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Impact of switching from neutral protamine hagedorn insulin (NPH) to glargine insulin on glycemic control and clinical outcomes in pediatric patients with type 1 diabetes

Hiba Abdelmunim Suliman Elsheikh [a,*], Safaa Badi [b], Ahmed Hafiz Kamal [c], Mazen Karar [c], Mohamed Fouad [c], Omar Khalid [c], Omnia Abdullah [c], Setana Mamoun [c]

[a] Department of Clinical Pharmacy, The National University, Almughtaribeen University, Khartoum, Sudan
[b] Department of Clinical Pharmacy, Faculty of Pharmacy, Omdurman Islamic University, Khartoum, Sudan
[c] National University, Khartoum, Sudan

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ABSTRACT

Background: Treatment of type 1 diabetes requires insulin therapy, and various types of insulin can be used. Insulin glargine has been shown to provide effective glycemic control with reduced hypoglycemia. However, there are no prior studies investigating the effects of switching from neutral protamine hagedorn (NPH) insulin to glargine insulin in Sudan, due to limited use of glargine insulin and funding constraints.
Objective: This study aimed to assess the impact of switching from NPH insulin to glargine insulin on glycemic control in children with type 1 diabetes, and to identify factors precipitating the switch.
Methods: This observational cross-sectional study included 221 children (aged 1–19 years) with type 1 diabetes who switched from NPH insulin to glargine insulin at Mohamed Alamin Hamid Pediatric Hospital. Simple random sampling was used to select participants.
Results: Of the 221 participants, 83 (37.5 %) switched to glargine insulin, 60 (27.1 %) continued on NPH insulin, and 78 (32.5 %) started on glargine from the beginning. Switching to glargine insulin was associated with a statistically significant reduction in HbA1c ($P < 0.001$) and a significant decrease in fasting blood glucose (FBG) levels ($P < 0.001$). Additionally, 69.9 % of participants experienced an increase in their insulin dose ($P < 0.001$). The primary reason for switching, as reported by 57.8 % of caregivers, was that mixed insulin had not effectively controlled blood glucose, with 60.4 % of these participants experiencing hypoglycemia. Of those who switched, 94 % were satisfied, with 33.3 % reporting better blood sugar control and 89.7 % indicating improvements in general health. A significant increase in weight was observed after switching to insulin glargine ($P = 0.0001$).
Conclusion: Switching from NPH to glargine insulin among Sudanese pediatric patients with type 1 diabetes offer significant benefits in glycemic control, as reflected by improved HbA1c and FBG levels. Additionally, insulin dose and weight increased, contributing to enhanced overall health and blood glucose management. Hypoglycemia was a major reason for switching.

1. Introduction

Treatment of type 1 diabetes mellitus (T1DM) requires insulin therapy. The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive diabetes management in both adults and adolescents leads to better glycemic control and reduces the risk of complications.[1] Achieving optimal glycemic control is essential to decrease the morbidity and mortality associated with diabetes mellitus (DM) by preventing or delaying complications.[2] Insulin therapy for people with T1DM should aim to closely match the physiological insulin profile as much as possible.[3] Various types of insulin can be used in insulin injection therapy, and multiple methods exist for optimizing

Abbreviations: T1DM, Type 1 Diabetes Mellitus; NPH, Neutral Protamine Hagedorn; HbA1c, Hemoglobin A1c; FBG, Fasting Blood Glucose; MMAS, Morisky Medication-Taking Adherence Scale; SPSS, Statistical Package for the Social Sciences; IGF1R, Insulin-like Growth Factor Receptor 1; Gla-300, Insulin Glargine 300 units/mL; BMI, Body Mass Index; IGlar, Insulin Glargine; DKA, Diabetic Ketoacidosis; FPG, Fasting Plasma Glucose..

* Corresponding authors.
E-mail address: hooby1983@gmail.com (H.A.S. Elsheikh).

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metabolism through insulin management.[4] The introduction of longer-acting and rapid-acting insulin analogs, including once-daily basal insulin with a smooth 24-h action profile, has provided effective glycemic control with a reduced risk of hypoglycemia, particularly nocturnal hypoglycemia.[5] Hypoglycemia is a common complication of T1DM, especially in children. Preventing severe and recurrent hypoglycemia is a key goal of diabetes management.[6] Poor metabolic control and lifestyle irregularities are significant contributors to the exacerbation of hypoglycemia.[7,8] Studies have reported nocturnal hypoglycemia prevalence rates of up to 70 % in children and 50 % in adolescents.[9] Insulin glargine offers a consistent antihyperglycemic effect over nearly 24 h without a peak, distinguishing it from NPH insulin and long-acting zinc-based insulins.[10,11]

Evidence from large, randomized, controlled trials has confirmed the effectiveness and tolerability of insulin glargine compared to NPH insulin, with a tendency to cause less hypoglycemia.[12] However, studies on switching from premixed insulin to a glargine-based regimen in routine clinical practice are limited. Previous research has shown that switching to insulin glargine in T1DM patients who were not adequately controlled with premixed insulins resulted in significant improvements in glycemic control, as evaluated by HbA1c% and hypoglycemia incidence.[13] Other variables, such as insulin dose and fasting blood glucose, are also important metrics to assess the impact of glargine therapy.[14] In Sudan, statistics from 2015 showed that the incidence of T1DM among children and young individuals under 20 years old was 10.1 per 100,000, with a prevalence of 0.74 per 1000.[15] However, the use of long-acting insulin analogs is limited in many African countries due to funding restrictions and limited availability.[16,17]

To date, no studies have assessed the impact of switching from NPH insulin to insulin glargine in children with T1DM in Sudan. Therefore, this study aimed to evaluate the impact of this switch on glycemic control in Sudanese children with T1DM.

2. Methodology

2.1. Study design

This study was an observational, cross-sectional study conducted at Mohamed Alamin Hamid Pediatric Hospital. The study took place between November 2022 and February 2023 and included all children with type 1 diabetes mellitus (T1DM) who switched from neutral protamine hagedorn (NPH) insulin to insulin glargine. The diagnosis of T1DM was established according to the International Society for Pediatric and Adolescent Diabetes (ISPAD) Consensus Guidelines of 2018 (https://www.ispad.org/page/ISPADGuidelines2018).

2.2. Sample size and study setting

The sample size was calculated using the formula for prevalence studies without a finite population[18]:

n = \frac{Z^2 P(1-P)}{d^2}.

Where:

- n = sample size.
- Z = statistic at a 95 % confidence level.
- d = precision (5 % or 0.05).
- P = expected prevalence or proportion = 0.075 %.

Based on the prevalence calculated by Saad et al.[15] for children (6 months to 19 years) with T1DM in Khartoum State (2015), the total number of participants was 117 children and adolescents. A total of 221 participants (aged ≤19 years) were enrolled, though the study acknowledges that this sample size is limited, which may result in a smaller subgroup for analysis with restricted demographic characteristics. The study reports no selection bias in the sample. After obtaining written informed consent from the adolescents and their guardians, the 221 T1DM study subjects were divided into three groups based on their insulin therapy. Group 1 consisted of patients who switched to insulin glargine, Group 2 continued on NPH insulin, and Group 3 started on insulin glargine from the beginning. All included patients were switched from multiple daily NPH injections to a single bedtime injection of insulin glargine (Lantus).

2.3. Inclusion and exclusion criteria

Eligible participants were children and adolescents aged 19 years or younger who had switched from NPH insulin to insulin glargine, with a minimum of 3 months since their diabetes diagnosis and at least 3 months since switching insulin regimens. Exclusion criteria included individuals older than 19 years and those with less than 3 months of diabetes duration or less than 3 months on the switched insulin regimen.

2.4. Data collection

A detailed clinical history was collected through patient questionnaires and medical records (follow up card) which is used by the physician during periodic consultations. The following data were recorded: demographic information, duration of insulin switching, age at switching, weight at switching, reasons for switching, insulin compliance, satisfaction with the switch, and overall treatment satisfaction. The effectiveness of the insulin switch was assessed using the following criteria: Hemoglobin A1c (HbA1c) concentrations (before switching, after 3 months and last measurement after switching), fasting plasma glucose (FBG)(before and after 3 months of switching), and insulin dose (before and after switching). These data were obtained from patient medical records, ensuring no change in basal insulin prescriptions during the follow-up period. The questionnaire (previously validated) assessed general attitudes towards the switch, without delving into individual reasons for the change. Additional factors, including physical activity and satisfaction with the switch, were evaluated using a prepared checklist (Supplementary File S1). Insulin compliance was measured using the Morisky Medication-Taking Adherence Scale (MMAS) (4 items).[19]

2.5. Statistical methods

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 28 and Microsoft Excel version 13. Descriptive statistics, including frequency tables, figures, means, and standard deviations, were used to summarize the data. Inferential statistics were conducted to identify significant differences and associations between variables.

2.6. Ethical considerations

Parents/guardians of the included children and adolescents were fully informed about the study's objectives, and written consent was obtained for the use of their data for scientific purposes as data were collected through questionnaires (Supplementary File S2). The study was approved by the ethical committees of the Ministry of Health, Khartoum State General Directorate of Medical Treatment, General Administration of Strategic Private Health Care Institution Administration on 4/1/2022 under the title Assessment of the impact of glycemic control by switching from insulin NPH to insulin Glargine by HbA1c, fasting blood glucose and insulin dose at Mohamed Alamin Hamid Pediatric hospital, Khartoum /Sudan 2022/2023 (Supplementary File S3). No specific ethical approval number was provided in the approval letter.

3. Results

A total of 221 participants with T1DM were divided into three groups based on their insulin therapy. A total of 83 participants (37.5 %)

switched to insulin glargine, 60 participants (27.1 %) continued with mixed insulin, and 78 participants (35.2 %) started on long-acting insulin from the beginning of therapy. Among those who switched to glargine, 54.2 % were male. The mean age of the participants was 13 years (±3.3 years). The mean HbA1c level while using mixed insulin was 10.7 % (±2.4 %), while the mean HbA1c level after switching to insulin glargine was 8.2 % (±1.6 %) [Table 1].

The primary reason for switching from NPH insulin to insulin glargine, as reported by caregivers, was inadequate blood glucose control with mixed insulin. According to 57.8 % of participants' caregivers mixed insulin had not effectively controlled their children's blood glucose. Among these, 60.4 % reported experiencing hypoglycemia. The main source of information about insulin side effects for 59 % of caregivers was the prescribing physician.

3.1. Presence of side effects

A total of 37.3 % of participants reported experiencing side effects from insulin(NPH) use before switching to insulin glargine. Of these, 36.7 % cited muscle weakness as a side effect [Table 2].

3.2. Adherence to insulin

A total of 42.2 % of participants reported occasionally forgetting to take their insulin, while 19.3 % indicated they were careless about insulin adherence (Supplementary File S4).

3.3. Satisfaction with switching

A total of 78 participants (94 %) expressed satisfaction with the switch to insulin glargine. Of these, 89.7 % reported that the switch had improved their general health (Supplementary File S4).

3.4. Physical activity

Before switching to insulin glargine, only 7.2 % of participants were rated as highly active. After the switch, 54.2 % were rated as highly active [Fig. 1].

Table 1
Socio-demographic characteristics and clinical data.

Variables	Responses	N	%
Residence	Inside Khartoum	77	92.8
	Outside Khartoum	6	7.2
Gender	Female	38	45.8
	Male	45	54.2
Age (month/year)	Mean(SD)	13.2 (3.3)	
Age when switching (month/year)	Mean(SD)	11.6 (7)	
Weight (kg)	Mean(SD)	41.1(13.9)	
Weight (kg) when switching	Mean(SD)	35 (13.8)	
Duration of Switching (Month/year)	6 months-11 month	15	18.1
	1 year −2 years	36	43.4
	more than 2 years	27	32.5
	Missed	5	6.0
HbA1c(%) level when patients were using mixed insulin	Mean(SD)	10.7(2.4)	
HbA1c (%)level when changed to glargine insulin during three months	Mean(SD)	9.2(1.9)	
Last HbA1c(%) level after changing to glargine insulin	Mean(SD)	8.2(1.6)	
FBG (mg/dl) level when patients were using mixed insulin	Mean(SD)	265.6 (125.9)	
FBG(mg/dl) level when changed to glargine insulin during three months	Mean(SD)	159.8 (57.6)	

Table 2
Reasons for switching from NPH Insulin to Glargine and presence of side effects.

Responses	Reasons for Switching / Side Effects	N (%)
Reasons for Switching	Not controlled blood sugar	48 (57.8 %)
	Multiple number of doses	23 (27.2 %)
	Side effects	24 (28.9 %)
	Hearing of side effects	19 (22.9 %)
Sources of Information	Physician	49 (59.0 %)
	Pharmacist	40 (48.2 %)
	TV or Radio	1 (1.2 %)
	Internet	13 (15.7 %)
	Experience from other parents	25 (30.1 %)
	Others	6 (7.2 %)
Side Effects Presence	No	53 (62.7 %)
	Yes	30 (37.3 %)
Side Effects (if present)	Effect on kidney function	1 (3.3 %)
	Effect on vision	2 (6.7 %)
	General weakness after change, weight increase	1 (3.3 %)
	Hypoglycemia	2 (6.7 %)
	Increased weight	1 (3.3 %)
	Problems with hearing, fatigue, vomiting	1 (3.3 %)
	Sensitivity	8 (26.7 %)
	Sensitivity and muscle weakness	3 (10 %)
	Weakness of muscle	11 (36.7 %)

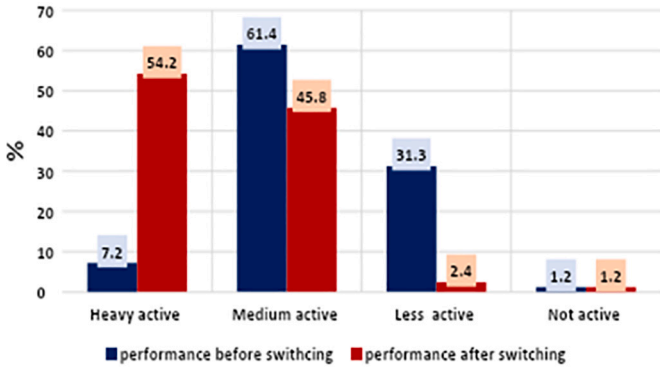

Fig. 1. Physical Activity.

3.5. Tests of significance and associations

The Chi-square test was used to determine the association between HbA1c levels after three months of switching and other factors, such as gender, duration of switching, and adherence to insulin. No statistically significant associations were found ($P > 0.05$). However, an independent sample *t*-test revealed a statistically significant difference in mean age between the HbA1c-controlled and uncontrolled groups ($p = 0.020$). Repeated measures ANOVA indicated a statistically significant difference in HbA1c levels before switching, after switching, and at the last reading ($P < 0.001$). Similarly, paired sample *t*-tests showed a statistically significant difference in fasting blood glucose (FBG) levels before and after switching ($P < 0.001$).

Paired sample t-tests revealed a statistically significant difference in participants' weight before and after switching to insulin glargine ($P = 0.000$). One-way ANOVA indicated that the weight change after

switching was not significantly associated with the duration of switching ($P = 0.138$). The insulin dose increased in 69.9 % of participants after switching to insulin glargine. The Chi-square test revealed that the duration of switching was significantly associated with an increase in insulin dose ($P = 0.002$), but no significant association was found with HbA1c levels [Tables 3, 4] [Fig. 2].

4. Discussion

Numerous studies have compared NPH and glargine as basal insulin treatments for glycemic control in pediatric patients with type 1 diabetes (T1DM). However, to the best of current knowledge, this is the first study to examine the impact of switching from NPH to insulin glargine in Sudan.

Among the 83 participants who switched to insulin glargine, more males (45) than females[38] made the switch. This contrasts with a study in Egypt, where a higher number of females[15] than males[12] switched from NPH to insulin glargine.[14]

The participants' weight significantly increased after switching to insulin glargine, which is consistent with the Egyptian study, where a significant increase in BMI was observed after switching to insulin glargine ($p = 0.004$).[14] However, other studies have reported that insulin glargine is associated with less weight gain compared to NPH insulin.[20] A meta-analysis of randomized controlled trials found that insulin detemir was associated with significantly smaller weight gain than human insulin (by 0.26 kg/m^2; $p = 0.012$).[21] In a retrospective study, no statistically significant increase in body weight was reported,[28] while another study suggested that newer forms of insulin treatment might lead to less weight gain.[29] Some studies attribute the weight gain associated with glargine to its metabolic characteristics, which are similar to human insulin but with a slightly higher affinity for the insulin-like growth factor receptor 1 (IGF1R).[22,23]

Regarding glycemic control, a significant improvement was observed in HbA1c levels ($p < 0.001$) after switching to insulin glargine. This finding aligns with a recent study by Salah NY, which reported significantly lower HbA1c levels in the glargine group at the end of the study compared to baseline ($p = 0.024$).[13] Previous studies have also reported improvements in HbA1c after switching to glargine insulin.[24–28] However, these results contrast with those of Hassan M. Mona,[14] who found no significant improvement in HbA1c levels ($p = 0.9$) after switching to glargine. A meta-analysis also reported that long-acting insulin analogues had a small but significant effect on reducing HbA1c levels (-0.07; $p = 0.026$) compared to NPH insulin.[21] This is consistent with the study by Päivärinta M, which found similar improvements in glycemic control.[30]

The variations in HbA1c results could be attributed to individual-specific differences related to biological variation, which strongly influences HbA1c levels.[31] Additionally, HbA1c has become a standard measure for evaluating individual treatment success and compliance. In the study, 80.7 % of participants reported careful adherence to insulin dosing, with more than half being particularly diligent about their insulin doses. The sample size and treatment regimen could contribute to these variations.

A statistically significant difference in fasting blood glucose (FBG) levels was also observed before and after the switch ($p < 0.001$). This is consistent with the findings of Urakami T, who reported a significant decrease in FPG levels ($p < 0.01$) after 12 months of treatment with insulin glargine. Urakami attributed this to increased insulin resistance during puberty, which was not observed in type 2 diabetes.[32] The findings on glycemic control also align with studies by Urakami et al. and Colino et al.,[26] both of which reported significant decreases in HbA1c and FBG levels. In contrast, Laviola L.[22] reported no statistically significant changes in FPG.

Regarding dose changes during the switch, 69.9 % of participants experienced an increase in their insulin dose, with a significant difference ($p < 0.001$). This contrasts with a study in Egypt, which found a significant decrease in basal insulin doses after switching to insulin glargine.[14] The difference might be attributed to the shorter treatment duration of 6 months in the Egyptian study, compared to the longer duration in the current study. The Findings are similar to those in retrospective studies, such as Laviola L., where basal insulin doses were only slightly increased, with a higher increase in the Gla-300 group.[22] The study demonstrated a direct relationship between the duration of switching and the increase in insulin dose, with a significant difference ($p = 0.002$). This aligns with findings from a study in Japan, which reported no statistically significant difference in basal, bolus, and total insulin doses during a one-year period between insulin glargine and insulin detemir groups among T1DM patients.[33]

Additionally, 57.8 % of caregivers reported that the main reason for switching to glargine was that mixed insulin had not adequately controlled their children's blood glucose levels, with 60.4 % (29 participants) experiencing hypoglycemia. A high satisfaction rate of 94 % was noted among those who switched, with 33.3 % of patients achieving better blood sugar control. This is consistent with the findings of Monami M., who reported a reduced risk of nocturnal and severe hypoglycemia in their comparison of NPH and insulin glargine,[21] as well as the study in Egypt, which showed a significant reduction in hypoglycemia and diabetic ketoacidosis (DKA) attacks ($p < 0.001$).[14]

In contrast to the present findings, a systematic review found no therapeutic advantage of insulin glargine over other insulin formulations when considering both glycemic control and the frequency and severity of hypoglycemia.[34] Additionally, another meta-analysis comparing NPH insulin and insulin glargine reported no significant differences in the risk or rate of any type of hypoglycemia when the same bolus insulin was used in both treatment arms.[35] Similarly, a recent systematic review comparing quality of life and patient-reported outcomes between insulin glargine and NPH insulin found no consistent differences in these measures.[36]

These results contradict the findings of Polonsky, whose study, consistent with those observed in the present study, reported improved patient satisfaction with insulin glargine, particularly regarding less frequent severe hypoglycemia.[37] The differences in study results may be attributed to individual variations. Self-management plays a crucial role in managing T1DM, enabling patients to assess their response to insulin therapy, monitor blood glucose targets, and prevent hypoglycemia or hyperglycemia, which aids in therapeutic adjustments.[38]

Table 3
HbA1c and fasting blood glucose comparisons at different times.

Metrics	Condition/Factor	Mean (SD)	*P* Value
HbA1c Levels	When using mixed insulin	10.8 (2.4)	<0.001
	After 3 months with long-acting insulin	9.3 (1.9)	
	Last HbA1c after switch	8.2 (1.6)	
FBG Levels	When using mixed insulin	265.6 (125.9)	<0.001
	After switching to long-acting insulin	159.8 (57.6)	
Demographics and HbA1c Control	Age - controlled vs. uncontrolled	12.9 (3.2) vs. 16.2 (3.4)	0.020
	Weight - controlled vs. uncontrolled	40.8 (3.9) vs. 46.7 (15.6)	0.328
	Gender - Female vs. Male (controlled)	45.3 % vs. 54.7 %	0.280

Table 4
Dose and duration comparisons after switching.

Duration of Switching	Dose Increase	P Value
6–11 months	9.3 % (Increased) vs. 41.7 % (Not increased)	0.002
1–2 years	48.1 % (Increased) vs. 41.7 % (Not increased)	
More than 2 years	42.6 % (Increased) vs. 16.7 % (Not increased)	

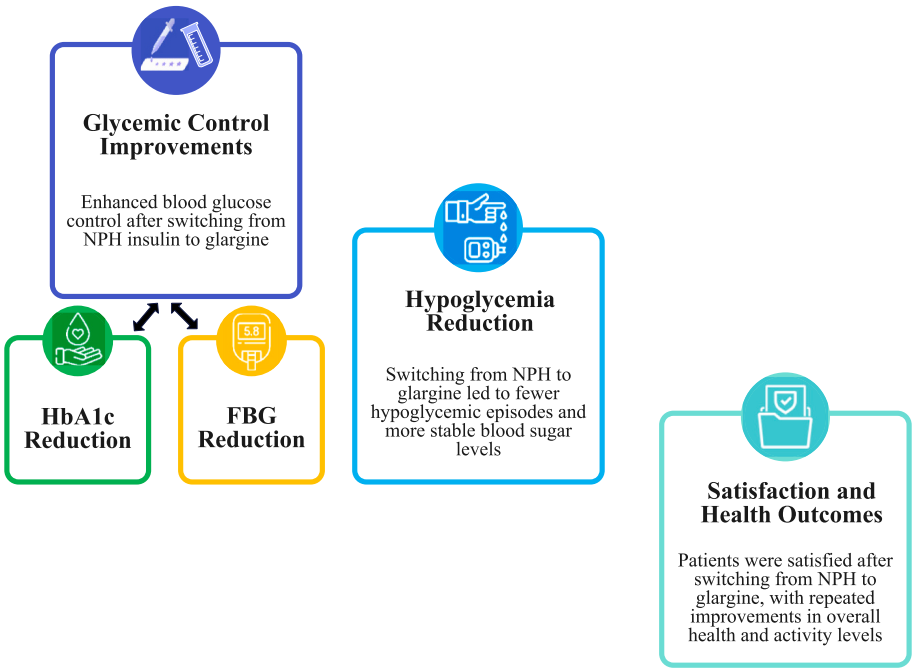

Fig. 2. Benefits From Switching from NPH To Glargine Insulin.

A total of 94 % of the participants were satisfied with switching, most of whom reported an improvement in their general health. This is consistent with the findings of Ashwell SG, who reported that insulin glargine plus insulin lispro improved treatment satisfaction and reduced the negative impact of diabetes on quality of life compared to NPH insulin.[39]

Satisfaction with the switch to insulin glargine was also reflected in changes in physical activity levels; after switching, 54.2 % of participants were rated as highly active, although this did not result in a significant difference in glycemic control.

One of the key reasons for satisfaction with switching was the reduced occurrence of side effects, with 16.7 % of participants reporting fewer side effects. The most common side effects were muscle weakness (36.7 %) and sensitivity (26.7 %), consistent with findings from a study in Turkey, which reported no side effects observed in patients switching to insulin glargine.[24]

This study has several important limitations. It was conducted at a single center, and data were collected retrospectively, which, along with the relatively low number of patients, may affect the generalizability of the results. However, this limitation does not diminish the significance of the study, as it is the first to examine the effects of switching to long-acting insulin among T1DM patients in Sudan. The continuous monitoring and follow-up with participants provided accurate data and allowed for close monitoring and anticipation of potential confounders.

5. Conclusion

The prevalence of Sudanese pediatric patients with type 1 diabetes transitioning from NPH insulin to glargine insulin is relatively high, with hypoglycemia being a primary reason for the switch. Switching from NPH to glargine can offer significant improvements in glycemic control, as demonstrated by better HbA1c and fasting blood glucose (FBG) levels. Additionally, increases in weight and insulin dose were observed, contributing to overall improvements in general health and blood glucose management. However, further comparative studies are needed to examine the long-term effects of this transition and to explore potential differences in outcomes based on individual patient characteristics.

Ethics statements

Ethical approval for this study was obtained from the Research Ethics Committee, National University/Sudan. Informed consent was obtained from the guardians of all study participants. Ethical clearance was also granted by the ethical committees of the Ministry of Health, Khartoum State General Directorate of Medical Treatment, General Administration of Strategic Private Health Care Institution Administration (Supplementary File S3).

Availability of data and materials

The data supporting the findings of this study are available upon request from the corresponding author.

CRediT authorship contribution statement

Hiba Abdelmunim Suliman Elsheikh: Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Safaa Badi:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Ahmed Hafiz Kamal:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Mazen Karar:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Mohamed Fouad:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Omar Khalid:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Omnia Abdullah:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Setana Mamoun:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

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Declaration of competing interest

The authors declare that there are no conflicts of interest in relation

to the research, authorship, or publication of this article.

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Appendix A. Supplementary data

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