Insulin Treatment Regimen of Type 1 Diabetic Children and Adolescents Attending Children Welfare Teaching Hospital/ Medical City

Swalin Moris Shamoon[1], Munib Ahmed Alzubaidi[2]

ABSTRACT:

BACKGROUND:
Insulin therapy is the cornerstone treatment of type I diabetes mellitus in children and adolescents. Different insulin types and administrative techniques are present with various efficacy and safety.

OBJECTIVE:
To evaluate the difference in the efficacy between conventional regimen and multiple daily doses regimen in treatment and supervision of type I DM among the pediatric age group.

PATIENTS & METHODS:
The present study is a clinical prospective follow-up study conducted in the Diabetic clinic of the Children Welfare Teaching Hospital at Medical Complex in Baghdad city- Iraq for a 10-month duration from the 1st of December, 2020 till the 30th of September, 2021 on a convenient sample of 75 children and adolescents with type I diabetes mellitus divided into two groups; group I (50 children treated by conventional insulin therapy) and group II (25 children treated by basal-bolus dose insulin therapy). The outcomes assessed were the number of diabetic ketoacidosis attacks & and causes, the number of hypoglycemia attacks & and causes, anthropometric measures (weight, height & BMI), and HbA1c value. The pediatrics with type I diabetes were checked out by direct contact for a 6-month from the 1st visit to the 2nd visit with phone calling follow-up to record the outcomes.

RESULTS:
Mean HbA1c level in group II diabetic children was significantly lower than the mean HbA1c of group I diabetic children at the 2nd visit (p<0.001) with no momentous discrepancy in weight, height, and BMI between the two study groups. Growth velocity was calculated and in comparison, between conventional insulin therapy and multiple daily injection regimes, no significant difference was observed (P > 0.05). The insulin dose/Kg is marked up in type I diabetic children and adolescents treated with multiple daily injection regimens.

CONCLUSION:
The multiple daily injection regimen of insulin therapy for type I diabetic children and young adults is more effective in glycemic control.

KEY WORDS: Insulin, Glycemic control, Type 1 Diabetes, Adherence, Multiple daily injections (MDI), HbA1c, Hypoglycemia, Quality of life, Self-monitoring.

[1] *Azadi teaching hospital / kirkuk health directorate.*
[2] *College of medicine / University of Baghdad.*

INTRODUCTION:

Type 1 DM is among the most prevailing metabolic illnesses in pediatrics [1]. That percentage is upsurging worldwide [2], with described increments of 2–5 % per year in the Middle East [3]. In Iraq, the incidence of T1DM in Basra City is 5–9.99/100,000 per year and was rising between 2012 and 2016 [4]. Likewise, in Al-Nassiryah City the incidence was also rising in the past 5 years[5].

Type 1 DM
Definition
Earlier termed insulin-dependent diabetes mellitus (IDDM) or juvenile diabetes, T1DM is expressed via little or no levels of endogenic insulin and by credence on exogenetic insulin to avoid the elaboration of ketoacidosis, an acute lethal complexity of T1DM[6].

Insulin types

Presently types of insulins are divided on the basis of their extent of action as rapid, short, intermediate, and long-acting, which are vacant in a concentration of 100 U/mL (U-100). Applicable mixtures as they may be framed for younger patients necessitate small doses. The objective of the insulin-replacing regimen in order to trigger the normal figure of insulin secretion as nearly as possible. This intention can best be accomplished with the help of a basal-bolus regimen using MDI or continuous subcutaneous insulin infusion (CSII) pump therapy[6,7].

Insulin forms:

A-Short-Acting (Prandial or Bolus) Regular Insulin

Regular insulin is given before meals to lessen the after-meal elevation in glucose amount. It makes hexamers after injection into the subcutaneous space slowdown its absorption[8].

B-rapid-acting (Prandial or Bolus) Insulin Analogs

When correlated to regular insulin, the rapid-acting insulin analogs advance lower after-meal hyperglycemia and less late after-meal hypoglycemia. Injection of rapid-acting insulin 15-20 minutes pre-prandial leading to greatest diminution of after-meal glucose expedition, in comparison to 30 or more minutes before-meal for regular insulin. All rapid-acting insulin, omitting fast-acting insulin aspart, are permitted for use in pumps [8].

C-Intermediate-Acting Insulins (NPH)

NPH insulin is an intermediate-acting insulin, whose start action is about 2 hours, whose apex response is 6-14 hours, and whose extent of action of 10-16 hours (reliant on the size of the dose). Due to its outspread peak and long extent of action, NPH can be delivered as basal insulin only when dosed at bedtime, or basal and prandial insulin when dosed in the morning[8].

D-Long-Acting (Basal) Insulin Analogs

Long-acting insulins afford basal insulin coverage. Basal insulins depress hepatic gluconeogenesis to inhibit glucose levels from going up throughout the fasting state in insulin-deficient patients. Amid patients with T1DM, basal insulins also avoid ketogenesis [8].

1-Insulin Glargine (Lantus)
2-Insulin Detemir (LEVEMIR)
3-Insulin Degludec (TRESIBA)
Insulin administration

Plasma insulin status in non-diabetic persons is described by rather lesser basal levels which are meal-stimulated spikes in insulin concentrations. Besides, the dose which is injected is set analytically, so it misses the accuracy of endogenously secreted insulin. Thus, no insulin replacement therapy will accurately duplex the pattern of normal insulin secretion; there will be periods of elevated plasma insulin concentrations that may yield hypoglycemia and intervals of low insulin levels that lead to hyperglycemia. So, the objective of existing insulin therapies is to decrease the recurrence and severity of expidition into the hyper- and hypoglycemic range [7].

A- Conventional regimen

Two shots of NPH and regular insulin or rapid-acting analog are given per day; one in the morning before breakfast and the second shot in the evening before dinner. Two-thirds of the total daily dose is in the morning and one-third in the evening, two-thirds NPH, and one-third is regular or rapid-acting analog. It yields the least physiologic profile with a significant danger of hypoglycemia before lunch and during the early night mixed with breakthrough hyperglycemia ahead of supper and breakfast[9]. A few studies have displayed bettered A1C levels in adults with type 1 diabetes who use continuous infusion pumps. Nonetheless, studies have not displayed the preferred strength universally for either way. Hence, the choice between multiple daily injections or a continuous pump regimen should be individualized [10].

The DCCT and its checkout, the EDIC studies, settled conventional regimens using either MDI or CSII as the definitive therapy of T1DM. Nevertheless, insulin only performs if the youngster accepts it, and other factors should be mentioned when ruling the best insulin therapy for a particular patient.

B-Multiple daily injection regimen

The Diabetes Control and Complications Trial (DCCT) revealed an excellent connection among the extent of metabolic control and diabetes problems [11]. Profound treatment of T1DM can be yielded by using multiple daily injections (MDI) of rapid-acting insulin and a once-daily injection of long-acting insulin, which mimes endogenous insulin secretion purported by continuous basal insulin secretion and meal-relating peaks. Insulin glargine (Lantus; Aventis Pharmaceuticals, US) is an obvious basal insulin analog produced by recombinant DNA technology with a duration of action of nearly 24 hours and lesser reactions [12].

Appealingly, the rapid-acting insulin bolus is given 10 to 15 minutes pre-meal, nevertheless, this is a difficult target to accomplish in many young with T1DM. For the most accurate dosing of bolus insulin, it is crucial to use an insulin-to-carbohydrate ratio (ICR) and insulin sensitivity or correction factor, along with the amount and order of change in sensor glucose levels in patients using continuous glucose monitoring equipment.

C-Insulin Pens

Insulin pens were imported primarily in 1981 as injection devices. Insulin pens are acceptable, portable, and are broadly used as a part of MDI treatment. Recently, insulin pens are accessible as disposable pens containing prefilled cartridges or recyclable insulin pens with convertible insulin cartridges. Several insulin pens allow the advantage of ½ unit dosing, a demanding need for pediatric patients and those adults with high insulin sensitivity and low insulin demand [13].

The rapid evolution of insulin pumps in the United States could be owing to the reality that the United States was the country where the first produced insulin pump was created[14].

PATIENTS & METHODS:

A clinical prospective follow-up study was conducted in the Diabetic clinic of the Children Welfare Teaching Hospital (CWTH) at the Medical Complex in Baghdad city- Iraq for the 10-month duration from the 1st of December, 2020 till the 30th of September, 2021.

Inclusion criteria

1. Type I diabetes mellitus.

2. Children and adolescents (age 2-18 years).

3. Diabetes mellitus duration of more than 6 months.

4. Patients on conventional insulin therapy and change to basal-bolus regimen for more than 6 months.

Exclusion criteria

1. Diabetes mellitus that is diagnosed within the first year of life.

2. Patients on conventional insulin therapy and change to basal-bolus regimen for less than 6 months.

3. Lost to follow up.

4. Parental refusal to study participation.

5. Honeymoon period.

Sampling

A conductive sample of 75 children and adolescents with T1DM presented to the Diabetic clinic of CWTH and split into two groups; group I (50 children treated by conventional insulin regimen) and group II (25 children treated by multiple daily injections regimen).

Data Collection

The data was collected from children and adolescents directly by the researcher or from parents or records and filled in a prepared questionnaire. The following materials were checked in every patient:

1. Sociodemographic characteristics including Age, gender, and residence.
2. Disease duration and total daily insulin dose.
3. Maternal characteristics of type I diabetic children and adolescents: Mother occupation, educational level, and caregiver type.
4. HbA1c level at the 1st visit and at the 2nd visit.
5. Anthropometric measurements at the 1st visit and the 2nd visit: Weight, height, and BMI.

Treatment regimens

❖ Group I diabetic children and adolescents received two daily injections of either Actrapid and Insulintard (lente) insulin or Mixtard insulin alone subcutaneously.

❖ Group II diabetic children and adolescents received basal-bolus doses of Aspart and Glargine insulin as multiple daily injections.

Follow up

The children and young adults with T1DM were checked up for 6 months from the 1st visit to the 2nd visit by direct contact while visiting the clinic or by phone call follow-up the outcomes or from patient records for those who could not be caught.

Outcome measures

- **Diabetic ketoacidosis**
- **Severe hypoglycemia**
- **Anthropometric measurements**

The body mass index was calculated by the researcher by the following equation: $BMI = Weight/Height^2$ in meters.

- **Glycemic control**

RESULTS:

This study included children with T1DM sorted into two groups; Group I (50 children treated by conventional insulin therapy) and Group II (25 children treated by basal-bolus dose insulin therapy).

There was greatly compelling cooperation between employee mothers and group II diabetic children ($p < 0.001$). A highly significant association was observed between the higher educational level of mothers and group II diabetic children ($p < 0.001$). No substantial discrepancies were noted between diabetic children of this two studied groups regarding caregivers ($p = 0.2$). (*Table 1& figure 1*)

Table 1: Distribution of maternal characteristics according to studied groups.

Variable	Study groups				P
	Group I		Group II		
	No.	%	No.	%	
Mother Occupation					<0.001
Employee	2	4.0	9	36.0	
Housewife	48	96.0	16	64.0	
Total	50	100.0	25	100.0	
Mother educational level					<0.001
Illiterate	9	18.0	0	-	
Primary level	23	46.0	5	20.0	
Secondary level	15	30.0	11	44.0	
Higher educational level	3	6.0	9	36.0	
Total	50	100.0	25	100.0	
Caregiver					0.2
Parents	49	98.0	23	92.0	
Relatives	1	2.0	2	8.0	
Total	50	100.0	25	100.0	
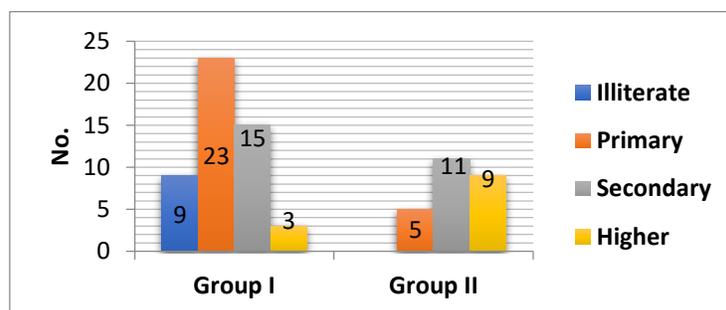
Figure 1: Distribution of maternal educational level according to studied groups.

As shown in (*Table 2*), the HbA1c level, weight, and BMI of group I children were not significantly changed between the 1st and the 2nd visits (p > 0.05), while the mean height of group I children was significantly increased at the 2nd visit (p < 0.001).

Table 2: Distribution of glycemic profile and anthropometric measures of group I children between 1st and 2nd visits.

Variable	1st visit	2nd visit	P
	Mean±SD	Mean±SD	
HbA1c (%)	9.8±2.4	9.5±2.2	0.3
Height (cm)	133.8±17.4	136.4±17.6	<0.001
Weight (Kg)	33.5±13.2	36.6±19	0.14
BMI (Kg/m^2)	17.9±3.6	18±3.4	0.7

As shown in (*Table 3*), the HbA1c level and BMI of group II children were not significantly changed between the 1st and the 2nd visits (p > 0.05), whilst the means height and weight of group II children were significantly increased at the 2nd visit (p < 0.001, p = 0.03, respectively).

Table 3: Distribution of glycemic profile and anthropometric measures of group II children between the 1st and the 2nd visits.

Variable	1st visit Mean±SD	2nd visit Mean±SD	P
HbA1c (%)	8.6±2.2	8.5±1.7	0.7
Height (cm)	133.3±19.3	135.9±19.3	<0.001
Weight (Kg)	32.7±10.2	34.7±11.3	0.03
BMI (Kg/m^2)	17.8±2.8	18.2±3.3	0.5

Mean HbA1c level at the 2nd visit of group II diabetic children was significantly lower than the mean HbA1c at the 2nd visit of group I diabetic children (p < 0.001). No great changes were observed between diabetic children of the two study groups regarding height (p = 0.9), weight (p = 0.6), and BMI (p=0.8) at the 2nd visit. (*Table 4*)

Table 4: Distribution of diabetic children according to glycemic profile and anthropometric measures at the 2nd visit.

Variable	Study groups		P
	Group I Mean ± SD	Group II Mean ± SD	
HbA1c (%)	9.5±2.1	8.5±1.7	0.04
Height (cm)	136.4±17.6	135.9±19.3	0.9
Weight (Kg)	36.6±19	34.7±11.3	0.6
BMI (Kg/m^2)	18±3.4	18.2±3.3	0.8

Regarding patients on multiple daily injection regimes, it was shown that height velocity was increased significantly during the follow-up period for all age groups; < 5 years (P =0.015), 5- 10 years (P =0.005), and > 10 years (P =0.000) as shown in Table 5.

Table 5: Disposal of diabetic children accordant to height velocity follow-up among patients with multiple daily injection regimens between 2 visits.

Age range	Height velocity		P value
	First Visit	Second visit	
<5 years	0.00±0.00	5.00±2.00	**0.015**
5-10 years	0.00±0.00	5.33±2.73	**0.005**
>10 years	0.00±0.00	5.20±3.01	**0.000**

The recent study revealed that the height velocity was increased markedly during the follow-up period for all age groups; < 5 years (P =0.012), 5- 10 years (P =0.000), and > 10 years (P =0.000) for patients on conventional insulin therapy as displayed in (table 6).

Table 6: Disposal of diabetic children accordant to height velocity follow-up among patients with conventional insulin therapy (group 2) between 2 visits.

Age range	Height velocity		P value
	First Visit	Second visit	
<5 years	0.00±0.00	7.00±2.58	**0.012**
5-10 years	0.00±0.00	4.43± 1.60	**0.000**
>10 years	0.00±0.00	±3.17 5.50	**0.000**

Regarding the comparison between conventional insulin therapy and multiple daily injection regimes, no significant difference was observed (P > 0.05) As shown in (Table 7)

Table 7: Distribution of diabetic children according to the Comparison of height velocity between group I and group II in 2 visits.

Age range	Height velocity difference (Second-first visit)		P value
	Group 1	Group 2	
<5 years	7.00±2.58	5.00±2.00	0.267
5-10 years	4.43± 1.60	5.33±2.73	0.362
>10 years	±3.17 5.50	5.20±3.01	0.760

DISCUSSION:

This study showed that children with type I diabetes mellitus treated by multiple daily injections (basal-bolus dose insulin therapy) had a marked escalation in means of height and weight over 6 months of follow-up (p< 0.001, p =0.03, respectively). This finding is consistent with the results of the Alderisio et al[15] retrospective study in Italy which reported weight and height gain for children and adolescents with type I diabetes mellitus after treatment with multiple daily injections of insulin. However, this study's findings are inconsistent with the results of Wang et al [16] meta-analysis and prospective cohort study in China which found that weight and height gain was more prevalent among type I diabetic children managed with conventional insulin regimens than children treated with multiple daily injections of insulin. This inconsistency might be attributed to differences in sociocultural habits between communities in addition to differences in sample size and methodology between the two studies. The weight and height gain in this study represented the growth of children in follow-up duration. A study conducted in the UK revealed that insulin administration of patients with both type I and type II diabetes mellitus led to weight gain[17]. This study also found that the mean height of children treated with conventional insulin therapy was significantly increased over 6 months of follow-up (p 0.001). This finding is similar to the results of the Santi et al[18] meta-analysis study in Italy which reported that linear growth for type I diabetic

children and adolescents treated by conventional insulin therapy is significantly increasing.

This study found that the mean HbA1c level after 6 months follow up (the 2nd visit) of type I diabetic children treated by multiple daily injections of insulin was significantly lower than the mean HbA1c of type I diabetic children treated by conventional regimen (p<0.04). These findings are in agreement with different literature such as the Al-Mendalawi study in Iraq [19] and Sharef et al [20] retrospective cohort study in Oman which reported that switching treatment of type I diabetic children and adolescents from conventional insulin regimen to multiple daily injections of insulin led to improvement of glycemic control protracted by HbA1c level.

Although a significant difference in HbA1c control between many daily injections of insulin and conventional regimen, each treatment regimen in this study had no independent significant effect on the HbA1c level of type I diabetic children over 6 months' follow-up (p = 0.3, p =0.7, respectively).

The aforementioned study raised a highly compelling association among employee mothers of type I diabetic children treated by multiple daily injections (p<0.001). This finding is analogous to the results of the Herbert et al [21] study in the USA which documented that the insulin regimen of type I diabetic children is related to parental occupation. Our study also found a highly significant association between the higher educational level of mothers and type I diabetic children treated by

multiple daily injections (p<0.001). This finding coincides with the results of Jeraiby's study in Saudi Arabia [22], which revealed a significant relationship between mothers' educational level and their awareness regarding insulin regimens of type I diabetic children. Gomes et al [23] multicenter studies in Brazil found that economic state, children's age, ethnicity, and care level were the dominant factors affecting intensive insulin regimens.

CONCLUSION:

- The multiple daily injections regimen of insulin therapy for type I diabetic children and adolescents is effective in glycemic control.
- The multiple daily injections regimen of insulin therapy is effective in growth for the type I diabetic pediatric age group.
- The insulin dose/Kg is marked up in type I diabetic patients managed by multiple daily injection regimens.
- The risk of diabetic ketoacidosis and hypoglycemia in type I diabetic children and adolescents treated with multiple daily injections or conventional insulin regimens is close.
- The mothers' educational level and employment are related to the decision of insulin regimen for type I diabetic children and adolescents.

REFERENCES:

1. Ziegler R, Neu A. Diabetes in Childhood and Adolescence. Dtsch Arztebl Int 2018;115:146-56.
2. Tuomilehto J. The emerging global epidemic of type 1 diabetes. Curr Diab Rep 2013;13:795-804.
3. Mamoulakis D, Galanakis E, Bicouvarakis S, Paraskakis E, Sbyrakis S. Epidemiology of childhood type I diabetes in Crete, 1990–2001. Acta Paediatr 2003;92:737-39.
4. Almahfoodh D, Alabbood M, Alali A, Mansour A. Epidemiology of type 1 diabetes mellitus in Basrah, Southern Iraq: A retrospective study. Diab Res Clin. Pract 2017;133:104-8.
5. AL-Rubaee RJ. Newly diagnosed type 1 Diabetes Mellitus in Dhi-qar City (IRAQ) sociodemographic study. IOSR Journal of Dental and Medical Sciences 2013;10:53-62
6. Britta M. Svoren, Nicholas Jospe. Diabetes mellitus in children, in Robert M. Kleigman, Bonita F. Stanton, Joseph W. St Geme, Nina F. Schor. Nelson Textbook of Pediatrics, 21st Edition. Philadelphia, Elsevier 2020:2760-90.
7. Mark A. Sperling, William V. Tamborlane, Tadej Battelino, Stuart A. Weunzimer, Moshe Phillip. Diabetes mellitus, in: Mark A. Sperling. Pediatric Endocrinology, 5th edition. Elsevier, Saunders 2021: 846-900.
8. Donner T, Sarkar S. Insulin – Pharmacology, Therapeutic Regimens, and Principles of Intensive Insulin Therapy. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK278938/
9. Cowie CC, Rust KF, Byrd-Holt DD. Prevalence of diabetes and high risk for diabetes using A1C criteria in the U.S. population in 1988–2006. Diabetes Care 2010;33:562–68.
10. Nowicka P, Santoro N, Liu H. Utility of hemoglobin A1c for diagnosing prediabetes and diabetes in obese children and adolescents. Diabetes Care 2011;34:1306–11.
11. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977-86.
12. Schober E, Schoenle E, Van Dyk J, Wernicke-Panten K; Pediatric Study Group of Insulin Glargine. Comparative trial between insulin glargine and NPH insulin in children and adolescents with type 1 diabetes mellitus. J Pediatr Endocrinol Metab 2002;15:369-76.
13. Selam JL. Evolution of diabetes insulin delivery devices. J Diabetes Sci Technol 2010; 4:505-13.
14. Selam JL. CSII in Europe: an analysis of articles published in Infusystems International. Infusystems Int 2007; 6:14–16.
15. Alderisio A, Bozzetto L, Franco L, Riccardi G, Rivellese AA, Annuzzi G, et al. Long-term body weight trajectories and metabolic control in type 1 diabetes patients on insulin pump or multiple daily injections: A 10-year retrospective controlled study. Nutr Metab Cardiovasc Dis 2019; 29:1110-17.
16. Wang X, Zhao X, Chen D, Zhang M, Gu W. Comparison of Continuous Subcutaneous Insulin Infusion and Multiple Daily Injections in Pediatric Type 1 Diabetes: A Meta-Analysis and Prospective Cohort Study. Front Endocrinol 2021;12:608232.
17. Russell-Jones D, Khan R. Insulin-associated weight gain in diabetes--causes, effects and

coping strategies. Diabetes Obes Metab 2007;9:799-812.

18. Santi E, Tascini G, Toni G, Berioli MG, Esposito S. Linear Growth in Children and Adolescents with Type1 Diabetes Mellitus. Int J Environ Res Public Health. 2019;16(19):3677.

19. Al-Mendalawi M. Switching to Multiple Daily Insulin Injections in Children and Adolescents with Type 1 Diabetes: A Question of Standards. Oman Med J 2015; 30: 307-8.

20. Sharef SW, Ullah I, Al-Shidhani A, Al-Farsi T, Al-Yaarubi S. Switching to multiple daily insulin injections in children and adolescents with type 1 diabetes: revisiting benefits from Oman. Oman Med J 2015; 30:83-89.

21. Herbert LJ, Wall K, Monaghan M, Streisand R. Parent Employment and School/Daycare Decisions among Parents of Young Children with Type 1 Diabetes. Child Health Care 2017;46:170-80.

22. Jeraiby M. Awareness of Preconception Care and Its Related Factors Among Women of Childbearing Age with Type 1 Diabetes in the South of Saudi Arabia: A Cross-Sectional Survey Study. Int J Gen Med 2021; 14:8583-89.

23. Gomes MB, Negrato CA, Cobas R, Gonçalves PR, da Silva PCB, Carneiro JRI, et al. Determinants of intensive insulin therapeutic regimens in patients with type 1 diabetes: data from a nationwide multicenter survey in Brazil. Diabetol Metab Syndr 2014;6:67. Available from: https://doi.org/10.1186/1758-5996-6-67.