RESEARCH PAPER

Comparative Effectiveness of Vildagliptin and Metformin on Glycaemic Control in Patients with Newly Diagnosed Type 2 Diabetes Mellitus: A Six-Month Prospective Comparative Study

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ABSTRACT

Background: The magnitude of glycaemic change after treatment initiation varies between individuals. Baseline glycaemia may be associated with subsequent change, although change-score analyses can be affected by regression to the mean and mathematical coupling.

Methods: This study included 60 patients (30 per treatment group) from a prospective, single-centre study at SVRRGG Hospital, Tirupati, India, conducted from December 2023 to August 2024. HbA1c, FBS, and PPBS were recorded at baseline, three months, and six months; the present analysis compared baseline with six-month values. Six-month change was calculated as follow-up minus baseline. Linear regression examined the association between baseline HbA1c and HbA1c change, unadjusted and adjusted for age, sex, and treatment group.

Results: Among 60 patients, mean HbA1c decreased from 7.99 ± 0.84% to 7.33 ± 0.68%, a mean change of −0.66 percentage points (95% CI −0.80 to −0.51). Mean FBS changed by −51.85 mg/dL (95% CI −66.73 to −36.97) and mean PPBS by −97.33 mg/dL (95% CI −116.83 to −77.84). Baseline HbA1c was inversely associated with HbA1c change (unadjusted coefficient −0.393 per 1% higher baseline HbA1c; 95% CI −0.537 to −0.250; $p<0.001$). The association remained after adjustment for age, sex, and treatment group (−0.373; 95% CI −0.475 to −0.272; $p<0.001$).

Conclusion: All three glycaemic measures decreased on average over six months. Higher baseline HbA1c was associated with a larger numerical reduction, but this exploratory association may reflect mathematical coupling and regression to the mean and should not be interpreted as proof of a biological treatment-response advantage.

Keywords: Type 2 diabetes mellitus; HbA1c; fasting blood sugar; postprandial blood sugar; glycaemic change.
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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease characterised by hyperglycaemia arising from insulin resistance, progressive pancreatic beta-cell dysfunction, or both. Persistent hyperglycaemia is associated with microvascular and macrovascular complications, making timely assessment and sustained glycaemic management central components of care. Glycated haemoglobin (HbA1c) is widely used to assess longer-term glycaemic exposure and is linked to diabetes-related outcomes; it reflects average glycaemia over approximately the preceding two to three months. Fasting blood sugar (FBS) and postprandial blood sugar (PPBS) provide complementary snapshots of glucose regulation at different times of the day. [1,2,3,4]

Clinical response after starting glucose-lowering treatment is heterogeneous. The magnitude of observed change may be influenced by baseline glycaemia, treatment selection and dose, adherence, diet, physical activity, concomitant illness, and other patient-level factors. Baseline values are especially important when interpreting follow-up

measurements because people with higher initial measurements may have greater numerical scope for improvement. In addition, measurement variability can cause unusually high baseline values to be followed by values closer to a person's usual level, a phenomenon known as regression to the mean. [5]

The association between baseline HbA1c and a change score requires particular caution when change is defined as follow-up HbA1c minus baseline HbA1c. Baseline HbA1c is mathematically part of that outcome, which can create an inverse association even when the association does not represent a distinct biological response mechanism. Methodological literature has shown that baseline values and change scores are often negatively correlated and that such correlations should not automatically be interpreted as evidence of treatment-response modification. [5,6]

The study purpose is to describe six-month glycaemic changes and examine whether baseline HbA1c is associated with the numerical change in HbA1c after accounting for age, sex, and treatment group.

This question may be useful for generating hypotheses about patterns of glycaemic change in routine clinical settings. However, a small, single-centre dataset with limited covariate information cannot reliably separate biological response from measurement variation, adherence, lifestyle, or other unmeasured influences. [7]

Aim and Objectives

Aim: To estimate six-month glycaemic change among adults with newly diagnosed T2DM and examine the association between baseline HbA1c and HbA1c change.

Primary objective: To estimate the association between baseline HbA1c and six-month HbA1c change, defined as the six-month value minus the baseline value.

Secondary objectives

1. To describe baseline-to-six-month changes in FBS and PPBS.
2. To explore associations of age, sex, and treatment group with six-month HbA1c change.

MATERIAL AND METHODS

Study design and setting: This study was a prospective study carried out in the Department of General Medicine at SVRRGG Hospital, Tirupati & Department of Pharmacology at S.V.Medical College,Tirupati from December 2023 to August 2024.

Study population: Adults 30–60 years of age with newly diagnosed type 2 diabetes mellitus were considered eligible after providing written informed consent. Participants of both sexes were included. Patients were excluded when diabetic retinopathy, nephropathy or neuropathy, substance abuse, hepatic or renal disease, allergy to either study medication, pregnancy or lactation, or an immunocompromised condition such as HIV infection or previous renal transplantation was present.

Sample size calculation: For sample-size estimation, the study used a two-sided alpha of 0.05 and 80% statistical power, with an assumed standard deviation of 0.98 and an anticipated clinically meaningful between-group HbA1c difference of 0.8 percentage points. The stated equation was n = 2(Zα + Zβ)^2σ^2/d^2. Substitution of Zα=1.96, Zβ=0.84, σ=0.98, and d=0.8 produced n=23.53, which was rounded to 24 participants per group. A 10% allowance for nonresponse and an additional 10% allowance for attrition led to a planned sample of 30 participants in each group, giving a total target of 60.

Randomization, treatment, and follow-up: The 60 eligible participants were divided equally into Group A (vildagliptin) and Group B (metformin) according to the odd-even numbering procedure. Group A received oral vildagliptin 50 mg once daily, one-half hour before breakfast, whereas Group B received oral metformin 500 mg once daily, one-half hour before breakfast. Treatment was continued throughout the study period, with evaluations scheduled at baseline, 3 months, and 6 months. Six participants discontinued during follow-up—two from the vildagliptin group and four from the metformin group—and were replaced using the same eligibility and allocation process so that 30 participants remained in each arm. Therefore, the reported analysis represents the maintained final cohort rather than an intention-to-treat population.

Variables

Outcome variables

- Change in HbA1c from baseline to six months.
- Change in FBS from baseline to six months.
- Change in PPBS from baseline to six months.

For each measure, change was calculated as the six-month value minus the baseline value. A negative value indicates a reduction.

Potential explanatory variables

- Baseline HbA1c, FBS, and PPBS.
- Age.
- Sex.
- Treatment group.

Data management: Each participant was assigned a unique study identifier, and duplicate entries, missing measurements, inconsistent visit dates, and implausible values were checked. The treatment group, participant status, and measurements at each visit was verified before the analysis dataset is finalised.

Reference ranges used in figures: The graphical displays used standard reference benchmarks solely to aid interpretation. The fasting glucose figure shows the commonly used normal fasting plasma glucose interval of 70–99 mg/dL. The postprandial graph uses a normal two-hour glucose value of less than 140 mg/dL. For HbA1c, the figures show the normal threshold of less than 5.7% together with the 7.0% treatment target used in the study tables. These benchmarks were provided for context and were not applied as eligibility criteria.

Statistical analysis: Continuous variables were summarised using means and standard deviations or medians and interquartile ranges, depending on their distribution. Categorical variables were summarised as frequencies and percentages. The distribution of six-month changes in HbA1c, FBS, and PPBS was examined. Associations between baseline characteristics and glycaemic change was initially be assessed using suitable univariable methods. Multivariable linear regression was considered for the change in HbA1c. Effect estimates with 95% confidence intervals were reported alongside p-values. Statistical significance was assessed using a two-sided threshold of 0.05, without treating statistical significance as a substitute for clinical relevance.

Ethical considerations: The study protocol was approved by the Institutional Ethics Committee of S.V. Medical College, Tirupati. The archived approval communication is dated March 1, 2023 and states that the protocol had been reviewed during the committee meeting of February 24, 2023; the application reference is recorded as Lr. No. 12/2023. The exact formal IEC approval/reference number should be cross-checked with the original ethics records before manuscript submission. All participants provided written informed consent. No external sponsor supported the study; the principal investigator financed the work independently.

RESULTS

Among 60 patients, 30 in the vildagliptin group and 30 in the metformin group. Mean age was 48.17 ± 7.94 years; 30 records were female and 30 male. Baseline mean HbA1c was 7.99 ± 0.84%.

Table 1: Analysis population and baseline characteristics

Characteristic	Overall (n=60)	Vildagliptin (n=30)	Metformin (n=30)
Chart records, n	60	30	30
Age, years, mean ± SD	48.17 ± 7.94	47.47 ± 8.12	48.87 ± 7.82
Female, n (%)	30 (50.0)	14 (46.7)	16 (53.3)
Male, n (%)	30 (50.0)	16 (53.3)	14 (46.7)
Baseline HbA1c, %, mean ± SD	7.99 ± 0.84	8.04 ± 0.65	7.94 ± 1.00
Baseline FBS, mg/dL, mean ± SD	173.37 ± 56.47	175.97 ± 62.00	170.77 ± 51.28
Baseline PPBS, mg/dL, mean ± SD	281.97 ± 95.37	269.00 ± 90.23	294.93 ± 100.08

Across all chart records, mean HbA1c decreased by 0.66 percentage points, mean FBS by 51.85 mg/dL, and mean PPBS by 97.33 mg/dL. Paired tests indicated that each mean change differed from zero (all p<0.001).

Table 2: Six-month change in glycaemic parameters

Outcome	Paired n	Baseline, mean ± SD	Six months, mean ± SD	Mean change (95% CI)	Paired p
HbA1c	60	7.99 ± 0.84	7.33 ± 0.68	-0.66 (-0.80, -0.51)	<0.001
FBS	60	173.37 ± 56.47	121.52 ± 22.85	-51.85 (-66.73, -36.97)	<0.001
PPBS	60	281.97 ± 95.37	184.63 ± 38.21	-97.33 (-116.83, -77.84)	<0.001

Baseline HbA1c was inversely associated with the six-month change score: higher baseline values were associated with more negative change scores (greater numerical reductions). The unadjusted coefficient was −0.393 (95% CI −0.537 to −0.250; p<0.001). After adjustment for age, sex, and treatment group, the coefficient was −0.373 (95% CI −0.475 to −0.272; p<0.001). Age and sex were not associated with HbA1c change in the adjusted model. Treatment group remained associated with the change score.

Table 3: Exploratory associations with HbA1c change

Variable	Unadjusted coefficient (95% CI)	P value	Adjusted coefficient (95% CI)	P value
Baseline HbA1c (per 1% higher)	−0.393 (−0.537, −0.250)	<0.001	-0.373 (-0.475, -0.272)	<0.001
Age (per year)	0.005 (−0.014, 0.023)	0.618	0.002 (-0.009, 0.013)	0.678
Female vs male	0.047 (−0.247, 0.340)	0.751	-0.035 (-0.204, 0.134)	0.677
Vildagliptin vs metformin	−0.693 (−0.924, −0.463)	<0.001	-0.658 (-0.827, -0.488)	<0.001

Model specification: outcome = six-month HbA1c minus baseline HbA1c, in percentage points. Adjusted model includes baseline HbA1c, age in years, female sex (reference: male), and vildagliptin group (reference: metformin); n=60. Negative coefficients indicate a more negative change score. The baseline-HbA1c/change association is vulnerable to mathematical coupling and regression to the mean.

DISCUSSION

In this study, among 60 newly diagnosed Type 2 DM patients, mean HbA1c, FBS, and PPBS were lower at six months than at baseline. Mean HbA1c declined by 0.66 percentage points, while mean FBS and PPBS declined by 51.85 mg/dL and 97.33 mg/dL, respectively.

The main association was between higher baseline HbA1c and a more negative six-month HbA1c change score. The estimated coefficient was −0.393 percentage points of change per 1-percentage-point higher baseline HbA1c in the unadjusted model and −0.373 after adjustment for age, sex, and treatment group. The persistence of the coefficient after adjustment indicates that these measured covariates did not explain the association in this dataset. It does not, however, demonstrate that higher baseline HbA1c biologically causes a stronger response to treatment.

A key interpretive issue is that the outcome is defined as follow-up HbA1c minus baseline HbA1c. Baseline HbA1c therefore appears on both sides of the regression relationship: it is the predictor and also a component of the calculated outcome. This mathematical coupling can induce a negative association, while random measurement variation can additionally produce regression to the mean. People with unusually high baseline results may have lower subsequent measurements even without a differential treatment effect. These are established methodological concerns in analyses of change scores. [5,6] Consequently, the baseline-HbA1c coefficient should be viewed as a descriptive association and not as a validated marker for selecting treatment or forecasting an individual patient's response.

Age and sex were not statistically associated with HbA1c change in the adjusted model. Given only 60 records, the lack of statistical evidence should not be taken to mean that age and sex have no relationship with glycaemic response. Confidence intervals and statistical power are limited, and residual confounding remains plausible.

Treatment group was associated with HbA1c change in the adjusted model, with a coefficient of −0.658 percentage points for vildagliptin compared with metformin. This is an exploratory model estimate from the supplied chart, not a definitive comparative-effectiveness result. The average reductions in HbA1c and glucose values are consistent with improved glycaemic measurements over time. HbA1c is commonly used to monitor longer-term glycaemia, and measurements at approximately three-month intervals are clinically informative after treatment changes. [1,2] Nevertheless, interpretation requires the assay method, treatment exposure, adherence, and timing of measurements to be documented. [7]

Strengths and limitations

A strength of the study is the planned collection of repeated glycaemic measurements at baseline, three months, and six months. The current analysis uses the available baseline and six-month measurements to describe change and examine a focused association.

Several limitations materially constrain interpretation. The sample was small and drawn from a single centre. The regression was exploratory and adjusted for only age, sex, and treatment group. Important potential confounders, including adherence and lifestyle factors, were unavailable. The analysis used change scores, which are vulnerable to mathematical coupling and regression to the mean, and the small sample limits precision. The results therefore cannot establish causal predictors, validate an individual response model, or support a treatment recommendation. Findings should be confirmed in a larger, prospectively specified study with a clearly documented cohort, robust allocation and follow-up procedures, and an analysis plan established before examining outcomes.

CONCLUSION

Among 60 adults with newly diagnosed T2DM, mean HbA1c, FBS, and PPBS decreased between baseline and six months. Higher baseline HbA1c was associated with a larger numerical HbA1c reduction after adjustment for age, sex, and treatment group; however, mathematical coupling

and regression to the mean may explain part of this relationship.

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