Intensification of Diabetes Treatment with Long-Acting Insulin Shows no Benefit over Other Diabetes Treatment

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ABSTRACT: **Background:** Control of diabetes is challenging, and frequent treatment changes are needed.

Objective: To study the effect of the recommendation to start insulin glargine or insulin determir (long-acting insulin treatment, LAI) at discharge from hospital, on glucose control in the community setting.

Methods: Included were type II diabetes patients who were referred to and received a consultation from the hospital diabetes clinic during their hosptialization, as part of a routine consultation for diabetes management. During the visit, all patients were recommended long-acting insulin-based treatment, as inpatient treatment and at discharge. Follow-up was done by the primary physician in the community or by a community-based diabetes clinic. Glycosylated hemoglobin, glucose levels and other laboratory tests were obtained from the community health records before hospitalization and 6–12 months later. Medical treatment was ascertained by reviewing the actual usage of prescriptions.

Results: Eighty patients (58% males, mean age 64.1 ± 12.7 years) were included in the analysis. HbA1c levels were 10.1 ± 2.4% before admission, but improved significantly at follow-up (8.6 ± 2.2%, $P < 0.001$). Seventy-one percent of the patients were taking the LAI treatment and the rest were using non-LAI medications. Changes in diabetes control were similar between the LAI and non-LAI groups (HbA1c was reduced by 1.5 ± 3.2% and 1.9 ± 3.1% respectively). The rate of repeated admissions was also similar, averaging at 1.3 admissions for both groups, the minority of which were related to glucose control.

Conclusions: Insulin glargine or determir-based treatment does not show any superiority over other anti-diabetes treatment. It is our opinion that this treatment should be used as tailored therapy and should not be recommended routinely to all patients.

IMAJ 2011; 13: 537–541

KEY WORDS: diabetes control, long-acting insulin, glycosylated hemoglobin

With the increasing prevalence of diabetes mellitus worldwide, the treating physicians are faced with the challenge of how to achieve optimal glucose control. While the benefit of lowering blood glucose and HbA1c levels is unquestionable and was shown repeatedly to reduce diabetes complications [1], obtaining this elusive goal remains difficult [2]. The progressive nature of this disease, with the ongoing decline in the mass and function of beta cells, requires strict follow-up and relatively frequent treatment adjustments [3].

Many new glucose-lowering medications have been added to the arsenal of treatment during the last decade, both in the tablet and injection form. However, the addition of the new long-acting insulins has changed significantly the way we view insulin treatment in diabetes patients. Whereas previously, insulin treatment was the 'last stand' of treatment and preferably avoidable, today the addition of insulin glargine (Lantus®, Sanofi-aventis) and determir (Levemir®, Novo Nordisk) has become more frequent in the early stages of diabetes treatment [4]. These treatments were shown in clinical trials to be efficacious and also to have lower rates of serious treatment side effects (such as hypoglycemia) [5,6]. Current practice is often based on long-acting insulin as basal insulin, with additional oral agents as add-ons [7].

Because of these advantages, since August 2007 long-acting insulin-based treatment is recommended to all hospitalized diabetes patients in our center, regardless of their prior diabetes treatment. The purpose of this study was to examine the effects of this strategy on diabetes control in the community. Since our experience taught us that between 30% and 80% of the patients continue in the community the treatment that was recommended at hospital discharge, we assumed that the patients not receiving the recommended treatment could serve as controls. The hypothesis of the study was that LAI-based treatment is superior to other anti-diabetes medications for diabetes treatment intensification. The aim of the study was therefore to examine the effects of the recommendations for LAI-based treatment on glucose control and rehospitalization in the community setting.

*The first two authors contributed equally to this study

LAI = long-acting insulin

PATIENTS AND METHODS

The study was approved by the Institutional Review Board. Since the long-acting insulin protocol is recommended to almost all inpatient diabetes patients in our medical center, the patients included in this study did not have to sign an informed consent. Audit of the medical records of patients in the community setting was possible because all health management organizations responsible for the health insurance of Israeli citizens have electronic health records.

INCLUSION AND EXCLUSION

Included in this analysis were all inpatients who were referred to the hospital diabetes clinic during their hospitalization between 1 January and 31 December 2008. These patients were referred to the clinic by physicians of the different hospital departments and units, as part of a routine inpatient diabetes consultation, for the purpose of instructing patients how to inject themselves with insulin. We excluded from the analysis any patients (either inpatients or outpatients) who had type 1 diabetes mellitus, outpatients who had not been hospitalized during the study period, and patients who were not recommended LAI. One additional patient was excluded since the diagnosis of diabetes was not confirmed. The referring physicians responsible for the inpatient treatment and the family practitioners responsible for the treatment following the hospitalization were not aware that the patients' data had been collected.

DATA COLLECTION

- *General information and additional diseases:* The EHR of each patient was reviewed, and the data included general information (age, gender and marital status), evidence of atherosclerotic vascular disease (ischemic heart disease, stroke, any coronary intervention) and information about atherosclerosis risk factors (hypertension, hyperlipidemia, smoking).
- *Blood test information:* The control status of diabetes was ascertained by reviewing the HbA1c and fasting plasma glucose levels before and after the hospital admission. The date of reference was regarded as the date of the visit to the hospital diabetes clinic. Pre-DOR data were the FPG and HbA1c levels that were the last values measured in the HMO community clinic (Clalit Health Services) within the 12 months that preceded the DOR. If HbA1c levels were not performed, the patient was withdrawn from the study, unless he/she was diagnosed with diabetes during the current admission. Post-admission data included the first HbA1c and FPG levels measured between 6 and 12 months after the DOR. If HbA1c levels were not measured during this time frame, data were searched for an additional period of 2 months before and after the time frame, but not less than 4 months and not more than 14 months after the DOR. If HbA1c levels were not measured during this time frame, the patient was withdrawn from the study.
- The electrolyte levels (sodium and potassium) and the kidney function tests (urea and creatinine) that were reviewed in this analysis were measured during the same time frame as the HbA1c levels (for both pre- and post-DOR). The lipid levels included in this analysis were measured before the DOR.
- *Repeated admissions, diabetes-associated admissions and diabetes clinic follow-up:* This refers to the number of admissions during a follow-up period of 12 months after the DOR was elicited from the EHR. If the reason for admission was related to glucose control (either hypersomolar state or hypoglycemia), the admission was considered a diabetes-associated admission. Additional reasons for hospitalization, including diabetic foot, congestive heart failure and any cardiovascular event, were not considered a diabetes-associated admission and were counted only as repeated admissions. If a patient had two or more visits with a diabetes specialist within 12 months after the DOR, he/she was considered as "diabetes clinic follow-up."
- *Medication and compliance:* The EHR was reviewed for each of the diabetes drug classes, and the number of prescriptions drawn from the pharmacy was obtained. The patient was considered 'treated' with a specific medication if he/she used at least two prescriptions within the 12 months before the DOR and/or at least two prescriptions within the 12 months after the DOR. If the number of used prescriptions for a specific drug class was 0 or 1 during any specific time frame, the patient was considered as not using that specific drug for that time frame.

STATISTICAL ANALYSIS

The present study was designed to have 80% power to detect a true, between-group difference of 1.0 ± 1.5% in HbA1c, using the *t*-test for independent samples and assuming a two-sided alpha of 0.05. The paired sample *t*-test was used to ascertain significant changes between pre- and post-DOR laboratory values (except lipid levels). Patients were then categorized as long-acting insulin users (LAI) or non-users (non-LAI) based on the actual treatment with long-acting insulin (either insulin glargine or determir) after the DOR. The Student *t*-test was used to compare between LAI and non-LAI patients. Comparisons of the non-quantifiable data were done using the chi-square test. All quantifiable data are presented as mean ± standard deviation, and the non-quantifiable data are presented as the number (%).

EHR = electronic health record
DOR = date of reference
FPG = fasting plasma glucose
HMO = health management organization

RESULTS

Included in this study were 137 patients who fulfilled the inclusion criteria. The EHRs of 32 patients (23%) were not obtained because they were not registered members of the local Clalit Health Services clinic and access to the data was not permitted. The records of 24 patients (18%) were missing HbA1c levels at pre-DOR, post-DOR or both, and these patients were therefore excluded. One patient died during the follow-up period and was omitted from the analysis. The final database included 80 patients (58%).

DEMOGRAPHICS, CHRONIC ILLNESSES AND REASON FOR ADMISSION

Of the 80 patients, 46 (58%) were males (mean age 64.1 ± 12.7 years) and 54 (68%) were married. Additional diseases, cardiovascular risk factors and basic laboratory results are presented in Table 1.

The reasons for admission to hospital varied and were mostly not related to direct glucose control (data not shown). However, 14 patients (18%) were admitted due to a hyperosmolar state and 5 (6%) because of hypoglycemia that was attributed to diabetes treatment. In addition, 5 patients (6%) were hospitalized with new-onset diabetes mellitus that presented as a hypersomolar state.

DIABETES CONTROL BEFORE AND AFTER THE DOR

The status of diabetes control was poor. Before admission, mean HbA1c was 10.1 ± 2.4% and the FPG 13.6 ± 7.6 mmol/L. These levels were measured on average 160 ± 106 days before the DOR. Seventy-six patients (95%) had a HbA1c level above 7% (53 mmol), and 44 of them (60%) had a level above 9%. After the DOR, diabetes control improved significantly. HbA1c levels were reduced by an average of 1.5 ± 3% and the FPG levels by 4.4 ± 9.6 mmol/L. These levels were measured on average 258 ± 96 days after the DOR. Still, 53 (72%) of the patients had a HbA1c level above 7% but only 27 (37%) had a level above 9%. The laboratory results and medication profile of the patients before and after the DOR are shown in Table 2.

Table 1. Baseline information of the 80 patients included in the analysis

Demographics	
Age (yrs)	64.1 ± 12.7
Male sex (n, %)	46 (58%)
Married status (n, %)	64 (68%)
Additional cardiovascular risk factors and diseases	
Hypertension (n, %)	56 (70%)
Hyperlipidemia (n, %)	67 (84%)
Smoking (n, %)	14 (18%)
Ischemic heart disease (n, %)	31 (39%)
Congestive heart failure (n, %)	13 (16%)
Cerebrovascular disease (n, %)	7 (9%)
Post-coronary intervention (n, %)	16 (20%)
Baseline (pre-DOR) laboratory data	
Total cholesterol (mmol/L)	4.92 ± 1.32
LDL cholesterol (mmol/L)	3.11 ± 1.24
HDL cholesterol (mmol/L)	1.09 ± 0.28
Triglycerides (mmol/L)	2.57 ± 2.57
Sodium (mmol/L)	138 ± 4
Potassium (mmol/L)	4.5 ± 0.4
Urea (mmol/L)	17.5 ± 12.9
Creatinine (mmol/L)	97.2 ± 44.2

Quantifiable data are presented as mean ± SD
LDL = low density lipoprotein, HDL = high density lipoprotein

DIABETES CONTROL ACCORDING TO TREATMENT

Of the 80 patients who were recommended for the LAI-based therapy, 57 (71%) continued the recommended treatment and 23 (29%) received treatment that did not include the new LAIs. The comparison between the groups showed that the groups were comparable in all aspects, except for the rate of hypoglycemia on admission, history of congestive heart failure, past coronary intervention, and a tendency for a reduction in kidney function – all of which increased the chances of the patient to receive the LAI-based therapy in the community setting. On the other hand, a newly diagnosed diabetes mellitus status reduced the chances of being treated with LAI in the community. Demographic information, additional diseases and the pre-DOR laboratory results and treatment profile are given in Table 3. The LAI-based treatment did not show any superiority over non-LAI based treatment post-DOR. Mean HbA1c had decreased from 10.2 ± 2.6 to 8.7 ± 2.2% in the LAI group ($P < 0.001$) and from 10.2 ± 2.3 to 8.2 ± 2.3 % in the non-LAI group ($P = 0.004$). Mean FPG had decreased from 13.8 ± 7.5 to 9.5 ± 4.5 mmol/L in the LAI group ($P = 0.001$) and from 13.5 ± 7.3 to 9.7 ± 4.6 mmol/L in the non-LAI group ($P = 0.04$). Among the

Table 2. Laboratory results and medication profile before and after the DOR

	Pre-DOR	Post-DOR	*P* value
Laboratory data			
HbA1c (%)	10.2 ± 2.5	8.6 ± 2.2	< 0.0001
Mean of difference (%)	1.6 ± 3.2		
Fasting plasma glucose (mmol/L)	13.7 ± 7.4	9.6 ± 4.5	< 0.001
Mean of difference (%)	4.4 ± 9.5		
Sodium (mmol/L)	138 ± 4	139 ± 3	0.016
Potassium (mmol/L)	4.5 ± 0.4	4.6 ± 0.5	0.09
Urea (mmol/L)	17.5 ± 12.9	18.9 ± 12.1	0.047
Creatinine (mmol/L)	97.2 ± 44.2	97.2 ± 44.2	0.44
Diabetes medication profile			
Sulphonyl urea (n, %)	32 (40%)	12 (15%)	< 0.0001
Metformin (n, %)	39 (49%)	30 (38%)	0.020
Rosiglitazone (n, %)	5 (6%)	2 (3%)	0.016
Sitagliptin (n, %)	0	3 (4%)	0.048
Repaglinide (n, %)	7 (9%)	14 (18%)	0.021
Total Insulin (n, %)	27 (34%)	61 (76%)	< 0.0001
Long-acting insulin (n, %)	8 (10%)	57 (71%)	< 0.0001

DOR = date of reference: the date of the diabetes clinic visit when long-acting insulin treatment was recommended

Table 3. Demographic information, additional diseases and the pre-DOR laboratory results and treatment profile according to post-DOR treatment

	LAI (n=57)	No LAI (n=23)	*P* value
Demographics			
Age (mean ± SD)	65.5 ± 12.4	60.4 ± 13.2	0.11
Male sex (n, %)	32 (56%)	14 (61%)	0.34
Married status (n, %)	36 (63%)	18 (78%)	0.002
Cardiovascular risk factors and diseases			
Hypertension (n, %)	41 (72%)	15 (65%)	0.14
Hyperlipidemia (n, %)	48 (84%)	19 (83%)	0.66
Smoking (n, %)	10 (18%)	4 (17%)	0.97
Ischemic heart disease (n, %)	23 (40%)	8 (34%)	0.26
Congestive heart failure (n, %)	12 (21%)	1 (4%)	< 0.0001
Cerebrovascular disease (n, %)	5 (9%)	2 (9%)	0.98
Post-coronary intervention (n, %)	13 (23%)	3 (13%)	0.02
Reasons for admission and follow-up			
Hyperosmolar state	9 (16%)	5 (22%)	0.10
Hypoglycemia	5 (9%)	0	0.002
New-onset diabetes mellitus	2 (4%)	3 (13%)	< 0.0001
Diabetes clinic follow-up	29 (51%)	6 (26%)	< 0.0001
Pre-DOR Laboratory data			
HbA1c (%)	10.2 ± 2.6	10.2 ± 2.3	0.96
Fasting plasma glucose (mmol/L)	13.8 ± 7.5	13.5 ± 7.3	0.90
Sodium (mmol/L)	138 ± 3	137 ± 4	0.24
Potassium (mmol/L)	4.6 ± 0.5	4.5 ± 0.2	0. 41
Urea (mmol/L)	19.3 ± 14.3	12.5 ± 5.7	0.04
Creatinine (mmol/L)	101 ± 48	80 ± 25	0.06
Pre-DOR diabetes medication profile			
Sulphonyl urea (n, %)	22 (39%)	10 (43%)	0.32
Metformin (n, %)	29 (51%)	10 (43%)	0.14
Rosiglitazone (n, %)	5 (9%)	0	0.002
Repaglinide (n, %)	6 (11%)	1 (5%0	0.044
Total insulin (n, %)	22 (39%)	5 (22%)	< 0.001
Long-acting insulin (n, %)	7 (12%)	1 (5%)	< 0.015

DOR = date of reference: the date of the diabetes clinic visit when basal insulin-based treatment was recommended

LAI = long-acting insulin-based treatment, i.e., long-acting insulin that the patients were taking

non-LAI patients, 4 patients (17%) were taking insulin treatment that was not glargine or determir (either mixed insulin or NPH – neutral protamine Hagedorn, also known as isophane insulin). Results remained the same after omitting these patients from the analysis.

REPEATED HOSPITALIZATIONS FOLLOWING DOR

Thirty-three patients (41%) were readmitted during the 12 month follow-up after the DOR, and 25 of them were readmitted more than once (31%, average number of readmissions during follow-up 1.4 ± 2.4). Reasons for the admission varied, but in six patients it was diabetes-associated (8% of the database and 18% of the patients who required readmission). When analyzing the admission data of the two treatment groups, long-acting insulin-based therapy had no effect on the number of readmissions after the DOR. Of the 57 patients receiving long-acting insulin, 23 required readmission (40% compared to 43% in the non-LAI group) and 18 required more than one readmission (32% compared to 30% in the non-LAI group). The average number of readmissions in the LAI group was 1.3 ± 2.5 compared to 1.3 ± 2.5 in the non-LAI group ($P = 0.98$). In four patients receiving LAI treatment (7% in the LAI group and 17% in the readmitted LAI group) the admission was diabetes-associated, as compared to two patients in the non-LAI group (9% of the non-LAI group and 20% of the readmitted non-LAI group) ($P = 0.49$).

DISCUSSION

During the last decade the use of insulin in the early stages of diabetes has become more frequent. Common practice suggests adding a once-a-day insulin injection for treatment intensification of uncontrolled diabetes [8], but there is no consensus regarding the optimal insulin to be used, and the type of insulin is a subject of ongoing debate. In the literature the data are equivocal, with some studies showing superiority of the new long-acting insulins over other insulins [9] and others showing no such difference [10,11].

Our data suggest that basal insulin-based treatment using insulin glargine or determir is not superior to other medications when upgrading diabetes treatment. We found that HbA1c and FPG levels decreased to the same extent regardless of the treatment. We also found no improvement in all-cause readmissions and diabetes control-associated readmissions of patients treated with new long-acting insulin. Based on prior experience, we assumed that the between-group difference would be 1 ± 1.5% in HbA1c; however, in this study sample the between-group difference was much smaller, and the standard deviation was more than twice our estimates. We propose that the improved reduction in HbA1c levels observed in the patients treated with non-LAI does not signify superiority of non-LAI based treatment and is clinically insignificant. Therefore, the data shown here refute our baseline hypothesis on the superiority of the new long-acting insulin compared to other treatments for diabetes treatment intensification.

The effect of treatment selection on the number of readmissions is an important issue. Our data suggest that the number of readmissions of severely diabetic patients with very high baseline HbA1c levels is extremely high. In our database, many of the participants required more than one readmission during 12 months of follow-up. Most of the reasons for the admissions were not directly related to glucose control, and most were attributed to diabetes complications such as diabetic foot. It is therefore logical to assume that any effect on glucose control-related admissions is too small to be noticeable in this study group and may be obscured by the high readmission rate in our study population.

Our study is not without limitations. A major limitation was the lack of randomization of treatment. Like all non-randomized studies, our study too could be subject to biases that may have impaired our results. Since the decision regarding the treatment prescribed was made by the community clinic physician, the allocation of patients to the different treatment groups (LAI vs. non-LAI) may have been subject to variables that could by themselves influence the quality of treatment (such as disease severity, where the severe cases were allocated to LAI and the non-severe cases to non-LAI based treatment). With that in mind, we recommend that additional larger randomized studies be undertaken to confirm our results. Another major limitation of our study was the sample size. Some might argue that the small sample size prevents us from reaching our conclusions. Despite a relatively high flow of patients in our hospital clinic, we managed to obtain complete data and included fewer than 100 patients over a period of 12 months. Nevertheless, our study was powered to detect a clinically meaningful difference and, therefore, we claim that our results are valid. However, again, we stress the importance of larger randomized studies regarding this issue as well. Additional limitations of our study include the lack of information on disease duration, the dosage of pre-DOR treatment and other parameters that may influence the treatment change. These parameters were unavailable in the EHRs and were therefore not analyzed. This important information on each patient will definitely help in tailoring treatment intensification to each patient; however, our study was designed to answer the question whether the new LAIs should be given to all diabetes patients regardless of the disease duration, prior medical treatment, etc. Our answer to this question is a resounding no: There is no rationale to use the new LAIs for *all* diabetes patients, and we recommend (and currently practice) tailoring treatment to each patient. In this context we suggest that the new LAIs may still have superior results when used to intensify diabetes treatment in patients with evidence of hypoglycemia episodes. Despite the lack of data in our study, this treatment (insulin glargine and determir) probably does reduce the occurrence of hypoglycemic events as well as hypoglycemia-associated admissions.

An additional point worth mentioning is the undisputed difficulty in controlling diabetes. More than 90% of the patients in our database had HbA1c levels above 7% at study entry, and more than half had a level above 9%. This may be used as a sign of severe diabetes, and may also be associated with low beta cell function and/or poor compliance with treatment and diet. We believe the latter may be responsible for the fact that almost 20% of diabetes patients do not measure their HbA1c level on a regular basis (these patients were excluded from the analysis), and this may also explain the increased variance of time between tests. Regardless of the reason for the difficulty in controlling diabetes, the mere admission of a diabetes patient and the recommendations to change treatment had a positive effect on the quality of treatment in the community setting. It is our belief that the collaboration of efforts between hospital and community doctors to improve the treatment of diabetes (and probably all other cardiovascular risk factors) is likely to be beneficial for the patient.

It is our belief that the new long-acting insulins should not be routinely recommended to all diabetes patients in the attempt to intensify treatment. We propose that this treatment be used as tailored therapy, and that changing the oral hypoglycemic medication profile and/or adding an insulin that is not long acting is an equivalent option for diabetes control.

Acknowledgments

We thank Dr. Mona Boaz for the statistical analysis.

This study was not supported by any industrial or government funding.

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