/kg/day (IQR) | 1.04 (0.41) | 1.68 (0.38) | **<0.001**[d] |
| Duration of insulin treatment | | | |
| Mean duration of insulin treatment, y (SD) | | | |
| 1-5 | 9 (20.5) | 4 (8.7) | 0.283[b] |
| 6-10 | 17 (38.6) | 20 (43.5) | |
| >10 | 18 (40.9) | 22 (47.8) | |
| Height | | | |
| Mean height, metres (SD) | 1.59 (0.09) | 1.57 (0.07) | 0.427[a] |
| Waist circumference | n=43 | n=45 | |
| Median waist circumference, cm (IQR) | 98.00 (18.00) | 99.00 (14.00) | 0.148[d] |
| Pre-insulin body weight | | | |
| Mean pre-insulin body weight, kg (SD) | 79.18 (14.94) | 73.87 (13.92) | 0.085[a] |
| Fasting Plasma Glucose | n=30 | n=19 | |
| Mean fasting plasma glucose, mmol/L (SD) | 9.54 (4.03) | 12.64 (4.44) | **0.015**[a] |
| Random Blood Sugar | n=44 | n=45 | |
| Mean random blood sugar, mmol/L (IQR) | 10.35 (2.64) | 11.70 (3.79) | 0.055[a] |
| HbA1c | | | |
| Mean HbA1c, % (SD) | 9.94 (1.92) | 10.31 (1.72) | 0.341[a] |
| Body Mass Index, kg/m$^2$ (SD) | | | |
| Normal 18.5-24.9 | 4 (9.1) | 7 (15.2) | 0.635[b] |
| Overweight 25.0-29.9 | 19 (43.2) | 17 (37.0) | |
| Obese ≥30 | 21 (47.7) | 22 (47.8) | |
| Hypoglycemia | | | |
| No | 33 (75.0) | 10 (21.7) | 0.728[c] |
| Yes | 10 (22.7) | 4 (8.7) | |
| Not assessed | 1 (2.3) | 32 (69.6) | |
| Medication adherence | | | |
| Poor | 6 (13.6) | 27 (58.7) | **<0.001**[c] |

| | | | |
|---|---|---|---|
| Good | 37 (84.1) | 19 (41.3) | |
| Not assessed | 1 (2.3) | 0 (0.0) | |
| Diet control | | | |
| Poor | 21 (47.7) | 9 (19.6) | **0.001**[c] |
| Good | 17 (38.6) | 35 (76.1) | |
| Not assessed | 6 (13.7) | 2 (4.3) | |
| Physical activity | | | |
| No | 21 (47.7) | 22 (47.8) | **0.007**[c] |
| Yes | 14 (31.8) | 3 (6.5) | |
| Not assessed | 9 (20.5) | 21 (45.7) | |

[a]Independent T test [b]Pearson Chi-Square [c]Fisher's Exact Test [d]Mann-Whitney Test *Abbreviations*: *n* number, *SD* standard deviation, *IQR* interquartile range, y years, *T2DM* Type 2 Diabetes Mellitus, *OGLD* oral glucose lowering drug, *TDD* total daily dose, *SDI* Standard Dose Insulin, *HDI* High Dose Insulin; Statistically significant at p values ($p<0.05$) are in bold

**The use of SDI and HDI on body weight change and HbA1c**

Comparisons of body weight change and glycaemic control between the SDI and HDI groups are presented in Table 2. Both groups exhibited an increase in body weight from baseline during the study period. However, the magnitude of weight change was smaller in the SDI group compared with the HDI group. The mean body weight change was 3.07 ± 4.90 kg in the SDI group and 5.57 ± 6.69 kg in the HDI group, corresponding to a mean difference of −2.50 kg (95% CI −4.95 to −0.05). This difference was statistically significant ($t$ (82.51) = −2.03, $p$ = 0.045).

With respect to glycaemic control, the SDI group had lower follow-up HbA1c levels than the HDI group. The mean follow-up HbA1c was 9.55 ± 1.95% among patients receiving SDI, compared with 10.39 ± 1.86% among those receiving HDI. The between-group difference in HbA1c was −0.84% (95% CI −1.64 to −0.04), which was statistically significant ($t$(88) = −2.09, $p$ = 0.040).

**Table 2** Body weight change and HbA1c between SDI and HDI regimens

| **Variables** | **SDI (n=44) Mean (SD)** | **HDI (n=46) Mean (SD)** | **Mean difference (95% CI)** | **P value[a]** |
|---|---|---|---|---|
| Body weight change (kg) | 3.07 (4.90) | 5.57 (6.69) | -2.50 (-4.95, -0.05) | **0.045** |
| HbA1c (%) | 9.55 (1.95) | 10.39 (1.86) | -0.84 (-1.64, -0.04) | **0.040** |

[a]Independent T test; Statistically significant at p values ($p<0.05$) are in bold

**Missing Data Pattern Analysis**

From the sample size of n=90, the percentages of missing data ranged from 0% for majority of the variables to 4 5.6% for baseline FBS. Variables with missing data were baseline RBS (n=1, 1.1%), medication adherence (n=1, 1.1%), follow-up RBS (n=3, 3.3%), diet control (n=8, 8.9%), physical activity (n=30, 33.3%), follow-up FBS (n =33, 36.7%) and hypoglycemia (n=33, 36.7%). Little's MCAR test confirmed that data were missing completely at random ($X^2$= 40.151, df =95, p=1.000) allowing multiple imputation to be employed to preserve sample size w ith minimal risk of bias. The final MLR model excluded variables with missingness more than 20%.

**Regression Analysis and Diagnostic Validation**

Diagnostic validation confirmed that both regression models satisfied all parametric assumptions across the imp uted datasets. As presented in Table 3, the regression models for body weight change and follow-up HbA1c dem onstrated normal residual distributions, homoscedastic error variances and residuals showed no autocorrelation.

No multicollinearity or influential outliers were detected. Visual diagnostic plots for both models are included in Figure S4 and S5.

**Table 3** Diagnostic Assessment across Regression Models

| Diagnostic Parameter | Acceptance Threshold | MLR 1: Body weight change | MLR 2: Follow-up HbA1c | Assumption Status |
|---|---|---|---|---|
| Residual Distribution | Bell Curve/ Diagonal P-P Alignment | Normal (Mean=-7.89 X $10^{-17}$, S D =0.96) | Normal (Mean = 3.77 X $10^{-15}$, S D = 0.988) | Met |
| Homoscedasticity | Uniform scatter, n o funneling | Rectangular dispersion around 0 | Rectangular dispersion around 0 | Met |
| Linearity | Straight-line bivariate trend | Confirmed via partial regression plots | Confirmed via partial regression plots | Met |
| Residual Independence | Durbin-Watson 1.5 - 2.5 | DW = 2.036 | DW = 1.828 | Met |
| Multicollinearity | VIF< 5 (Tolerance> 0.20) | VIF range: 1.062 - 1.811 | VIF range: 1.207 - 2.193 | Met |
| Influential Outliers | Cook's distance D < 1.0 | Maximum D = 0.121 | Maximum D = 0.020 | Met |

**Factors Associated with Body Weight Change**

Results from the pooled MLR between independent variables and body weight change are shown in Table 4. The overall pooled model, derived using an enter selection approach was statistically significant explaining 30.5% of variance in body weight change (mean $R^2$ = 0.305, (range: 0.300-0.314) mean Adjusted $R^2$ = 0.226; F (9, 80) = 3 .807-4.071, p < 0.001). No evidence of multicollinearity was observed (VIF <2; tolerance >0.2). TDD was indep endently associated with body weight change in the MLR model. Specifically, every 10 units increase in TDD w as associated with a 0.74 kg increase in body weight (B = 0.074, SE = 0.019, t = 3.997, p < 0.001, 95 CI [0.038, 0.110]). In addition, pre-insulin body weight appeared associated with body weight change. Patients with higher baseline pre-insulin body weight demonstrated weight loss by the end of the study period (B = -0.092, SE = 0.04 4, t = -2.091, p = 0.037, 95 CI [-0.178, -0.01]). However, it may be worth noting that duration of insulin treatmen t showed a non-significant positive marginal trend (B = 0.324, SE = 0.186, t = 1.743, p = 0.081, 95 CI [-0.040, 0. 689]). Each additional year of insulin treatment was likely related to a 0.324kg weight gain but this association d id not achieve statistical significance.

Although other variables such as age, duration of T2DM, physical activity, hypoglycaemia, OGLD com binations, medication adherence, and dietary control were associated with body weight change in univariate anal yses, none remained statistically significant after adjustment in the MLR model. In addition, since the combinati on OGLD of monotherapy sodium glucose transporter-2 (SGLT2) or DPP4 inhibitors was represented by only 2 patients in the HDI group, this variable was also excluded from the final model to prevent biasness.

**Table 4** Factors associated with body weight change in patients with T2DM on insulin treatment

| **Variables** | **B[a]** | **95% CI** | | **P value** | **B[b]** | **95% CI** | | **P value** |
|---|---|---|---|---|---|---|---|---|
| Age | 0.08 | -0.03 | 0.19 | 0.174 | 0.05 | -0.07 | 0.16 | 0.439 |
| Duration of T2DM | 0.37 | 0.14 | 0.59 | 0.001 | 0.10 | -0.18 | 0.38 | 0.474 |
| Duration of insulin treatment | 0.56 | 0.24 | 0.88 | 0.001 | 0.32 | -0.40 | 0.69 | 0.081 |
| TDD | 0.05 | 0.02 | 0.08 | 0.003 | 0.07 | 0.04 | 0.11 | **0.000** |
| Dose Classification of Insulin | | | | | | | | |
| Standard | Ref | | | | | | | |
| High | 2.51 | 0.07 | 4.94 | 0.044 | - | - | - | - |
| Physical Activity | | | | | | | | |
| No | Ref | | | | - | - | - | - |
| Yes | -1.41 | -4.37 | 1.55 | 0.347 | | | | |
| Hypoglycemia | | | | | | | | |
| No | Ref | | | | - | - | - | - |
| Yes | 0.38 | -2.51 | 3.28 | 0.793 | | | | |
| Combination of insulin | | | | | | | | |
| Human | Ref | | | | | | | |
| Analogue | -3.20 | -8.63 | 2.24 | 0.248 | -1.35 | -6.29 | 3.58 | 0.591 |
| Human+Analogue | -1.35 | -4.90 | 2.19 | 0.455 | -3.12 | -6.79 | 0.44 | 0.085 |
| Combination of OGLD | | | | | | | | |
| Not on any OGLD | Ref | | | | - | - | - | - |
| Metformin only | 0.97 | -2.73 | 4.67 | 0.607 | | | | |
| Metformin+SGLT2i | -2.26 | -9.87 | 5.35 | 0.560 | | | | |
| Metformin+DPP4i | 0.86 | -5.42 | 7.13 | 0.789 | | | | |
| Metformin+SGLT2i+DPP4i | -5.56 | -17.83 | 6.71 | 0.374 | | | | |
| Monotherapy SGLT2i or DPP4i | 6.84 | -2.17 | 15.84 | 0.137 | | | | |
| Medication adherence | | | | | | | | |
| No | Ref | | | | | | | |
| Yes | 0.90 | -1.69 | 3.49 | 0.497 | 1.84 | -0.89 | 4.57 | 0.186 |
| Diet Control | | | | | | | | |
| Poor | Ref | | | | | | | |
| Good | 0.79 | -1.90 | 3.48 | 0.564 | -1.01 | -3.63 | 1.61 | 0.450 |
| Pre-Insulin Body Weight | -0.06 | -0.14 | 0.03 | 0.202 | -0.09 | -0.18 | -0.01 | **0.037** |

Model "enter" SPSS Statistics [a] Pooled Unstandardised regression coefficient [b] Pooled Standardised regression coefficient VI F <5, tolerance >0.2
Model fit statistics reflect the average of 5 imputed datasets: mean $R^2$ is 0.305 (range 0.300-0.314), mean adjusted $R^2$ is 0.22 6.
*Abbreviations*: *T2DM* Type 2 Diabetes Mellitus, *OGLD* oral glucose lowering drug, *SGLT2i* sodium-glucose cotransporter-2 inhibitor, *DPP4i* Dipeptidyl Peptidase 4 inhibitor, *TDD* total daily dose, *SDI* Standard Dose Insulin, *HDI* High Dose Insulin, *Ref* reference, statistically significant at p values ($p<0.05$) are in bold

**Factors Associated with Follow-up HbA1c**

Table 5 represents the results from the pooled MLR evaluating the factors associated with follow-up HbA1c levels among patients with T2DM receiving insulin therapy. The MLR analysis identified age, use of combined metformin plus DPP-4 inhibitors, insulin analogue use and mixed human/analogue insulin regimens as factors significantly associated with follow-up HbA1c levels. The final model was statistically significant (mean $R^2$ = 0.351 (range: 0.348- 0.355), mean adjusted $R^2$ = 0.229, F (14, 67) = 2.628-2.951, p = 0.002) and explained 35.1% of the variance in follow-up HbA1c. No multicollinearity was detected (VIF <5; tolerance >0.2). e Aging was significantly associated with lower HbA1c levels, with a 0.05% reduction in HbA1c per additional year of age (B = -0.048, SE = 0.021, t = -2.297, p = 0.022, 95% CI [-0.089, -0.007]). Compared with patients not receiving any OGLDs, those treated with combined metformin and DPP-4 inhibitors had significantly lower HbA1c levels (B = -3.662, SE = 1.098, t = -3.336, p = 0.001, 95% CI [-5.814, -1.510]). In contrast, insulin regimen type was significantly associated with higher HbA1c levels. Patients receiving insulin analogue therapy had higher HbA1c levels compared with those receiving human insulin alone (B = 2.810, SE = 0.925, t = 3.037, p = 0.002, 95% CI [0.998, 4.622]). Similarly, patients receiving combined human and analogue insulin regimens had higher HbA1c levels than those on human insulin alone (B = 1.332, SE = 0.667, t = 1.997, p = 0.046, 95% CI [0.024, 2.639]). (. Other variables such as duration of T2DM, total daily insulin dose, medication adherence and diet control were not independently associated with follow-up HbA1c after adjustment in the MLR model.

**Table 5** Factors associated with HbA1c in patients with T2DM on insulin treatment

| **Variables** | **b[a]** | **95% CI** | | **P value** | **b[b]** | **95% CI** | | **P value** |
|---|---|---|---|---|---|---|---|---|
| Age | -0.05 | -0.09 | -0.01 | 0.008 | -0.05 | -0.09 | -0.01 | **0.022** |
| Duration of T2DM | -0.08 | -0.16 | -0.01 | 0.032 | -0.04 | -0.13 | -0.05 | 0.403 |
| Duration of Insulin Treatment | -0.06 | -0.17 | 0.05 | 0.264 | -0.01 | -0.14 | 0.11 | 0.842 |
| TDD | 0.01 | 0.00 | 0.02 | 0.024 | 0.01 | -0.00 | 0.02 | 0.206 |
| Dose Classification of Insulin | | | | | | | | |
| Standard | Ref | | | | | | | |
| High | 0.84 | 0.05 | 1.63 | 0.037 | - | - | - | - |
| Combination of OGLD | | | | | | | | |
| Not on any OGLD | Ref | | | | | | | |
| Metformin only | -0.13 | -1.33 | 1.07 | 0.828 | -0.41 | -1.61 | 0.79 | 0.502 |
| Metformin + SGLT2i | 0.19 | -2.28 | 2.66 | 0.879 | -1.21 | -3.63 | 1.22 | 0.329 |
| Metformin + DPP4i + SGLT2i | 2.16 | -1.83 | 6.14 | 0.288 | -0.23 | -4.00 | 3.53 | 0.903 |
| Monotherapy SGLT2i or DPP4i | -1.99 | -4.92 | 0.93 | 0.182 | -2.22 | -4.96 | 0.53 | 0.114 |
| Metformin + DPP4i | -0.86 | -2.90 | 1.18 | 0.407 | -3.66 | -5.81 | -1.51 | **0.001** |
| Medication Adherence | | | | | | | | |
| Poor | Ref | | | | | | | |
| Good | -1.06 | -1.87 | -0.25 | 0.011 | -0.33 | -1.23 | 0.57 | 0.471 |
| Combination of insulin | | | | | | | | |
| Human only | Ref | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Analogue only | 1.64 | -0.03 | 3.32 | 0.055 | 2.81 | 0.10 | 4.62 | **0.002** |
| Human and analogue insulin | 1.61 | 0.52 | 2.71 | 0.004 | 1.33 | 0.02 | 2.64 | **0.046** |
| Diet control | | | | | | | | |
| Poor | Ref | | | | | | | |
| Good | 0.45 | -0.45 | 1.34 | 0.327 | 0.23 | -0.72 | 1.19 | 0.628 |
| Physical Activity | | | | | | | | |
| No | Ref | | | | | | | |
| Yes | -0.52 | -1.41 | 0.36 | 0.246 | - | - | - | - |
| Hypoglycemia | | | | | | | | |
| No | Ref | | | | | | | |
| Yes | -0.00 | -1.74 | 1.73 | 0.996 | - | - | - | - |
| Pre-Insulin Bodyweight | -0.01 | -0.04 | 0.02 | 0.498 | -0.01 | -0.04 | 0.02 | 0.422 |

Model "enter" SPSS Statistics [a] Pooled Unstandardised regression coefficient [b] Pooled Standardised regression coefficient; VI F <5, tolerance >0.2
Model fit statistics reflect the average of 5 imputed datasets: mean R2 is 0.351 (range 0.348-0.355), mean adjusted R2 is 0.22 9.*Abbreviations*: *T2DM* Type 2 Diabetes Mellitus, *OGLD* oral glucose lowering drug, *TDD* total daily dose, *SDI* Standard Dose Insulin, *HDI* High Dose Insulin, *Ref* reference, *NS* non-significant; Statistically significant at p values (p<0.05) are in b old

**Sensitivity Analyses for Continuous Dose and Alternative Thresholds**

Sensitivity analyses for both body weight change and follow-up HbA1c support the strength of our MLR model. Similarly to the continuous dose of TDD, alternative thresholds of 1.25u/kg/day (B = 3.001, p = 0.044) and 1.5u/ kg/day (B = 3.220, p = 0.036) demonstrated a statistically significant positive linear association with body weigh t change. However, at extreme thresholds of 1.0 units/kg/day, 1.75 units/kg/day and 2.0 units/kg/day showed non -significance (Figure S2). In contrast, similar sensitivity analyses showed non-significant association (p>0.100) f or follow-up HbA1c at continuous doses or alternative thresholds of insulin indicating a glycemic response plate au (Figure S3).

**Discussion**

This retrospective study evaluated the effects of SDI versus HDI on body weight change and glucose control in T2DM patients at a primary health clinic in Malaysia. To our knowledge, no prihighlor studies have compared SDI versus HDI in Malaysia with a similar research objective. There was a statistically significant difference in mean body weight change, with a more pronounced weight gain observed in the HDI group than in the SDI group. This finding is consistent with two major long-term landmark trials. Both the UK Prospective Diabetes Study Group and the Diabetes Control and Complications Group reported significantly greater weight gain in intensive insulin therapy than in conventional insulin therapy.[16,17] The pronounced weight gain could be attributed to the amplified effect of IAWG such as increased appetite and the anabolic effects due to unphysiological quantities of exogenous insulin.

In the present study, TDD was independently associated with body weight change. The positive linear association between TDD and weight gain observed here is consistent with prior studies conducted in diverse clinical settings.[18,19] For example, a prospective cohort study conducted in an outpatient diabetes clinic reported

that percentage weight gain was significantly correlated with both initial and average insulin dose per kilogram; findings that mirror the associations identified in our MLR analysis.[19] Several biological mechanisms have been proposed to explain this relationship. Insulin is a potent anabolic hormone that suppresses lipolysis while promoting lipogenesis and adipocyte differentiation.[9] At higher, non-physiological systemic concentrations, insulin may exacerbate energy storage and fat accumulation, contributing to progressive weight gain. Sustained hyperinsulinemia may also worsen peripheral insulin resistance through increased adiposity, thereby creating a self-reinforcing cycle that necessitates further insulin dose escalation.

Although did not achieve statistical significance, duration of insulin therapy demonstrated positive trends with body weight change reflecting evidences that insulin-associated weight gain is not limited to the initiation phase but may continue over time. Jansen et al[20] demonstrated that weight gain following insulin initiation was most pronounced during the early treatment period but persisted at a slower yet clinically relevant rate during long-term follow-up, averaging approximately 1.2 kg per year beyond the first nine months of therapy. Our findings extend this observation by highlighting that cumulative insulin exposure, reflected by both dose and duration, remains an important consideration in long-term weight trajectories among insulin-treated patients with T2DM. In routine clinical practice, HDI is commonly prescribed as a consequence of insulin intensification strategies when glycaemic targets are not achieved with lower doses.

In the present study, patients receiving HDI had higher mean HbA1c levels compared with those receiving SDI. This observation likely reflects the underlying clinical complexity of patients requiring higher insulin doses, rather than a direct effect of insulin dose escalation per se. Individuals prescribed with HDI often have longer disease duration, greater insulin resistance, and multiple metabolic comorbidities, which may limit the effectiveness of insulin intensification alone in achieving glycaemic targets. Consistent with this interpretation, previous studies have reported that high-dose insulin of more than 1 unit/kg/day was associated with a reduced likelihood of achieving HbA1c targets such as <8% or <9%.[21] Even in cohorts prescribed with very high insulin doses (>200 units/day), only modest improvements in HbA1c have been observed, with a substantial proportion of patients still having HbA1c results above recommended glycaemic thresholds despite treatment intensification.[14] These findings collectively suggest diminishing glycaemic improvements with escalating insulin doses, particularly when insulin resistance predominates. Current clinical guidelines emphasize individualized glycaemic targets, typically <7% for most adults and <7–7.5% or <8% for older adults or those with significant comorbidities.[22] Within this context, the higher HbA1c levels observed among HDI recipients in our study underscore the challenge of achieving optimal glycaemic control through insulin dose escalation alone and highlight the need for complementary or insulin-sparing strategies where feasible.

Interestingly, neither TDD nor insulin dose classification was independently associated with HbA1c in the multivariable analysis. Even at different thresholds, dose classification was not statistically significantly associated with HbA1c implying that higher insulin doses are likely prone to significant weight gain but no significant difference in glycemic control. Thus, this phenomenon implies that further dose escalation of insulin may possibly be counterproductive. This finding contrasts with previous studies in which insulin dose emerged as a key determinant of glycaemic control. For example, a prospective observational cohort study with four years of follow-up identified insulin dose as one of the strongest predictors of average HbA1c, with higher doses associated with worsening glycaemic control over time.[23] The discrepancy between our findings and those reported previously may be partly attributable to differences in dose thresholds used to define high-dose insulin. In our

study, HDI was defined using a higher cut-off (≥1.5 units/kg/day), potentially limiting the ability to detect dose-related associations within the available sample size. Moreover, insulin dose alone may not fully capture the complexity of insulin effectiveness in real-world settings. Factors such as injection technique, injection site rotation, adherence, and timing of administration which were beyond the scope of this study are potentially linked to insulin pharmacodynamics and may substantially influence glycaemic outcomes. Nonetheless, the consistently higher mean HbA1c observed among patients receiving HDI in this study indicates that insulin dose escalation alone may be insufficient to achieve optimal glycaemic control in some patients.

An important finding of this study was the association between insulin regimen type and HbA1c levels. The use of insulin analogue therapy, either alone or in combination with human insulin, was associated with higher HbA1c levels compared with human insulin alone. Although insulin analogues are designed to more closely mimic physiological insulin secretion, evidence demonstrating substantial superiority over human insulin in terms of HbA1c reduction has been inconsistent. Some clinical trials have reported modest HbA1c advantages with complete analogue-based basal–bolus regimens compared with human insulin-based regimens.[24] However, these benefits are most apparent when analogue insulin is used comprehensively across both basal and prandial components. In the present study setting, a full analogue-based basal–bolus regimen was not feasible. Access to rapid-acting insulin analogues is restricted to tertiary specialist care and primary health clinics are limited to premixed analogue formulations, predominantly insulin aspart/protamine (NovoMix).[25] As such, the potential glycaemic advantages reported in controlled trial settings may not be directly transferable to real-world primary care contexts, particularly in resource-constrained systems.

The combination of metformin and DPP-4 inhibitors was significantly associated with lower HbA1c levels compared with no oral glucose-lowering drug use. This finding is consistent with evidence from a systematic review which reported that basal insulin in combination with metformin or metformin plus DPP-4 inhibitors achieved effective glycaemic control with a favourable safety profile.[26] In contrast, other OGLDs combinations were not significantly associated with HbA1c in this study. Although combinations involving SGLT2 inhibitors are proven to reduce HbA1c, the lack of significant association observed here is likely attributable to the relatively small number of patients receiving SGLT2 inhibitors containing regimens in this cohort, limiting statistical power.

This study has several limitations such as the inability to establish a causal relationship since it was conducted retrospectively. Convenient sampling resulted in a lack of stratification of the baseline characteristics of the patients, leading to increased variation. High TDD of insulin could potentially be a marker of severe insulin resistance, poor adherence, inadequate dietary control, uncontrolled disease or treatment intensification. Hence, the observed association with higher HbA1c is subjected to various confounding factors. Other key predictors, such as body fat composition, sleeping patterns, stress levels, insulin injection technique, and treatment satisfaction, were not assessed in the present study. Furthermore, the information on hypoglycemia, medication adherence, diet control, and physical activity was entirely based on subjective assessments by the prescriber, which could be a source of inaccuracy and disparity. The study site was a public primary health clinic, representing a limited-resource setting healthcare facility. Therefore, the results of this study may not be suitable for extrapolation to tertiary hospitals or private healthcare facilities, where a wider range of treatment options is available. It is also important to consider that a large proportion of the patients were overweight or obese, which could affect the results of this study. The lack of a full insulin analogue regime and the controlled usage of newer antidiabetics

such as DPP4 and SGLT2 inhibitors may also affect the results of the study.

**Conclusion**

In this retrospective cohort study, higher insulin dose exposure supports the association of greater body weight gain and higher mean follow-up HbA1c levels compared with standard insulin dosing. Body weight change was associated with TDD of insulin and pre-insulin body weight, while age, insulin regimen, and selected OGLD combinations were associated with follow-up HbA1c. These findings highlight that insulin dose escalation alone is likely insufficient to achieve optimal glycaemic control and may be accompanied by unintended weight gain. Prospective studies are needed to clarify temporal relationships and to formulate insulin optimisation strategies that better balance glycaemic control with long-term metabolic outcomes in patients with T2DM.

**Ethical Approval**

Ethical approval by the Medical Research and Ethics Committee, Ministry of Health Malaysia (NMRR ID-24-00392-WLQ) and Ethics Committee of UKM (JEP-2024-200) was obtained before the study initiation.

**Authors' Contribution**

Conceptualization: Meredith, Ernieda
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**Conflicts of Interest**

The authors declared no conflict of interest.

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**Declaration of Generative AI and AI-Assisted Technologies**

During the preparation of this work, the author(s) used ChatGPT and Gemini for polishing the language. The author(s) reviewed the output carefully and take full responsibility for the final content of the manuscript.

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