Original Report:
Diabetes

Insulin Detemir in Combination with Oral Antidiabetic Drugs Improves Glycemic Control in Persons with Type 2 Diabetes in Near East Countries: Results from the Lebanese Subgroup

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Objective: To evaluate the effectiveness and safety of insulin detemir treatment as add-on therapy in a real-world setting of Lebanese insulin naïve persons, with type 2 diabetes poorly controlled on oral antidiabetic drugs (OADs).

Methods: Our study was a prospective, observational study representing the Lebanese arm of the multinational prospective and observational study involving 2,155 persons across Near East countries, Lebanon, Pakistan, Israel and Jordan. Effectiveness endpoints were changes in HbA1c, fasting and post-prandial glucose (FPG, PPG) after 24 weeks of treatment with insulin detemir in eligible persons. Safety endpoints were number of hypoglycemic events, incidence of adverse drug reactions (ADRs), serious ADRs, adverse events, and body weight change between baseline and end of treatment.

Results: 868 persons were included (mean age: 59.5 ± 10.4 years, men: 55.3%). Glycemic control improved with significant reduction in mean HbA1c from 9.7 ± 1.6% to 7.2 ± 1% (P<.0001). The percentage of persons who achieved the target of HbA1c<7% increased from .7% at baseline to 39% at week 24. Mean FPG decreased significantly from 213.7 ± 60.1 mg/dL to 120.3 ± 25.7 mg/dL (P<.001), and mean PPG from 271 ± 65.3 mg/dL to 158.1 ± 36.4 mg/dL (P<.0001). The rate of major hypoglycemic episodes decreased from .1498 at baseline to .0448 at week 24. Three adverse events but no ADR or serious ADR were reported. Body weight decreased from 80.4±13.2 Kg to 79.9±12.5 Kg (P<.0001).

Conclusions: Initiating insulin detemir in a clinical health care setting among Lebanese with type 2 diabetes mellitus on OADs improves glycemic control with no increase in hypoglycemia, adverse events or weight compared with baseline. *Ethn Dis*.2017;27(1):45-54; doi:10.18865/ed.27.1.45.

Keywords: Glycemic Control; Insulin Detemir; Lebanese Population; Oral Antidiabetic Drugs; Type 2 Diabetes Mellitus

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Introduction

Developing countries from the Near East region face a serious socioeconomic burden related to the rising trend in the prevalence of diabetes. In particular, the International Diabetes Federation reports a 14.53% prevalence of diabetes in Lebanon in 2013.[1] In parallel, the availability of local clinical data is essential to increase awareness and provide appropriate guidance on the management of type 2 diabetes mellitus (T2DM).[2]

A substantial number of persons with T2DM needs insulin therapy after 9 years or more of disease due to unremitting loss of β-cell function with a need of intensification to a basal-bolus insulin regimen after 3–5 years of basal insulin treatment.[3,4] The timely addition of insulin to oral antidiabetic (OADs) agents is a key step in the management of these patients. It prevents the chronic complications of diabetes through glycemic control, and aids in adapting to the progressive β-cell failure caused by extended exposure to hyperglycemia.[5-7]

The results of the United Kingdom Prospective Diabetes Study (UKPDS)[5] allowed the American Association of Clinical Endocrinologists (AACE) to set a target glycosylated hemoglobin A1c (HbA1c) of ≤6.5%,[7] and the American Diabetes Association (ADA) to recommend an HbA1c level <7%.[8] However, although the efficacy and safety of insulin therapy in T2DM are well-established, guide-

lines and clinical practice differ in the timely initiation of insulin.[9]

Further, hypoglycemia is the main restricting factor in insulin dependent glycemic management. Other hurdles to insulin therapy are: physical and psychosocial morbidity; mortality;[10] individual and physician concerns about weight gain;[5,6,11,12] possibility of insulin-associated atherogenicity; injection-site pain; and economic considerations.[5,11,12] In parallel, insulinotherapy is pivotal in the management of T2DM, but no consensus exists about the best ways to overcome the aforementioned barriers when initiating insulin therapy.[13,14] The addition of a long-acting basal insulin formulation to an existing OAD regimen, followed by aggressive titration of the dose to achieve glycemic targets has gained popularity in recent years. It has also been recommended in the recent guidelines and targets for glycemic control published by IDI,[13] and ADA–EASD[15] as a simple treat-to-target approach, following its success in clinical trials.[13-18]

The development of long-acting basal insulin analogues with improved pharmacokinetics, which are able to more closely mimic endogenous insulin secretion, has been shown to have a positive effect on the balance between effective glycemic control and hypoglycemic risk.[19] Two bioengineered basal insulin analogues, including insulin glargine and insulin detemir, have been found to enable this treat-to-target approach with a reduced risk for hypoglycemia compared with that found with a conventional, human insulin-based formulation, neutral protamine Hagedorn (NPH).[15-16] The analogue insulin detemir (IDet) belongs to a new class of non-crystalline form of long-acting insulin analogs.[20] It has more reproducible absorption and a prolonged time-action profile,[21] besides a less within-people variability for the pharmacodynamic endpoints compared with NPH insulin and insulin glargine.[20] It also offers a better reproducibility as compared with other basal insulins, reduces the risk of hypoglycemia,[20] and causes little or no weight gain.[22] It may lead patients to titrate their insulin doses more easily and, therefore, to more often achieve glycemic objectives.[20]

Our study aimed to evaluate the effectiveness and safety of 24-week insulin detemir treatment administered as add-on therapy in a real-world setting of OAD-treated, insulin naïve, T2DM Lebanese persons.

Importantly, achieving blood glucose control is a known prerequisite for improving an individual's outcomes in T2DM. Relevant clinical studies focus on a treatment's ability to achieve glycemic targets during strictly enforced regimens.[13] Plus, treatment strategies are less stringently monitored in the real clinical practice, and the general patient population is more diverse than those in clinical trials.[23] In this context, our study aimed to evaluate the effectiveness and safety of 24-week insulin detemir treatment administered as add-on therapy in a real-world setting of OAD-treated, insulin naïve, T2DM Lebanese persons.

Methods

Study Design and Population

Our study represents the Lebanese arm of a prospective, multicenter, multinational, 24-week observational study conducted across the Near East countries of Lebanon, Jordan, Pakistan and Israel. The multinational study (NCT00842192) involved 2,155 participants from the Near East.

In Lebanon, inclusion criteria were persons with T2DM who were newly diagnosed or previously treated with one or more OADs (metformin, sulfonylureas, repaglinide, thiazolidinediones) and were starting insulin detemir with or without OAD therapy. Persons who were being treated with insulin detemir or any other insulin, persons with a hypersensitivity to insulin detemir or to any of the excipients, women who were pregnant, breast feeding, having the intention of becoming pregnant within next 6 months, or of childbearing potential who were not using adequate contraceptive methods were excluded from the study.

Eligible persons were recruited from primary and secondary care settings across the country from

April 2009 to August 2010. Selection of study participants was at the discretion of the individual physician. As participants were not randomized in this study, allocation of personal identification was accomplished by unique person numbers.

Data Collected

The participants' demographic data, past history of T2DM, and the reason for adding on insulin detemir were first collected. Then, effectiveness parameters were collected: determination of glycemic control by identifying the level of HbA1c, fasting plasma glucose (FPG), variability in FPG, post-prandial plasma glucose (PPG) levels, persons achieving target of HbA1c of <7%, insulin therapy and OAD therapy. Safety parameters were also reported: hypoglycemic episodes, adverse drug reactions (ADRs), serious ADRs (SADRs) and body weight.

These parameters were recorded for the entire observation period at routinely scheduled three consecutive clinic visits conducted at week 0 (baseline visit), week 12 (interim visit) and week 24 (final visit). Data for safety and effectiveness parameters were collected from the participants' records, recall and diaries. Data on measurement of all study parameters (either at the clinic or self-reported) depended on routine practice. This was believed to be consistent for each participant at the baseline as well as the scheduled visits.

Study Endpoints

The primary effectiveness endpoint was change in HbA1c from baseline to 12 and 24 weeks. Secondary endpoints were assessed at 12 and 24 weeks of treatment compared with baseline: percentage of participants achieving HbA1c <7% and ≤6.5%, glucose variability measured as change in FPG, post-prandial glycemic control measured as change in PPG, change in insulin dose and oral OAD therapy.

The primary safety endpoint was change in number of hypoglycemic episodes from the 4 weeks preceding the baseline visit compared with after 12 and 24 weeks of IDet treatment. Information on hypoglycemic episodes was collected based on participant's recall of the last 4 weeks before baseline, weeks 12 and 24. Secondary safety endpoints were the number of ADRs and change in body weight after approximately 12 weeks and 24 weeks of treatment compared to baseline.

A hypoglycemic event was defined as an event with one of the following characteristics: 1) symptoms of hypoglycemia that resolve with oral carbohydrate intake, glucagon or intravenous glucose or any symptomatic or asymptomatic plasma glucose <3.11 mmol/l; 2) nocturnal hypoglycemic events were defined as individualized symptomatic events consistent with hypoglycemia, that occur while the patient is asleep, between bedtime after the evening insulin injection and before getting up in the morning (if relevant, before morning determination of FPG and before morning injection). Major hypoglycemic events were defined as events with severe central nervous system symptoms consistent with hypoglycemia in which the participant was unable to treat himself/herself and had a plasma glucose <3.11 mmol/l, or reversal of symptoms after either glucagon or intravenous glucose administration.

Treatment Regimen

Insulin detemir was introduced to participants already receiving one or more OADs (biguanides, repaglinide, thiazolidinediones, sulfonylureas, or alpha-glucosidase-inhibitors). The OAD+insulin regimen was initiated for the newly diagnosed patients by the treating physician as part of routine clinical care. The starting dose and subsequent adjustments of the treatment regimen were at the individual physician's discretion. Insulin detemir was administrated according to the approved label.

The clinical supplies coordination did not provide any products or devices for this trial as commercially available OADs and insulin detemir were used in this observational study. Insulin detemir (Levemir®) available as 3 mL Penfill cartridges (100 U/mL) or 3 mL FlexPen® devices (100 U/mL, 5 FlexPen® devices/package) was prescribed.

Statistical Analysis

With a statistical power >99% to detect a 1% change in HbA1c from baseline, a standard deviation of 1.2 and an estimated drop-out rate of 20%, 2,000 persons from the 4 participating countries were considered sufficient to evaluate primarily the safety of IDet; approximately 900 persons participated from Lebanon.

Demographic and clinical characteristics were summarized using means and standard deviations for continuous variables and frequency and percentages for categorical vari-

ables. Statistical analysis was performed using paired *t*-tests for continuous variables and chi-square test for categorical data. Missing data were reported when appropriate. Statistical analysis was based on two-sided tests with a significance level of 5%.

The safety analysis set comprised all participants who had received at least one dose of insulin detemir. The full analysis set (FAS) comprised all participants who had received at least one dose of insulin detemir and had any post-baseline data. The effectiveness analysis set (EAS) comprised all participants in FAS who had a final visit at week 24 and at least one measurement concerning FPG, PPG, most recent HbA1c, weight or hypoglycemic episodes at baseline and final visit.

Statistical analysis was performed using SAS version 9.1.3. (SAS® Institute Inc., Cary, North Carolina, USA).

Ethical Considerations

The study was approved by the ethics committee of each participating center. It was performed in accordance with the regulatory requirements for observational studies in Lebanon, and the Declaration of Helsinki. All participants completed an informed consent form before their enrollment.

Results

Participants' Disposition and Demographics

894 Lebanese participants were initially enrolled, 815 persons (91.2%) completed the study due to withdrawal of 53 persons, loss of contact (n=45) and other reasons (n=8). Thus, FAS and safety analysis sets were composed of 868 (97.1%), while EAS included 814 (91.1%) participants.

The mean age of the 868 participants was 59.5 ± 10.4 years, 55.3% were men. In 95% of the cases, the main reason for starting insulin detemir was to improve glycemic control. Participants' demographics and reasons for adding insulin detemir are displayed in Table 1.

Table 1. Baseline characteristics and demographics – full analysis set, n=868

Variables	
Sex, n (%)	
Men	480 (55.3)
Women	388 (44.7)
Age, years, mean ± SD	59.5 ± 10.4
Min-max	24.4-91.4
Weight, kg, mean ± SD	80.4 ± 13.6
Min-max	36.0-136.0
Height, m, mean ± SD	1.68 ± .08
Min-max	1.5-2.0
BMI, kg/m^2, mean ± SD	28.4 ± 4.2
Min-max	16.0-49.9
Duration of diabetes mellitus, years, mean ± SD	10.0 ± 5.4
Min-max	0-50.0
Reasons for adding insulin detemir, n (%)	
Improve glycemic control	829 (95.5)
Reduce blood glucose variability	416 (47.9)
Participant dissatisfaction with current therapy	365 (42.1)
Unstable diabetes	362 (41.7)
Improve weight control	225 (25.9)
Reduce risk of hypoglycemia	122 (14.1)
Change due to insulin pen	120 (13.8)
Other	55 (6.3)

BMI, body mass index; SD, standard deviation.

Primary Effectiveness Results

Glycemic control improved as the mean HbA1c was significantly reduced from 9.7 ± 1.6% at baseline to 7.8 ± 1.0% at week 12 and to 7.2 ± 1.0% at week 24 (P<.0001) (Table 2).

Secondary Effectiveness Results

In the FAS, the percentage of participants who achieved the target of HbA1c <7% increased from .7% at baseline to 17.8% at week 12 and 39% at week 24. The percentage of participants who achieved the target of HbA1c of <6.5% increased from .4% to 5.8% at week 12 and 17.4% at week 24. Similarly, in the EAS, the percentage of participants who achieved the target of HbA1c of <7% increased from .8% at baseline to 18.2% at week 12 and 39% at week 24. The percentage of participants who achieved the target of HbA1c of <6.5% increased from .4% to 5.8% at week 12 and 17.4% at week 24.

Mean FPG levels were reduced from 213.7 ± 60.1 mg/dL at baseline to 120.3 ± 25.7 mg/dL at week

24 (P<.001). Mean PPG levels were significantly decreased from 271 ± 65.3 mg/dL at baseline to 158.1 ± 36.4 at week 24 (P<.0001). Also, the decrease in mean variability in FPG under insulin detemir treatment was -9 ± 21.3 mg/dL at week 12 and -11.7 ± 19 mg/dL at week 24 compared with baseline (P<.0001).

The mean daily dose of insulin detemir exposure was increased from 17.5 ± 7.4 U at baseline to 25.6 ± 10.1 U at week 12 and to 27.7 ± 10.8 U at the end of the study. Insulin detemir dosage per body weight was .22 ± .1 U/Kg at baseline, .32 ± .12 U/Kg at week 12 and .34 ± .13 U/Kg at week 24.

Biguanides (76.5%) and sulfonylureas (74.7%) were the most commonly prescribed OADs at baseline. After 12 weeks of treatment, the

Table 2. Change from baseline to endpoint in effectiveness variables following insulin detemir treatment (oral antidiabetic drugs) for 24 weeks – full analysis set (n=868)

	Baseline	Week 12	Week 24
HbA_{1c} level, %[a], mean ± SD	9.7 ± 1.6	7.8 ± 1.0	7.2 ± 1.0
Participants with HbA1c <7%, n (%)	6 (.7)	132 (17.8)	301 (39.0)
Participants with HbA1c <6.5%, n (%)	3 (.4)	43 (5.8)	134 (17.4)
FPG level, mg/dL[a], mean ± SD	213.7 ± 60.1	134.8 ± 32.8	120.3 ± 25.7
PPG level, mg/dL[a], mean ± SD	271.0 ± 65.3	177.4 ± 44.3	158.1 ± 36.4
Insulin detemir dosage, mean ± SD			
Daily, U/day	17.50 ± 7.4	25.6 ± 10.1	27.7 ± 10.8
Per body weight, U/kg	.22 ± .1	.32 ± .12	.34 ± .13
OAD therapy[b], n (%)			
Biguanides	664 (76.5)	666 (78.9)	642 (78.8)
Sulfonylureas	648 (74.7)	592 (70.1)	550 (67.5)
Thiazolidinediones	181 (20.9)	96 (11.4)	74 (9.1)
Glinides	77 (8.9)	74 (8.8)	66 (8.1)
α-Glucosidase inhibitors	50 (5.8)	29 (3.4)	39 (4.8)
Other	11 (1.3)	14 (1.7)	9 (1.1)
No treatment	3 (.3)	31 (3.7)	48 (5.9)

a. P<.0001, baseline vs week 24 (two-sided significance level of 5%).
b. A participant may have more than one OAD therapy.
FPG, fasting plasma glucose; HbA1c: glycosylated hemoglobin A1c; OAD: oral antidiabetic drugs; PPG: postprandial plasma glucose; SD: standard deviation.

Table 3. Change from baseline to endpoint in hypoglycemic episodes following insulin detemir treatment (± oral antidiabetic drugs) for 24 weeks – full analysis set (n=868)

Hypoglycemic episodes	n (%)		Number of episodes		Events per person year	
	Week 0[a]	Week 24[b]	Week 0	Week 24	Week 0	Week 24
Total						
All events	46 (5.3)	111 (12.8)	134	290	2.0069	1.8556
Daytime	45 (5.2)	102 (11.8)	93	211	1.3929	1.3501
Nocturnal	20 (2.3)	45 (5.2)	41	79	.6141	.5055
Due to fasting regimen	2 (.2)	12 (1.4)	3	20	.0449	.1280
Major						
All events	7 (.8)	5 (.6)	10	7	.1498	.0448
Daytime	5 (.6)	4 (.5)	5	5	.0749	.0320
Nocturnal	4 (.5)	2 (.2)	5	2	.0749	.0128
Due to fasting regimen	0 (.0)	0 (.0)	0	0	.0000	.0000
Minor						
All events	44 (5.1)	111 (12.8)	124	283	1.8571	1.8108
Daytime	41 (4.7)	101 (11.6)	88	206	1.3180	1.3181
Nocturnal	19 (2.2)	45 (5.2)	36	77	.5392	.4927
Due to fasting regimen	2 (.2)	12 (1.4)	3	20	.0449	.1280

Hypoglycemic events were collected based on participants' recall over the last 4 weeks before each visit.
One person year equals to 365.25 days.
a. Exposure year: 66.8.
b. Exposure year: 156.3.
%, proportion of participants exposed in the treatment period having an episode; N, number of participants having at least one hypoglycemic episode.

first two commonly received OADs were biguanides (78.9%) and sulfonylureas (70.1%). At the end of 24 weeks of treatment, the proportion of participants using biguanides increased minimally (78.8%) while that of sulfonylureas (67.5%) decreased compared with baseline (Table 2).

Primary Safety Results

The rate of total hypoglycemic episodes slightly decreased from 2.0069 at baseline to 1.8556 per person year at week 24, while the rate of major hypoglycemic episodes decreased from .1498 at baseline to .0448 per person year at week 24. The rate of daytime major hypoglycemic episodes decreased from .0749 at baseline to .0320 at week 24, while the rate of nocturnal major hypoglycemic episodes decreased from .0749 at baseline to .0128 per person year at week 24. The rate of total hypoglycemic episodes due to fasting regimen slightly increased from .0449 at baseline to .1280 per person year at week 24. No major hypoglycemic episodes due to fasting regimen were reported at baseline or week 24 (Table 3).

Secondary Safety Results

No ADRs, SADRs and serious adverse events (SAEs) were reported in Lebanese participants. A total of 3 moderate adverse events (AEs) (2 recovered, 1 recovering) were recorded in 2 participants (.2%) with reduction in dose (n=1), increase in dose (n=1) and no change in the dose (n=1).

Body weight was 80.4 ± 13.2 Kg at baseline, 80.1 ± 12.9 Kg at week 12 and significantly decreased to 79.9 ± 12.5 at week 24 compared with baseline value (P<.0001).

Discussion

Our study assessed the effectiveness and safety of 24-week insulin detemir administered as add-on therapy in a real-world setting of OAD-treated, insulin naïve, T2DM persons with suboptimal baseline glycemic control (HbA1c=9.7%) or with baseline blood glucose levels beyond recommended glycemic targets (FPG=213.7 ± 60.1 mg/dL, PP=271.0 ± 65.3 mg/dL).

Effective glycemic control was achieved with lower incidence of major hypoglycemic events and no significant weight gain.

Effective glycemic control was achieved with lower incidence of major hypoglycemic events and no significant weight gain. While weight gain is a prime concern in the first year of initiating insulin therapy in T2DM,[5,6] insulin detemir seemed to overcome this barrier in our study. Indeed, it reduced overall body weight by .5 kg after 24 weeks of treatment, while it was weight neutral according to the multinational results.[24] A significant weight loss was also observed in patients transferred from NPH insulin (.7 kg, P<.01) and insulin glargine (.5 kg, P<.05) to insulin detemir, as per the 14-week follow-up data of PREDICTIVE™ study.[25] Likewise, an average weight loss of .9 kg (P<.0001) was observed in a German subgroup of the PREDICTIVE™ study, with T2DM transferred to insulin detemir ± OADs from an OAD-only regimen, NPH insulin ± OADs, or insulin glargine ± OADs.[26] Given the global increase in obesity rates,[27] the finding that insulin detemir reduces weight gain in persons with T2DM makes it clinically advantageous compared with other available forms of insulin.[28] However, the weight loss could be attributable to reduced insulin requirements in the Lebanese patients who were on oral agents, in addition to certain lifestyle modifications such as improved diet and increased exercise.

The investigators mainly initiated insulin detemir as add-on therapy to improve glycemic control both in the Lebanese population and overall population evaluated in the multinational analysis of the study. However, sequence of other reasons for initiating therapy varied between the two populations. As such, the reduction in blood glucose variability, person dissatisfaction with current therapy and unstable diabetes were more prominent in the Lebanese participants. In contrast, the reduction of the risk of hypoglycemia and the improvement of weight control were more common reasons for initiating insulin detemir therapy in the overall study population. Moreover, the combination of insulin detemir with OADs showed to be safe with no ADRs/SAEs. Hence, insulin de-

temir plus OAD therapy seemed to meet the therapeutic expectations.

To reach a target HbA1c <7% using basal insulin plus OADs, the basal insulin should be initiated before HbA1c rises above 8.5%. In this sense, the mean level of overall HbA1c reduction found in studies investigating the addition of basal insulin to OADs was reported to be approximately 1.5%.[29] Accordingly, the effectiveness of insulin detemir for reducing baseline HbA1c in the Lebanese population by -2.5% (from 9.7 to 7.2%) was in line with the literature. It was also slightly better than multinational results in the four Near East countries (from 9.6 to 7.6; -2.0%),[24] indicating significantly improved glycemic control. When also compared with multinational results, reduction of the percentage of persons with HbA1c <7% was more pronounced in the Lebanese population both at weeks 12 (17.8% vs 13.2%) and 24 (26.9% vs 39%). Accordingly, a reduction of HbA1c of <7% is notable in a higher number of Lebanese patients since the mean HbA1c at baseline was 9.7%. The latter indicates a need for a more aggressive insulin regimen in a greater number of persons to achieve the desired HbA1c target. While HbA1c continued to fall, the achievement of greatest improvement in FPG at 12 weeks was suggested to indicate optimization of insulin detemir regimens within this timeframe with subsequent improvements in glycemic control made by adjusting prandial glucose.[13]

The incidence of major hypoglycemic events (overall, daytime, nocturnal) decreased in our study population, consistently with the multinational results.[24] This finding is encouraging as hypoglycemia remains one of the most disturbing side effects of insulin use.[10] Also, the achievement of a mean HbA1c of 7.2% at the end of study in the Lebanese population indicates less likelihood of hypoglycemia and is consistent with other studies. The introduction of long-acting insulin analogues minimized the risk of hypoglycemia, especially nocturnal episodes.[15,16] This difference with interventional studies can be explained by the nature of observational studies and the diabetes monitoring habits of Lebanese persons. First, observational studies have the advantage of studying large and heterogeneous populations. However, they have some limitations, such as a lack of control groups, potential person recall bias and possible variations in clinical practice between countries. Second, self-monitoring habits may be different across countries and may affect the glycemic control and hypoglycemia rates.[30] Indeed, a 24-week insulin detemir treatment was determined to have a promising safety profile based on the reduction in all types of major hypoglycemic episodes, in addition to the reporting of only three AEs in two persons, no ADRs nor SAEs. Similarly, the incidence of SADRs (0%) and ADRs (.4%) with insulin detemir treatment was indicated to be minimal at the end of 24-week treatment in the multinational results.[24] Given that insulin detemir was also associated with a low incidence of SADRs and ADRs in the Lebanese population, the safety data obtained in our study support past clinical studies indicating that the new basal analogue insulin detemir incurs low incidence of SADRs and ADRs.[24,31] They also suggest a low/similar risk of hypoglycemia, with less weight gain at equivalent levels of glycemic control compared with NPH insulin[12] or insulin glargine[16,22] when used as either an adjunct to oral therapy or as part of basal-bolus therapy.[12]

Not only a low incidence of safety events and no significant weight gain were reported for insulin detemir ± OADs in our 24-week treatment period, similar results were also found throughout the 52-week treatment period.[12,28] Nevertheless, considering insulin detemir for those persons who may be more vulnerable than those recruited into clinical trials seems reasonable.[12]

Although clinical trials support flexibility in injection frequency (once or twice daily), the pharmacodynamics profile of insulin detemir is best suited to once-daily use in persons with T2DM.[32] While data on frequency of injections was not collected in this study, similar studies with insulin detemir ± OADs showed that a once-daily injection was adequate for good glycemic control in the majority of persons (77% to 82%) with <25% persons requiring twice daily injections after 14 weeks of insulin detemir ± OADs.[25,31] Accordingly, an increase in the mean daily dose of insulin detemir from 17.5 ± .22 U/kg at baseline to 27.7 ± .34 U/kg at the end of the study in the Lebanese population is in line with the 52-week follow-up results of PREDICTIVE™ study.[27] The latter indicates that the proportion

of persons with T2DM using once-daily insulin detemir was 67% at the end of 52-week follow-up, with a slight increase observed in dosage.[12]

Likewise, considerable decrease in the proportion of persons receiving the sulfonylureas and thiazolidinediones was reported at the end of study, although the majority of the persons received biguanides, sulfonylureas and thiazolidinediones at each visit. This is consistent with the findings of international studies.[33] Hence, the advantages of insulin detemir could be of particular relevance in overcoming the barriers of insulin initiation and treatment adherence in persons.

In this regard, our findings strengthen the data on insulin detemir for glycemic control in T2DM persons associated with a minimized risk of hypoglycemia and weight gain from different person populations.[25,32,33] They are also consistent with clinical trial data of insulin detemir in comparison to other insulin types and can be relevant to routine clinical practice.[5,16,22] Consequently, insulin therapies like insulin detemir, which are better able to mimic the body's physiological responses, provide some scope for achieving an improved balance between glycemic control and treatment tolerability. This may support better person compliance and an improved quality of life when used in the primary care setting.[12]

Although our data are consistent with the longitudinal analyses of 52-week data from the observational PREDICTIVE™ study,[12,27] the first published analyses of long-term insulin detemir use in everyday practice are considered less reliable. The rationale is that observational studies are less stringently controlled than are clinical trials. For this reason, whether the advantages of insulin detemir related to improved balance between mean glycemic control and tolerability can be sustained over longer periods of treatment, needs to be further explored and clarified in ongoing studies. These should compare head-to-head treat-to-target with other long-acting basal insulins based on equitable once-daily dosing algorithms. Despite these drawbacks, observational studies have an important role to play in assessing a drug's performance in a real-world setting.[23]

Our study has some limitations. First, an improvement to the study would have been randomization. Second, while our findings are representative of the Lebanese population, they cannot be generalized to other demographic regions and ethnic groups and as such, may not be applicable to clinical practice in other regions.

Conclusions

To conclude, our study reports a significant reduction in HbA1c, which is correlated with the improvement in FPG. Furthermore, the variability in FPG also decreased demonstrating improved control over glycemic excursions. Thus, our study indicates an improvement of glycemic control and an absence of notable safety concerns such as ADRs, SAEs and weight gain. Ultimately, treatment initiation with a long-acting basal analogue insulin detemir offers a reasonable treatment paradigm with good safety and effectiveness profile among persons with T2DM.

Acknowledgments

We wish to thank Dr. Meltem Telaferli (CMR Director, BANE), Dr. Levent Sandalci (Medical Manager, BANE), Dr. Suzan Dumanli Ozgoksu for their support of the manuscript; Prof. Sule Oktay, MD, PhD and Cagla Isman, MD from KAPPA Consultancy Training Research Ltd (Istanbul, Turkey), and Racha Aaraj, PharmD, MSc, MPH from Phoenix Clinical Research (Beirut, Lebanon) who provided editorial support. We thank all the investigators who participated in this study.

Conflict of Interest

No conflicts of interest to report.

Author Contributions

Research concept and design: Echtay, Andari, Atallah, Moufarrege, Nemr; Acquisition of data: Echtay, Andari, Atallah, Moufarrege, Nemr; Data analysis and interpretation: Echtay, Andari, Atallah, Moufarrege, Nemr; Manuscript draft: Echtay, Andari, Atallah, Moufarrege, Nemr; Statistical expertise: Echtay, Andari, Atallah, Moufarrege, Nemr; Acquisition of funding: Echtay, Andari, Atallah, Moufarrege, Nemr; Administrative: Echtay, Andari, Atallah, Moufarrege, Nemr; Supervision: Echtay, Nemr

References

1. Diabetes Federation. *IDF Diabetes Atlas.* 6th ed. Melbourne, Australia; 2013. http://www.idf.org/diabetesatlas/6e. Last accessed 20 April 2016.
2. Garber AJ, King AB, Del Prato S, et al; NN1250-3582 (BEGIN BB T2D) Trial Investigators. Insulin degludec, an ultra-long-gacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN Basal-Bolus Type 2): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. *Lancet*. 2012;379(9825):1498-1507. http://dx.doi.org/10.1016/S0140-6736(12)60205-0. PMID:22521072.
3. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. *JAMA.*1999;281:2005–2012.
4. Home PD, Boulton AJM, Jimenez J,

Landgraf R, Osterbrink B, Christiansen JS. Issues relating to the early or earlier use of insulin in type 2 diabetes. *Pract Diabetes Int*. 2003;20(2):63-71. http://dx.doi.org/10.1002/pdi.433.
5. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352(9131):837-853. http://dx.doi.org/10.1016/S0140-6736(98)07019-6. PMID:9742976.
6. Chon S, Oh S, Kim SW, Kim JW, Kim YS, Woo JT. The effect of early insulin therapy on pancreatic β-cell function and long-term glycemic control in newly diagnosed type 2 diabetic patients. *Korean J Intern Med*. 2010;25(3):273-281. http://dx.doi.org/10.3904/kjim.2010.25.3.273. PMID:20830224.
7. Feld S. AACE diabetes guidelines. *Endocr Pract*. 2003;(suppl 1):5-11.
8. American Diabetes Association. Glycemic targets. *Diabetes Care*. 2015;38(suppl):S33-S40. http://dx.doi.org/10.2337/dc15-S009. PMID:25537705.
9. Cryer PE. The barrier of hypoglycemia in diabetes. *Diabetes*. 2008;57(12):3169-3176. http://dx.doi.org/10.2337/db08-1084. PMID:19033403.
10. Korytkowski M. When oral agents fail: practical barriers to starting insulin. *Int J Obes Relat Metab Disord*. 2002;26(s3)(suppl 3):S18-S24. http://dx.doi.org/10.1038/sj.ijo.0802173. PMID:12174319.
11. Heinemann L. Overcoming obstacles: new management options. *Eur J Endocrinol*. 2004;151(Suppl_2):23-30. http://dx.doi.org/10.1530/eje.0.151T023.
12. Marre M, Pinget M, Gin H, et al. Insulin detemir improves glycaemic control with less hypoglycaemia and no weight gain: 52-week data from the PREDICTIVE study in a cohort of French patients with type 1 or type 2 diabetes. *Diabetes Metab*. 2009;35(6):469-475. http://dx.doi.org/10.1016/j.diabet.2009.06.004. PMID:19914118.
13. International Diabetes Federation. Clinical Guidelines Task Force. Guideline for Management of PostMeal Glucose in Diabetes 2011. http://www.idf.org/2011-guideline-management-postmeal-glucose-diabetes. Last accessed 20 April 2016.
14. Riddle MC, Rosenstock J, Gerich J; Insulin Glargine 4002 Study Investigators. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care*. 2003;26(11):3080-3086. http://dx.doi.org/10.2337/diacare.26.11.3080. PMID:14578243.
15. Hermansen K, Davies M, Derezinski T, Martinez Ravn G, Clauson P, Home P. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naive people with type 2 diabetes. *Diabetes Care*. 2006;29(6):1269-1274. http://dx.doi.org/10.2337/dc05-1365. PMID:16732007.
16. Inzucchi SE, Bergenstal RM, Buse JB, et al; American Diabetes Association (ADA); European Association for the Study of Diabetes (EASD). Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2012;35(6):1364-1379. http://dx.doi.org/10.2337/dc12-0413. PMID:22517736.
17. Philis-Tsimikas A, Charpentier G, Clauson P, Ravn GM, Roberts VL, Thorsteinsson B. Comparison of once-daily insulin detemir with NPH insulin added to a regimen of oral antidiabetic drugs in poorly controlled type 2 diabetes. *Clin Ther*. 2006;28(10):1569-1581. http://dx.doi.org/10.1016/j.clinthera.2006.10.020. PMID:17157113.
18. Plank J, Bodenlenz M, Sinner F, et al. A double-blind, randomized, dose-response study investigating the pharmacodynamic and pharmacokinetic properties of the long-acting insulin analog detemir. *Diabetes Care*. 2005;28(5):1107-1112. http://dx.doi.org/10.2337/diacare.28.5.1107. PMID:15855574.
19. Valensi P, Cosson E. Is insulin detemir able to favor a lower variability in the action of injected insulin in diabetic subjects? Diabetes Metab 2005;31:4S34–9. 10.1016/S1262-3636(05)88265-5.
20. Kurtzhals P. Engineering predictability and protraction in a basal insulin analogue: the pharmacology of insulin detemir. *Int J Obes Relat Metab Disord*. 2004;28(suppl 2):S23-S28. http://dx.doi.org/10.1038/sj.ijo.0802746. PMID:15306834.
21. Hermansen K, Fontaine P, Kukolja KK, Peterkova V, Leth G, Gall MA. Insulin analogues (insulin detemir and insulin aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal-bolus therapy for patients with type 1 diabetes. *Diabetologia*. 2004;47(4):622-629. http://dx.doi.org/10.1007/s00125-004-1365-z. PMID:15298338.
22. Ligthelm RJ, Borzi V, Gumprecht J, Kawamori R, Wenying Y, Valensi P. Importance of observational studies in clinical practice. *Clin Ther*. 2007;29(6):1284-1292. http://dx.doi.org/10.1016/j.clinthera.2007.07.004.
23. Devries JH, Nattrass M, Pieber TR. Refining basal insulin therapy: what have we learned in the age of analogues? *Diabetes Metab Res Rev*. 2007;23(6):441-454. http://dx.doi.org/10.1002/dmrr.762. PMID:17668418.
24. Echtay A, Tsur A, Hasan MI, et al. Clinical experience with insulin detemir in patients with type 2 diabetes from the near East countries. *Diabetes Ther*. 2013;4(2):399-408. http://dx.doi.org/10.1007/s13300-013-0041-z. PMID:24108581.
25. Dornhorst A, Lüddeke HJ, Koenen C, et al; PREDICTIVE Study Group. Transferring to insulin detemir from NPH insulin or insulin glargine in type 2 diabetes patients on basal-only therapy with oral antidiabetic drugs improves glycaemic control and reduces weight gain and risk of hypoglycaemia: 14-week follow-up data from PREDICTIVE. *Diabetes Obes Metab*. 2008;10(1):75-81. PMID:18034846.
26. Meneghini LF, Rosenberg KH, Koenen C, Merilainen MJ, Lüddeke HJ. Insulin detemir improves glycaemic control with less hypoglycaemia and no weight gain in patients with type 2 diabetes who were insulin naive or treated with NPH or insulin glargine: clinical practice experience from a German subgroup of the PREDICTIVE study. *Diabetes Obes Metab*. 2007;9(3):418-427. http://dx.doi.org/10.1111/j.1463-1326.2006.00674.x. PMID:17391170.
27. Cefalu WT, Bray GA, Home PD, et al. Advances in the Science, Treatment, and Prevention of the Disease of Obesity: Reflections From a Diabetes Care Editors' Expert Forum. *Diabetes Care*. 2015;38(8):1567-1582. http://dx.doi.org/10.2337/dc15-1081. PMID:26421334.
28. Rosenstock J, Davies M, Home PD, Larsen J, Koenen C, Schernthaner G. A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes. *Diabetologia*. 2008;51(3):408-416. http://dx.doi.org/10.1007/s00125-007-0911-x. PMID:18204830.
29. Yki-Järvinen H, Kauppila M, Kujansuu E, et al. Comparison of insulin regimens in patients with non-insulin-dependent diabetes mellitus. *N Engl J Med*. 1992;327(20):1426-1433. http://dx.doi.org/10.1056/NEJM199211123272005. PMID:1406860.
30. Dornhorst A, Lüddeke HJ, Sreenan S, et al. Safety and efficacy of insulin detemir in clinical practice: 14-week follow-up data from type 1 and type 2 diabetes patients in the PREDICTIVE European cohort. *Int J Clin Pract*. 2007;61(3):523-528. http://dx.doi.org/10.1111/j.1742-1241.2007.01316.x. PMID:17313628.
31. Heise T, Pieber TR. Towards peakless, reproducible and long-acting insulins. An assessment of the basal analogs based on isoglycemic clamp studies. *Diabetes Obes Metab*. 2007;9(5):648-659. http://dx.doi.org/10.1111/j.1463-1326.2007.00756.x.

32. Dornhorst A, Lüddeke HJ, Sreenan S, et al; PREDICTIVE Study Group. Insulin detemir improves glycaemic control without weight gain in insulin-naïve patients with type 2 diabetes: subgroup analysis from the PREDICTIVE study. *Int J Clin Pract*. 2008;62(4):659-665. http://dx.doi.org/10.1111/j.1742-1241.2008.01715.x. PMID:18324957.
33. Ross S, Dzida G, Ji Q, et al; SOLVE Study Group. Safety of once-daily insulin detemir in patients with type 2 diabetes treated with oral hypoglycemic agents in routine clinical practice. *J Diabetes*. 2014;6(3):243-250. http://dx.doi.org/10.1111/1753-0407.12091. PMID:24103141.