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A comparative analysis of naïve basal insulin versus basal insulin plus sulfonylureas in patients with poorly controlled type 2 diabetes mellitus

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Abstract

Type 2 diabetes mellitus (T2DM) is a condition characterized by progressive pancreatic beta-cell dysfunction and insulin resistance. Despite lifestyle modifications and metformin treatment, T2DM often requires combination therapies, including insulin therapy. The mechanisms underlying the combination of insulin with sulfonylureas (SUs), typically referred to as bedtime insulin in conjunction with daytime SUs, are only partially understood. This study aims to clinically compare the effects of adding basal insulin to SUs versus twice-daily Neutral Protamine Hagedorn (NPH), focusing on the rationale underlying these results. A prospective cohort study was conducted at the Faiha Specialized Diabetes, Endocrine, and Metabolism Centre in Basrah (FDEMC), Iraq, from May 2024 to April 2025. The study comprised 153 patients diagnosed with uncontrolled T2DM for a minimum duration of one year, all of whom were receiving the maximum doses of metformin and glimepiride. The participants were divided into two groups: the first group (n = 84) received an addition of bedtime NPH insulin, while in the second group (n = 69), SU was withdrawn and twice-daily NPH insulin was introduced. Both groups maintained the maximum tolerable doses of metformin throughout the study. Glycemic parameters and additional anthropometric and biochemical measurements were evaluated at baseline and the three-month follow-up. Baseline characteristics were comparable between the two groups. After three months, both treatment groups demonstrated similar improvements in glycemic control, with a mean HbA1c of 9.3±1.8% in the SU group and 9.3±2.2% in the non-SU group (p=0.909). Patients in the non-SU group exhibited more favourable glycemic excursions (65.9±44.9 mg/dL vs 92.8±53.8 mg/dL, p=0.052), indicating a potentially distinct mechanistic regulation of glucose homeostasis by the two therapeutic approaches. Additionally, there were relatively few variations in excursions between the two time frames observed in the non-Su group (p=0.025). Female patients and obese patients within the non-sulfonylurea group exhibited statistically significant reductions in blood glucose excursions by the end of the study (p = 0.028 and p = 0.022, respectively). This study demonstrates that SU and non-SU treatments yield similar overall glycemic control, with equivalent reductions in HbA1c levels at three months. However, non-SU treatment showed significant benefits, particularly in glycemic excursions, indicating different mechanisms influencing glucose homeostasis. A notable relationship was found between glycemic variability and non-SU treatment, especially in female and obese patients. These findings highlight the need for personalized treatment strategies, particularly with non-SU medications for specific patient subpopulations. Future research should include larger, randomized controlled trials to clarify the clinical implications and mechanisms of these treatments.

Keywords: Beta-cell function, Glucose homeostasis. Insulin resistance, Neutral Protamine Hagedorn(NPH), Sulfonylureas, Type 2 diabetes mellitus.

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1. Introduction

Type 2 diabetes mellitus (T2DM) is a multifactorial metabolic disorder characterized by defects in insulin secretion and action. The pathogenesis of T2DM is significantly influenced by a progressive decline in pancreatic beta-cell function, coupled with increasing insulin resistance in peripheral tissues, particularly in muscle, liver, and adipose tissue [1].

Glycemic control is a critical component in the management of T2DM and the mitigation of associated complications. This control is influenced by a variety of factors, including genetic predisposition, patient adherence to dietary recommendations, medication regimens, self-monitoring of glucose levels when appropriate, and the presence of therapeutic inertia [2]. At the cellular level, persistent hyperglycemia exacerbates β cell dysfunction through the cytotoxic effects of elevated glucose levels, a phenomenon referred to as glucotoxicity, which contributes to a detrimental cycle of disease progression [3].

The prevalence of uncontrolled or poorly controlled glycemic levels is estimated to be approximately 50% among individuals with diabetes [4]. Inadequate glycemic control can lead to severe microvascular and macrovascular complications through multiple pathways, including increased oxidative stress, formation of advanced glycation end products (AGEs), activation of protein kinase C (PKC), and flux through the polyol pathway. Clinically, these alterations manifest as complications affecting the heart, kidneys, eyes, and nervous system [5].

Lifestyle modifications, such as dietary changes and increased physical activity, have been associated with improved glycemic control in the early stages of T2DM. These improvements are primarily attributed to enhanced insulin sensitivity, achieved through increased expression and translocation of GLUT4, improved mitochondrial function, and reduced inflammatory signaling in insulin-responsive tissues [6]. However, as β cell function progressively declines, the implementation of pharmacological interventions becomes imperative [7].

Metformin, an oral hypoglycemic agent, exerts its effects by activating AMP-activated protein kinase (AMPK). This activation leads to a reduction in hepatic gluconeogenesis, an increase in glucose utilization by peripheral tissues, and an inhibition of intestinal glucose absorption [8]. When glycemic targets are not achieved with metformin monotherapy, combination therapy is initiated using a second pharmacological agent that operates via a distinct mechanism of action [9].

SUs function as insulin secretagogues by binding to the SU receptor 1 (SUR1) subunit of the ATP-sensitive potassium (KATP) channels in the pancreatic β-cells. This interaction results in channel blockade, membrane depolarization, calcium influx through voltage-gated calcium channels, and subsequent exocytosis of insulin granules [10]. Beyond their insulin secretory effects, SUs may enhance hepatic and peripheral insulin sensitivity by reducing glucotoxicity. However, the chronic stimulation of insulin secretion independent of glucose concentrations raises concerns regarding potential β-cell exhaustion, characterized by hyperfunction or accelerated loss of β-cell functionality [7].

As T2DM advances, the oral agents administered at the maximum tolerated doses may become insufficient to attain and maintain the target haemoglobin A1c (HbA1c) level of 7 [2]. This therapeutic inadequacy signifies a progressive decline in β-cell functionality, with the majority of patients necessitating insulin therapy approximately 5 to 10 years post-onset of the disease [11]. According to current clinical guidelines, patients who fail to achieve the target HbA1c with dual or triple oral therapy or those presenting with an HbA1c level exceeding 9% should commence insulin therapy [12].

Insulin initiation may be approached through various strategies, including administering basal insulin (typically a long-acting insulin analogue) once daily, using premixed insulin formulations twice daily, or implementing intensive regimens involving multiple daily injections of insulin [12]. The rationale for employing the "evening and prandial" basal insulin strategy is based on the integration of SUs, which provides an incomplete basal insulin profile, with basal insulin, thus creating a synergistic mechanism: basal insulin limits hepatic glucose production during fasting and reduces fasting glucose levels, whereas daytime SUs enhance endogenous insulin secretion and modulate postprandial glucose levels [13].

This study evaluates and compares the efficacy and safety of combined oral anti-hyperglycemic agents including SU glimepiride 4 mg with daily bedtime Neutral Protamine Hagedorn (NPH), versus twice-daily basal insulin therapy without SU in patients with uncontrolled T2DM.

2. Material and Methods

2.1. Study Design and Setting

A prospective cohort study was conducted at Faiha Specialized Diabetes, Endocrine, and Metabolism Center (FDEMC) in Basrah, Iraq, from May 2024 to April 2025.

The study aimed to compare the clinical outcomes of patients with uncontrolled T2DM for more than a year who switched from oral antidiabetic agents to NPH due to inadequate glucose control. Participants were divided into two groups: (1) those who stopped sulfonylurea (SU) treatment and started NPH monotherapy, and (2) those who continued SU along with NPH therapy.

2.2. Participants and Intervention

The study enrolled 153 patients (61 males and 92 females) diagnosed with uncontrolled diabetes, as indicated by an HbA1c level greater than 9%. Participants received metformin at a dosage of 1 g twice daily in conjunction with glimepiride at a dosage of 4 mg each morning for a minimum duration of 12 months. The subjects were allocated into two distinct treatment groups. The first group (n = 84) was administered glimepiride at a dosage of 4 mg along with metformin at 1 g twice daily, supplemented by NPH insulin at bedtime, initiated at a dosage of 0.2 U/kg. The dosage of NPH insulin was subsequently adjusted based on self-monitoring of blood glucose (SMBG) results. The second group, the non-SU group (n = 69), was administered metformin at a dosage of 1 g twice daily, in conjunction with twice-daily NPH insulin. The initial insulin dosage was set at 0.2 units per kilogram, with two-thirds administered in the morning and one-third in the evening. This insulin dosage was subsequently adjusted by 2-4 units every three days based on self-monitored blood glucose (SMBG) results, while glimepiride was discontinued. Both groups were maintained on the maximum tolerable metformin dose and other standard care medications, including antihypertensive and lipid-lowering agents, as clinically appropriate.

2.3. Inclusion and Exclusion Criteria

The inclusion criteria for this study were as follows: a diagnosis of T2DM for a duration exceeding one year, with a most recent HbA1c > 9%, and currently undergoing dual oral antidiabetic therapy that includes glimepiride and metformin. Additionally, participants were required to demonstrate a willingness to initiate insulin therapy. The exclusion criteria included individuals with Type 1 Diabetes Mellitus, those with new-onset T2DM or a duration of diabetes mellitus of less than one year, patients already receiving insulin treatment, as well as individuals with chronic kidney disease, chronic liver disease, or those taking steroids or other medications that could influence glycemic control.

2.4. Anthropometric Measurements and Laboratory Assessments

All participants underwent height and weight measurements, from which the body mass index (BMI) was calculated using the formula: BMI = weight/height^2. Participants were subsequently categorized into two groups: obese (BMI $\geq$ 30 kg/m^2) and non-obese (BMI < 30 kg/m^2). Blood samples were obtained at the time of enrollment and after a three-month follow-up to assess the following parameters: HbA1c, fasting blood glucose (FBG), random blood glucose (RBG), and lipid profile components, including total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL). Glycemic excursions, defined as the difference between random (postprandial) and fasting (pre-prandial) blood glucose levels, were evaluated as an indicator of blood glucose variability.

2.5. Statistical Analysis

The data analysis was conducted utilizing the SPSS software. The continuous variables were compared between the two groups by applying the two-sample t-test, while categorical variables were analyzed using the Pearson Chi-square test or the Fisher's Exact test, as deemed appropriate. A pairwise statistical comparison between the groups was performed, with a p-value of less than 0.05 considered statistically significant. Additionally, the impact of factors such as age, sex, body mass index (BMI), lipid profiles, and duration of diabetes on treatment response was also evaluated.

3. Results

Baseline characteristics are presented in Table 1. There was no statistically significant difference between the two groups concerning age, sex, body mass index (BMI), initial HbA1c levels, fasting glucose, and lipid profiles.

Table 1.
Baseline Characteristics of Study Participants

Characteristic	Non-SU(n = 69)	SU(n = 84)	p-value
Age, years	54.0 ± 11.8	53.4 ± 9.0	0.694
Sex, n (%)			0.469
Male	29 (42.0)	32 (38.1)	
Female	40 (58.0)	52 (61.9)	
BMI, kg/m²	29.8 ± 6.3	30.4 ± 5.1	0.496
Obese, n (%)	34 (50.7)	40 (47.6)	0.703
OAD use*, n (%)			0.095
Yes	3 (4.3)	10 (11.9)	
No	66 (95.7)	74 (88.1)	
HbA₁c, %	11.6 ± 1.7	11.1 ± 1.5	0.110
≥ 10%, n (%)	56 (81.2)	64 (76.2)	0.457
< 10%, n (%)	13 (18.8)	20 (23.8)	
Fasting BG, mg/dL	288.7 ± 87.5	259.2 ± 78.9	0.082
≥ 300, n (%)	18 (42.9)	16 (28.1)	0.126
< 300, n (%)	24 (57.1)	41 (71.9)	
Random BG, mg/dL	342.6 ± 110.9	353.8 ± 89.2	0.690
Total Cholesterol, mg/dL	193.7 ± 49.2	186.3 ± 49.1	0.359
HDL, mg/dL	41.5 ± 8.8	41.8 ± 11.3	0.858
≥ 40, n (%)	41 (62.1)	43 (52.4)	0.237
< 40, n (%)	25 (37.9)	39 (47.6)	
Triglycerides, mg/dL	201.9 ± 96.4	229.8 ± 115.4	0.117
≥ 200, n (%)	32 (48.5)	44 (52.4)	0.362
< 200, n (%)	34 (51.5)	40 (47.6)	
LDL, mg/dL	131.4 ± 46.5	119.2 ± 41.9	0.095
Glycemic Excursions, mg/dL⁺	121.0 ± 113.7	114.7 ± 79.1	0.885

Note: *OAD: other oral antidiabetic drugs (excluding metformin and SU).
⁺Excursions = maximum post-prandial – pre-meal BG.
All data are presented as mean ± SD or n (%). Significant differences are highlighted in bold.

The primary outcomes of the treatment after three months are presented in Table 2. No statistically significant differences were observed between the mean levels of Random Blood Glucose (RBG), Fasting Blood Glucose (FBG), and HbA1c across the groups. Nevertheless, reductions in excursions of blood glucose levels before and after the intervention were noted for all participants; this reduction was particularly significant in the non-Sulfonylurea group, with values decreasing from (121.0 ± 113.7) to (65.9 ± 44.9, p-value 0.025).

Table 2.
Main outcomes after 3 months treatment.

Outcome	Non-SU(n = 69)	SU(n = 69)	p-value
Glycemic Control			
HbA₁c, % (mean ± SD)	9.3 ± 2.2	9.3 ± 1.8	0.909
ΔHbA₁c, % (mean ± SD)	2.2 ± 2.1	1.9 ± 1.7	0.427
HbA₁c < 7%, n (%)	7 (14.3)	4 (6.6)	0.179
Fasting Blood Glucose (FBS)			
FBS at 3 mo, mg/dL (mean ± SD)	172.0 ± 75.1	149.8 ± 71.4	0.155
ΔFBS, mg/dL (mean ± SD)	110.8 ± 107.3	117.6 ± 100.9	0.785
FBS < 130 mg/dL, n (%)	16 (39.0)	25 (51.0)	0.255
Random Blood Sugar (RBS)			
RBS at 3 mo, mg/dL (mean ± SD)	219.0 ± 61.6	237.2 ± 74.0	0.258
ΔRBS, mg/dL (mean ± SD)	131.8 ± 129.4	117.1 ± 110.7	0.744
RBS < 180 mg/dL, n (%)	8 (23.5)	9 (16.4)	0.325
Glycemic Excursions			
Excursion₁ (baseline), mg/dL	121.0 ± 113.7	114.7 ± 79.1	0.885
Excursion₂ (3 mo), mg/dL	65.9 ± 44.9	92.8 ± 53.8	0.052
Within-group change, p	**0.025**	0.170	—

Note: Data are presented as mean ± SD or n (%). Δ indicates change from baseline. Significant within-group reduction in excursions ($p < 0.05$) is shown in bold.

Table 3 illustrates the associations of various factors with optimal glycemic control, including age, sex, BMI, lipid parameters, and duration of diabetes. However, none of these variables significantly influenced the differences in HbA1c between treatment groups after this study.

Table 3.
Factors associated with end-of-study HbA1c.

Characteristic	Category	Non-SU Mean ± SD (%)	SU Mean ± SD (%)	p-value
Age (years)	≥ 53	9.0 ± 2.4	9.1 ± 1.8	0.793
	< 53	9.6 ± 2.1	9.4 ± 1.9	0.765
Sex	Male	9.3 ± 2.2	9.1 ± 1.6	0.641
	Female	9.3 ± 2.3	9.4 ± 2.0	0.838
Duration of T2DM (years)	≥ 5	9.8 ± 2.2	9.3 ± 1.6	0.252
	< 5	8.6 ± 2.2	9.2 ± 2.4	0.443
BMI (kg/m²)	Obese	9.0 ± 2.2	9.3 ± 2.1	0.581
	Non-obese	9.8 ± 2.2	9.2 ± 1.6	0.263
OAD use*	Yes	5.9 ± 0.0	9.2 ± 1.2	0.055
	No	9.4 ± 2.2	9.3 ± 1.9	0.791
Baseline HbA1c (%)	≥ 10	9.4 ± 2.4	9.6 ± 1.9	0.690
	< 10	8.6 ± 0.9	8.1 ± 1.2	0.356
Fasting BG (mg/dL)	≥ 300	9.6 ± 2.8	10.3 ± 2.2	0.513
	< 300	9.0 ± 1.7	9.1 ± 1.4	0.728
Random BG (mg/dL)	≥ 339	9.5 ± 1.8	9.7 ± 2.1	0.821
	< 339	8.2 ± 1.3	8.6 ± 0.4	0.371
HDL (mg/dL)	≥ 40	9.5 ± 2.2	9.1 ± 1.9	0.516
	< 40	9.2 ± 2.2	9.5 ± 1.8	0.691
Triglycerides (mg/dL)	≥ 200	9.6 ± 2.4	9.5 ± 1.9	0.794
	< 200	9.1 ± 1.9	8.9 ± 1.6	0.788

Note: Data are presented as mean ± standard deviation.
Abbreviations: SU, sulfonylurea; non-SU, non-sulfonylurea; OAD, other oral antidiabetic drugs (excluding metformin and sulfonylureas).

Table 4 presents the parameters affecting glycemic excursions at the end of the study. Female and obese patients in the non-sulfonylurea (non-SU) group showed a statistically significant reduction in blood glucose excursions (p = 0.028). A similar significance was noted among obese patients in the non-SU group (p = 0.022).

Table 4.
Factors affecting glycemic excursions at end of study.

Characteristic	Category	Non-SU Mean ± SD (mg/dL)	SU Mean ± SD (mg/dL)	p-value
Age (years)	≥ 53	70.8 ± 49.0	98.6 ± 62.8	0.176
	< 53	56.2 ± 34.0	87.4 ± 45.5	0.098
Sex	Male	71.4 ± 58.3	87.3 ± 65.3	0.563
	Female	61.5 ± 32.2	95.5 ± 48.9	**0.028**
Duration of T2DM (years)	≥ 5	68.4 ± 54.0	94.8 ± 56.7	0.191
	< 5	63.4 ± 34.7	88.8 ± 50.3	0.175
BMI (kg/m²)	Obese	64.0 ± 32.2	102.0 ± 41.4	**0.022**
	Non-obese	55.6 ± 37.0	84.2 ± 63.5	0.157
Other OAD use*	Yes	77.0 ± 40.7	87.0 ± 61.4	0.817
	No	64.5 ± 46.1	93.8 ± 53.8	0.051
Baseline HbA1c (%)	≥ 10	64.9 ± 46.4	90.2 ± 54.8	0.101
	< 10	71.8 ± 40.4	104.0 ± 53.2	0.351
Fasting BG (mg/dL)	≥ 300	61.7 ± 40.4	78.9 ± 56.8	0.527
	< 300	64.3 ± 31.4	95.9 ± 48.4	0.063
Random BG (mg/dL)	≥ 339	70.3 ± 63.3	85.6 ± 43.2	0.642
	< 339	63.0 ± 20.2	110.5 ± 64.8	0.211
HDL (mg/dL)	≥ 40	59.1 ± 33.2	84.6 ± 50.3	0.141
	< 40	54.2 ± 35.4	104.9 ± 52.4	**0.014**
Triglycerides (mg/dL)	≥ 200	53.1 ± 32.3	88.7 ± 46.6	0.062
	< 200	59.9 ± 35.1	95.2 ± 58.8	0.059

Note: Data are presented as mean ± SD. Significant p-values (p < 0.05) are shown in bold.
Abbreviations: SU, sulfonylurea; non-SU, non-sulfonylurea; OAD, oral antidiabetic drug (excluding metformin and SU); BG, blood glucose; HDL, high-density lipoprotein.

4. Discussion

When oral hypoglycemic agents are no longer effective, an alternative strategy involves administering two or more insulin injections without the concomitant use of oral medications. This approach is adopted when oral agents fail to achieve adequate glycemic control [14].

Our prospective cohort study compared two insulin treatments regimens in patients with poorly controlled T2DM: basal insulin plus SUs versus twice-daily NPH without SU. The findings of the study demonstrate that both regimens achieved similar improvements in overall glycemic control as measured by HbA1c, fasting blood glucose, and random

blood glucose after three months of treatment as seen in Table 2. However, significant differences were observed in glycemic excursions, which may have implications for long-term outcomes.

A study involving 53 Chinese patients determined that glycemic control improvements were comparable when multiple insulin injections were compared with a regimen that involved the addition of evening insulin to ongoing oral therapy, including SU [9].

In our study, the findings suggest that both regimens, adding NPH insulin to SU or utilizing twice-daily NPH insulin, demonstrate equivalent efficacy in enhancing glycemic control, as measured by FBG, self-monitored blood glucose (SMBG), and HbA1c over a three-month duration. Notably, a marginally higher proportion of patients in the non-SU group (7 out of 49, 14.3%) achieved an HbA1c level below 7% compared to the SU group (4 out of 61, 6.6%); however, this difference was not statistically significant (p-value 0.179). These findings align with the Veterans Administration Cooperative Study of Diabetes Mellitus, which reported that transitioning individuals from bedtime insulin and daytime SU to twice-daily insulin injections resulted in additional subjects attaining near-normal glucose control without a statistically significant reduction in HbA1c levels [15].

In our study, we noted that both regimens, adding basal insulin to ineffective OADs or switching to twice-daily basal insulin, positively impacted the reduction of glycemic fluctuations. The decrease in glycemic variability was statistically significant in the latter regimen (p-value 0.025) as seen in Table 3. A clinical trial published in the Turkish Journal of Endocrinology & Metabolism 2014 show that the addition of basal insulin analogues to the treatment of T2DM who have not achieved appropriate glycemic control with OADs had a favorable effect on glycemic fluctuation. Though not statistically significant [16].

According to Table 4 glycemic excursions at the end of the three month study were significantly greater in the SU group compared to non-SU comparators across most patient subgroups. However, only a small percentage of these groups exhibited statistically significant differences between the two treatment arms, and the frequency of significant differences across all three factors was exceedingly low. Specifically, mean excursions in the SU group were notably higher in female patients (95.5 ± 48.9 mg/dL) compared to the non-SU group (61.5 ± 32.2 mg/dL) ($p = 0.028$). Moreover, subjects classified as obese (BMI ≥ 30 kg/m²) demonstrated increased SU-associated glycemic fluctuations (102.0 ± 41.4 mg/dL) relative to the non-SU group (64.0 ± 32.2 mg/dL; $p = 0.022$). Additionally, patients with a random pre-treatment glucose level of ≤ 339 mg/dL exhibited significantly greater SU-related mean excursions (109.4 ± 52.4 mg/dL) compared to the non-SU group (54.2 ± 35.4 mg/dL; $p = 0.014$). In contrast, variables such as age, duration of diabetes, baseline HbA_{1c}, fasting blood glucose, HDL levels, triglycerides, and the combinatory use of oral antidiabetic agents did not significantly influence the differences in glycemic excursions between SU and non-SU groups (all $p > 0.05$). These findings suggest that female sex, obesity, and lower baseline random glucose levels may serve as potential risk factors for increased glycemic variability in patients treated with Sus [17].

The result of our study is illustrated in Figure 1. A demonstrates that the short-term effectiveness of SU-based regimens is comparable to that of non-SU treatments in achieving reductions in fasting blood sugar (FBS) and random blood sugar (RBS). However, a significant distinction was observed concerning glycemic variability: individuals receiving SUs exhibited consistently higher variability, regardless of whether measurements were taken pre- or post-treatment. Despite comparable baseline mean HbA1c levels (9.3%) between the groups, the numerical reduction in mean HbA1c was slightly greater in the non-SU group (2.2% versus 1.9%), although this difference did not attain statistical significance Figure 1. B.

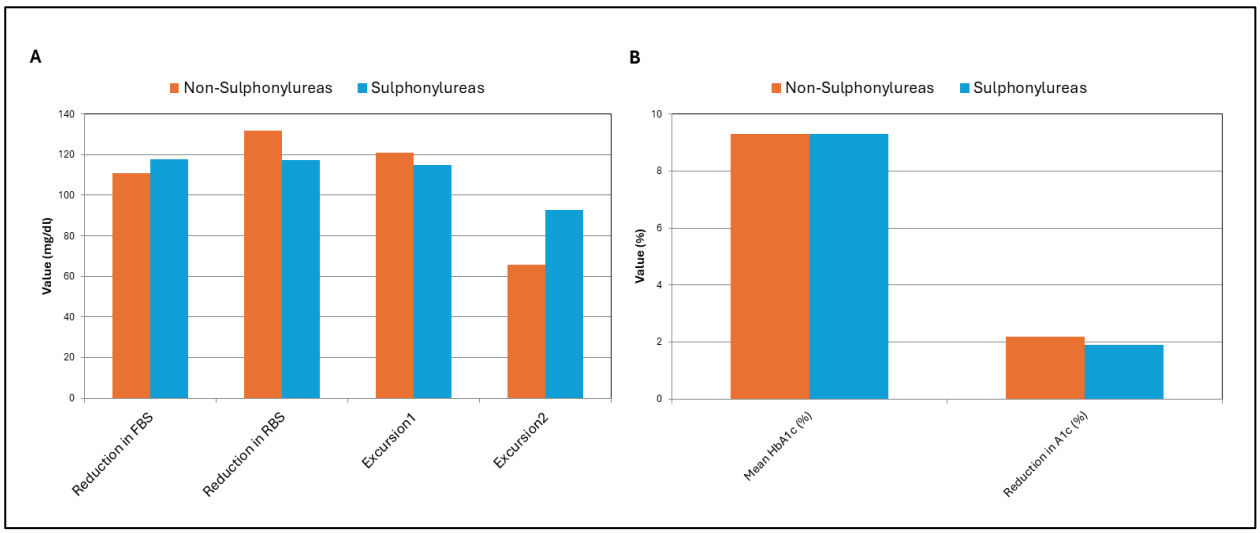

Figure 1.
Glycemic outcomes for SU versus non-SU.

(A)SU exhibited a reduction in fasting blood sugar (FBS) and post-treatment excursions to a lesser extent, while non-SU demonstrated a more efficient reduction in random blood sugar (RBS) and pre-treatment variability. The glycolic excursion 1 before the treatment and excursion 2 after the treatment were pronounced significantly between the two groups.

(B) Both patient groups participating in the study with an HbA1c level of 9.3%; the observed decreases were numerically, though not statistically, greater for the non-SU group (2.2% versus 1.9%).

The elevated glucose excursions associated with SU may suggest an increased exposure to oxidative stress, inflammation, and vascular dysfunction, potentially leading to exacerbated long-term metabolic and vascular complications. Consequently, while SU can achieve effective glycemic control, their association with greater variability necessitates careful consideration of the potential adverse effects, particularly in contexts of decreased perfusion, when selecting appropriate antidiabetic therapies [18].

Regarding the influence of sex, duration of diabetes, initial body mass index (BMI), and initial triglyceride levels on glycemic control between the two regimens, our study did not identify any statistically significant effects. Lee, et al. [19] conducted a retrospective study involving a cohort of Korean patients with T2DM who were receiving add-on therapies to metformin. Their findings indicated that users of SUs initially demonstrated a greater mean reduction in HbA1c compared to non-users. However, this difference was "erased after adjustment for covariates," implying that baseline characteristics such as sex, body mass index, duration of diabetes, and lipid parameters had minimal influence on the glucose-lowering response to Sus [19]. On the other hand a study on the effects of combined insulin-sulfonylurea therapy in T2DM found that one of the patient characteristics that best predicted a beneficial response to combined insulin-glyburide therapy in terms of a reduction in HbA1c levels was higher BMI [15]. This was in contrast with other study which suggested that relatively non-obese persons with short duration of type II diabetes are the best candidates for bed time insulin and day time sulfonylurea [20]. Another study found a significant correlation existed between initial concentrations of serum triglycerides and glycemic control at 12 months when evening insulin was added to oral therapy [21]. However, in our study we found that both female patients and patients with high BMI showed statistically significant response regarding excursion in blood glucose as measured by maximum difference between pre and post prandial blood glucose when kept on twice basal insulin. We failed to find previous studies with similar results and such results need to be investigated by more complex methods.

The comparable efficacy of both regimens in reducing HbA1c can be explained by their complementary effects on the pathways regulating glucose homeostasis. Basal insulin primarily suppresses hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis while promoting glucose uptake in peripheral tissues [22]. Insulin binds to its receptor, activating the insulin receptor substrate (IRS) proteins and initiating a signalling cascade involving phosphatidylinositol 3-kinase (PI3K) and protein kinase B (Akt), which ultimately leads to GLUT4 translocation to the cell membrane and increased glucose uptake [23]. SU, in contrast, act primarily on pancreatic beta-cells by binding to the SUR1 subunit of ATP-sensitive potassium (KATP) channels, leading to channel closure, membrane depolarization, and insulin secretion through a calcium-dependent mechanism [24]. This direct stimulation of endogenous insulin secretion provides additional insulin during the day, particularly to control postprandial hyperglycemia.

Differences in glycemic fluctuation can significantly affect the overall metabolism. Fluctuating blood sugar levels increases oxidative stress by stimulating the production of reactive oxygen species (ROS). This activation triggers redox-sensitive inflammatory pathways such as NF-κB and JNK and contributes to endothelial dysfunction by reducing nitric oxide availability. These effects worsen with the activation of protein kinase C (PKC) isoforms and the accumulation of advanced glycation end-products (AGEs), impairing insulin signalling and vascular function. As a result, these changes lead to progressive β-cell failure, insulin resistance, and microvascular and macrovascular complications. Importantly, transient fluctuations in glucose levels may have more harmful effects than sustained hyperglycemia, highlighting the clinical importance of glucose variability as a therapeutic target in treatment strategies. It causes significant harm through oxidative stress, increased inflammation, epigenetic changes, endothelial dysfunction, and rebound hypoglycemia [25-27].

Current clinical guidelines from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) do not support adding SU to basal insulin therapy. This recommendation is based on the increased risk of hypoglycemia associated with SU and their unclear additional glucose-lowering benefits. Evidence from randomized controlled trials shows that combining SU with basal insulin results in only limited improvements in HbA1c levels compared to safer alternatives like metformin, GLP-1 receptor agonists, or SGLT2 inhibitors. Additionally, these alternatives enhance insulin's effects and offer extra benefits, including weight loss, cardioprotection, and renoprotection [25, 28].

From a clinical perspective, our findings suggest that both treatment approaches can effectively improve glycemic control in patients with poorly controlled T2DM. Therefore, the choice between these regimens may depend on other factors, including patient preferences, risk of hypoglycemia, cost considerations, and concerns about long-term beta-cell function.

Our study has several methodological strengths, particularly its prospective design and the intentional recruitment of patients with severe glycemic dysregulation, indicated by an average baseline HbA1c of over 9%. Additionally, including comprehensive measurements of glycemic parameters, such as fasting and postprandial glucose levels, along with an analysis of the frequency and duration of glucose excursions, provides a deeper understanding of glucose metabolism beyond traditional HbA1c assessments. However, several critical limitations must be acknowledged. The short follow-up period of just three months is a significant constraint, limiting the ability to determine long-term clinical outcomes and accurately assess beta-cell function. As a result, the potential for detecting ongoing or progressive metabolic issues remains unclear. Furthermore, the lack of empirical data on essential biomarkers, such as oxidative stress, inflammatory mediators, and direct measurements of beta-cell function, significantly limits the evidence needed to support the proposed mechanisms behind the treatment effects in our study.

5. Conclusion

Our study found no statistically significant difference in terms of glycemic control between the regimen of adding basal insulin on top of oral antidiabetic drugs, including SUs and the regimen of twice-daily basal insulin without the use of SUs. Furthermore, we did not observe any statistically significant effects of the studied anthropometric variables such as age, sex, and BMI, as well as duration of diabetes and lipid profile, on the response to treatment between the two regimens. However, we found that both female patients and patients with high BMI showed statistically significant response regarding excursion in blood glucose as measured by maximum difference between pre and post prandial blood glucose when kept on twice basal insulin.

Future investigations should focus on evaluating long-term outcomes (e.g., preservation of beta-cell function, incidence of complications, and quality of life metrics) to enhance clinical decision-making in this challenging patient demographic. Such insights would be instrumental in elucidating the biological implications of sequential type-specific therapies and their cellular applications.

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