Flexible Insulin Therapy: Results of a Tunisian Experience

Hajer Kandara, Jemai Chaima, Abdennebi Cyrine, Jemel Manel, and Kammoun Ines

Abstract — Aims: To evaluate the adherence of type 1 diabetic patients to long-term flexible insulin therapy (FIT), and the impact of this approach on the glycemic balance, basal insulin dose and quality of life of patients.

Methods: This is a prospective descriptive study, conducted between January and April 2017, including 50 patients with type 1 diabetes having following the FIT of Department B of Endocrinology-Diabetology and Metabolic Disease service B at the National Institute of Nutrition and Food Technology of Tunisia.

Results: The FIT decreased mean HbA1c from 8.96% to 7.57% (p=0.04) and mean basal insulin dose from 0.35 to 0.27 IU/kg/day. Hypoglycemia's frequency decreased from 3.2±2.1 to 0.93±2.1 episodes/patient/week (p=0.03), with improved quality of life. However, there was a significant weight gain (p=0.02).

Conclusions: FIT allows for better glycemic control while reducing hypoglycemia, especially severe episodes, and improves the quality of life of patients with type 1 diabetes but seems to cause weight gain.

Index Terms — Flexible Insulin Therapy; Type 1 Diabetes; Therapeutic education; Blood glucose.

I. INTRODUCTION
Flexible insulin therapy (FIT) is the most appropriate therapeutic approach for patients with type 1 diabetes. However, it has several constraints, including the need to acquire dietary knowledge and to monitor capillary glycemia many times.

In Tunisia, FIT is not common. This study was aimed at assessing the adherence of patients with type 1 diabetes to long-term FI and determining the impact of FIT on the glycemic balance and patients’ quality of life.

II. MATERIALS AND METHODS
A. Patients
This is a descriptive retrospective study conducted between January and April 2017, about 50 patients with type 1 diabetes on FIT. We included patients over 14 years of age, on FIT for at least 1 year and who were hospitalized in Department B. We did not include patients put on FIT in another structure, unable to answer the questions, having psychiatric disorders, and those with eating behavior disorders.

Were assessed: demographic, anthropometric and diabetes characteristics, date of inclusion and adherence to FIT during follow-up, quality of life, and satisfaction with treatment (using two questionnaires: ADDQoL [19, 7, 8] and DTSQs). Patients were divided into two groups according to their adherence to the FIT: group AD (Patients adhering to the FIT at the time of inclusion in the study) and group AR (Patients who stopped the FIT before the inclusion in our study). For the AR group, the total duration of adherence in months and the reasons for abandonment were specified.

B. Description of the FIT Protocol adopted by the service
Departement B FIT protocol was inspired by the work of Sachon et al [30]. It was set up in the service in June 2009. Applicants for FIT were patients with type 1 diabetes for at least 6 months, on insulin analogs, wishing to be independent and to have the ability to understand the therapeutic modalities of FIT and to perform calculations. The protocol consists of a training program carried out during a 5-day hospital stay:

1. IF Protocol
1. The first day
At the first day of hospitalization, the level of therapeutic education concerning knowledge on diabetes and insulin treatment was assessed.

2. The second day: The fasting carbohydrate test
It begins one day after hospitalization at midnight and ends the third day at 9 am. Breakfast is made with tea or coffee without milk and sugar. Lunch and dinner are based on a salad without fat and 100 g of skinless chicken or grilled cutlet. A glycemic self-monitoring was performed every 2 hours. Blood sugar levels should not fluctuate more than 0.3 g/l. The dose of a unit of rapid analog insulin is administered before each meal to metabolize the proteins ingested. The fasting carbohydrate test makes it possible to determine the basal insulin dose (considered correct if the blood sugar remains stable between 1 and 1.5 g/l during the 24 hours), the sensitivity to insulin, the sensitivity to re-sugaring, and carbohydrate ratios. If the blood sugar level is higher than the set blood sugar targets, a correction was made and the blood sugar level was measured 4 hours later, to determine the patient's insulin sensitivity.

3. The last three days
Are devoted to providing intensive education by the doctor, dietitian and, nurse. It covers the diabetes definition's, the...
different types of insulin, their actions, techniques and injection sites, glycemic and HbA1c goals, glycemic self-monitoring and interpretation of results, the diabetes complications', hypoglycemia and hyperglycemia signs' and correction, and dietetic education (counting carbohydrates, and calculating prandial doses).

4. On leaving the hospital
Each patient receives a monitoring diary (including the glycemic self-monitoring diary and the food diary) to note diet (with the portions, timetable, carbohydrate count, and rapid analog doses). Subsequent follow-up is done 15 days after discharge from the hospital, then at 1 month and then every 3 months.

C. Subsequent monitoring
1. At three months
We assess:
- The monitoring diary and insulin doses;
- The weight change;
- The glycemic balance, the frequency of hypoglycemias, and ketoacidosis decompensations.

2. At six months
The patient is reviewed by the dietician and the doctor for an educational reminder and evaluation of:
- The glycemic self-monitoring.
- The ratios and basal insulin dose.

D. Statistical analysis
Statistical analysis was performed by IBM SPSS version 23 software. The comparison of percentages on independent series was performed by the Pearson Chi-square test, and by the Fisher's bilateral exact test if this test is not valid. The comparison of two means on independent series was carried out using Student's T-test and by the non-parametric Mann and Whitney test in case of invalidity of this test. Comparisons of more than 2 means on independent series were carried out using Snedecor's F test for parametric variance analysis (one-factor ANOVA). The links between two quantitative variables have been studied by the Bravais Pearson r test in the case of a normal distribution or the Spearman correlation coefficient in the case of a non-Gaussian distribution. The survival analysis was carried out according to the Kaplan-Meier method; the prognostic factor analysis was based on the Log-rank test for univariate analysis and the Cox model for multivariate analysis. The statistical threshold (α) has been set at 5%.

III. RESULTS

A. Clinical and metabolic characteristics of the general population, AR and AD groups, and factors associated with non-adherence to the FIT:

<table>
<thead>
<tr>
<th>Clinical and metabolic characteristics</th>
<th>General population (n=50)</th>
<th>AR Group (n=9)</th>
<th>AD Group (n=41)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>25,38±7,6</td>
<td>25,56±7,6</td>
<td>25,38±7,6</td>
<td>0.94</td>
</tr>
<tr>
<td>Mean (%)</td>
<td>26</td>
<td>22,22</td>
<td>26,82</td>
<td>0.571</td>
</tr>
<tr>
<td>Mean body mass index (BMI) (kg/m²)</td>
<td>22.48</td>
<td>22.54</td>
<td>22.48</td>
<td>0.963</td>
</tr>
<tr>
<td>Good socioeconomic level (%)</td>
<td>86</td>
<td>77.8</td>
<td>87.8</td>
<td>0.37</td>
</tr>
<tr>
<td>Mean diabetes duration (ans)</td>
<td>13,1±7.6</td>
<td>11.56</td>
<td>13.5</td>
<td>0.498</td>
</tr>
<tr>
<td>Social security (%)</td>
<td>94</td>
<td>66.67</td>
<td>39</td>
<td>0.127</td>
</tr>
<tr>
<td>Diabetes complications (%)</td>
<td>18</td>
<td>11.1</td>
<td>19.5</td>
<td>0.483</td>
</tr>
<tr>
<td>HbA1C (%)</td>
<td>-</td>
<td>10.6±0.92</td>
<td>9.51±2.19</td>
<td>0.391</td>
</tr>
<tr>
<td>Mean dose of basal insulin (IU)</td>
<td>-</td>
<td>16.1±6.35</td>
<td>17±7.04</td>
<td>0.229</td>
</tr>
<tr>
<td>Mean sensibility to re-sugaring</td>
<td>-</td>
<td>0.38±0.09</td>
<td>0.377±0.11</td>
<td>0.455</td>
</tr>
<tr>
<td>Mean insulin sensitivity</td>
<td>-</td>
<td>0.48±0.15</td>
<td>0.48±0.13</td>
<td>0.671</td>
</tr>
<tr>
<td>Mean dose of rapid insulin (UI/10g of carbohydrates)</td>
<td>-</td>
<td>1.72±0.49</td>
<td>1.89±0.3</td>
<td>0.688</td>
</tr>
<tr>
<td>Morning</td>
<td>-</td>
<td>1.08±0.3</td>
<td>1.01±0.22</td>
<td>0.545</td>
</tr>
<tr>
<td>Midday</td>
<td>-</td>
<td>1.34±0.28</td>
<td>1.43±0.21</td>
<td>0.351</td>
</tr>
</tbody>
</table>

B. Study of the FIT adherence

1. Study of the FIT adherence rate
The FIT adherence rate was 82%. 9 patients discontinued FIT during follow-up, including 3 in the first 6 months and more than half (55.6%) in the first year (n=5). The adherence rate was 94%, 90%, and 88% respectively at 6, 12 and 24 months.

2. Reasons for stopping the FIT
Most of the patients had abandoned FIT for lack of motivation (n=6). 2 patients had abandoned because of poor compliance and 2 others because of a denial of the disease. The other three cases of FIT discontinuation were due to pregnancy, depression, and the development of eating disorders.

C. Evolution of FIT parameters in the AD group

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Before the FIT</th>
<th>At inclusion in the study</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean dose of basal insulin (UI)</td>
<td>17±7.04</td>
<td>17.56 ± 7.13</td>
<td>0.109</td>
</tr>
<tr>
<td>Means dose of rapid insulin (UI/10g of carbohydrates):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morning</td>
<td>1.88±0.3</td>
<td>1.84±0.36</td>
<td>0.246</td>
</tr>
<tr>
<td>Midday</td>
<td>1.01±0.22</td>
<td>1.05±0.24</td>
<td>0.141</td>
</tr>
<tr>
<td>Evening</td>
<td>1.43±0.21</td>
<td>1.40 ± 0.28</td>
<td>0.442</td>
</tr>
</tbody>
</table>

D. Impact of the FIT in the AD group

1. Evolution of HbA1C in the AD group
The mean HbA1C decreased significantly (p<10-3) from 9.51±2.19% before starting the FIT protocol to 8.18±1.83% at inclusion in the study. The evolution of this parameter was biphasic: There is a reduction during the first 6 months followed by a re-ascent at 18 months. From the 18th month,
the mean HbA1c shows a linear decrease (Fig. 1). Age over 30 years was the only factor significantly associated with achieving the glycemic target (p=0.018; OR=1.57; 95% CI [1.108-2.204]) (Table 3).

![Fig. 1. Evolution of the average HbA1c in the AD group.](image)

**TABLE 3: FACTORS ASSOCIATED WITH ACHIEVING HbA1C GOALS IN THE AD GROUP**

<table>
<thead>
<tr>
<th>Factors</th>
<th>Achieving HbA1c goal (n=25)</th>
<th>Not achieving HbA1c goal (n=16)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age between 30 and 50 years (%)</td>
<td>40</td>
<td>63</td>
<td>0.018</td>
</tr>
<tr>
<td>Males (%)</td>
<td>31.3</td>
<td>24</td>
<td>0.436</td>
</tr>
<tr>
<td>Mean BMI (kg/m²)</td>
<td>23.53</td>
<td>23.55</td>
<td>0.328</td>
</tr>
<tr>
<td>Good socioeconomic level (%)</td>
<td>88</td>
<td>87.5</td>
<td>0.659</td>
</tr>
<tr>
<td>Mean diabetes duration (years)</td>
<td>14.3</td>
<td>12.19</td>
<td>0.252</td>
</tr>
<tr>
<td>Diabetes complications (%)</td>
<td>24</td>
<td>12.5</td>
<td>0.314</td>
</tr>
<tr>
<td>Mean basal dose of insulin (IU)</td>
<td>16.28</td>
<td>18.13</td>
<td>0.491</td>
</tr>
<tr>
<td>Mean resuming sensibility</td>
<td>0.37</td>
<td>0.36</td>
<td>0.825</td>
</tr>
<tr>
<td>Mean insulin sensibility</td>
<td>0.48</td>
<td>0.48</td>
<td>0.307</td>
</tr>
<tr>
<td>Mean rapid insulin dose's of the morning</td>
<td>1.87</td>
<td>1.90</td>
<td>0.3</td>
</tr>
<tr>
<td>Mean rapid insulin dose's of the midday</td>
<td>1.05</td>
<td>0.96</td>
<td>0.123</td>
</tr>
<tr>
<td>Mean rapid insulin dose's of the evening</td>
<td>1.43</td>
<td>1.43</td>
<td>0.563</td>
</tr>
</tbody>
</table>

2. **Achievement of the glycemic target in the AD group**

Before inclusion in the FIT protocol, 4.87% (n=2) of patients in the AD group met the HbA1c goal. This frequency had increased significantly (p=0.033) to 31.7% (n=13) at the time of inclusion in the study.

3. **Evolution of BMI**

The average BMI was 22.6 kg/m² before inclusion in the FIT protocol. It was 23.5 ± 3.37 at the inclusion in our study without a statistically significant difference (p=0.187). The evolution of BMI during follow-up was biphasic with an ascending phase until the 18th month followed by a decrease in mean BMI beyond the 18th month.

4. **Evolution of hypoglycemia**

Minor hypoglycemia significantly decreased from 2.39 when started on FIT to 1.22 episodes/patient/day during the study (p <0.0001). The major ones significantly decreased from 0.39 to 0.05 episodes/patient/month (p = 0.018). Neither age between 30 and 50 years, nor gender, socioeconomic level, BMI, nor basal insulin dose were significantly associated with the reduction of hypoglycemia.

5. **Evolution of ketoacidosis decompensations:**

The episodes of ketoacidosis decompensation significantly decreased from 0.63 on starting FIT to 0.05 episodes/patient/day at inclusion in the study (p <10^-6).

6. **Quality of life and satisfaction with the treatment**

1) **Quality of life**

The average general quality of life score was 0.78±0.99. The ADDQol score 2 was -1.1±1.2. The Weighted Composite Score was -1.46±2.22.

2) **Evaluation of satisfaction by the treatment using the DTSQ Score**

The mean overall score was 30.88±3.89. The average frequency of perception of hyperglycemia was 2.94±3.89. The average frequency of perception of hypoglycemia was 3.34±1.44.

**E. The constraints of FIT in the population**

The main constraints to the IF were: Glycemic measurements (64%), strips cost (36%), difficulties in calculating carbohydrates (34%), and problems with public health security (10%).

**IV. DISCUSSION**

The FIT adherence rate was 82%. The mean duration of FIT was 49.7 months in adherent patients (AD) (n=41). For the nonadherent group (AR) (n=9), one-third of the patients had abandoned FIT after the first six months, and more than a half (n=5) after the first year. Jhenani [5] prospectively studied 53 T1D patients, after inclusion in the same FIT protocol of our department. The average length of FIT adherence ranged from 6 to 33 months. The abandonment of the FIT occurred mainly in the first year of follow-up. The most common reason for stopping FIT in this group was the lack of motivation. Jacqueminet [10] has shown a similar result.

We found a significant improvement (p=0.0005) in mean HbA1c. Several studies report the benefit of FIT on HbA1c [6], [7], [8], [11], [12]. The maximum benefit was associated with the highest initial HbA1c [6], [11], [12], which is consistent with the results of our study with a mean initial HbA1C at 9.51%. Other studies with longer follow-up have shown similar results [7], [8].

We have shown a significant decrease in episodes of minor hypoglycemia/patient/day. Several studies report a decrease in this frequency. In the Siala series [4], the frequency of minor hypoglycemia was stabilized or decreased during follow-up in 14 patients, after 3 months of FIT. However, in the series by Benhamou et al [23], the frequency of hypoglycemia increased in 16% of patients, stabilized in 51%, and decreased in 32% of cases. The prospective DCCT study [1] showed an improvement in the glycemic balance with a reduction in the frequency and the severity of
microangiopathic complications but an increase in the frequency of hypoglycemia.

A significant decrease in episodes of major hypoglycemia/patient/day has also been shown. A similar result has been demonstrated by Samann [8] in more than 9500 patients. Several studies have shown a similar result [7], [10], [17], [18], [19], [20], [21].

The average BMI in the AD group had increased slightly without reaching the significance level. The literature reports weight stability during the first year of FIT [7], [12], [15], [27], [28]. In the DAFNE study [6], the authors concluded that weight gain was not significant (p=0.11) after 6 months of follow-up of patients on FIT against stability in the control group. Sarde and Benhamou [16,29] have shown weight gain.

The number of ketoacidosis decompensations/patient/6 months has significantly decreased. According to the literature, Ketoacidosis decompensations have been rarely evaluated in patients on FIT. In the Jenhani series [5] a significant drop in ketoacidosis has been reported (p=0.045). There were no decompensations in 72% of patients before FIT versus 91% of patients on FIT (p=0.039).

The mean daily dose of basal insulin (DBI) in the AD group increased, but not significantly. Our results agree with those reported in the literature. Siala [4] showed a non-significant increase in DBI at 9, 12, and 18 months, without reaching the initial DBI before FIT (p=0.31). Sarde [30] also noted an increase in DBI in one year.

Mean changes in the morning, midday, and eveningmealtimeinsulinratios(MIR)werenotsignificant. Siala [4] showed a significant increase (p=0.027), linked to food freedom, and errors in counting carbohydrates.

The Dcct study [1], [52] reported a positive impact of FIT on the experience of diabetes by inducing a significant reduction in complications without necessarily having the same impact on the patient's quality of life. In our study, the average general quality of life score of 0.78±0.99 indicates a satisfactory general quality of life. The average quality of life score without diabetes, -1.1±1.2, indicates that the quality of life of our patients would be better if they were not diabetic.

The average weighted composite score indicates that the quality of life of our patients would have been better in different areas.

A. Impact on quality of life and satisfaction with treatment:

The average weighted composite score of -1.46±2.22 indicates that the quality of life of our patients would have been better in different areas of life if they were not diabetic. Our results are consistent with studies evaluating the quality of life of patients on FIT in favor of a positive impact of this insulin therapy program [6], [7], [12], [13], [15], [25]. However, in the work of Jolly [14], the evaluation of the quality of life at 6 months estimated by the ADDQoL did not show a significant improvement in the quality of life scores by the FIT.

In our study, the mean overall score for treatment satisfaction (items 1 and 4 to 8) was 30.88±3.89. The DAFNE study [6] has just supported our results.

V. CONCLUSIONS:

In light of our results and those of the literature, we recommend FIT as a therapeutic approach for type 1 diabetes, emphasizing the value of long-term adherence. We emphasize the need to strengthen monitoring and consolidate the patient's educational prerequisites, especially during fragile periods.

We propose to establish a standardized monitoring protocol where the parameters to be looked for in the long term during monitoring must be specified; It can be designed as practical group workshops, with meals prepared by patients, assisted by the dietitian and the attending physician, trained at the FIT.

REFERENCES:


