Insulin Analogues (NovoMix® 30 FlexPen®, or Levemir® FlexPen®, and/or NovoRapid® Flex Pen®) in the management of diabetes mellitus in the Gulf Countries

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Abstract

Evaluation of safety and efficacy of insulin aspart (NovoRapid® FlexPen®), insulin detemir (Levemir® FlexPen®), biphasic insulin aspart 30 (NovoMix® 30 FlexPen®), and their combination for the treatment of type 1 and type 2 diabetes in the Gulf countries in a prospective, multicenter, open label, non-interventional, observational study. A total of 5,866 patients with type 1 or type 2 diabetes were followed for 6 months. The primary efficacy endpoint was the change in glycoslyated hemoglobin (HbA_{1c}) from baseline, while the secondary efficacy endpoints were the percentage of patients achieving HbA_{1c} less than 7.0% approximately 12 and 24 weeks compared to baseline and changes in fasting blood sugar and postprandial blood sugar after 12 and 24 weeks of treatment compared to baseline. The primary safety endpoint was the incidence of major hypoglycemic episodes during the 24 weeks of using the study medication, while the secondary safety endpoints were changes in the number of hypoglycemic episodes in the past 4 weeks prior to the routine visits at approximately 12 and 24 weeks of treatment. The reduction in glycemic control measured by mean HbA_{1c} from baseline to after 6 months was 2.4 (from 9.8 to 7.4, p-value < 0.0001) in all treatment groups after 24 weeks irrespective of the previous insulin regimen. The change in HbA1c after 24 weeks of treatment was 2.4 % in the Levemir® group, -2.3% in the NovoMix®30 group, 2.5% in the NovoRapid® group, 2.3 % in the combination group. The proportion of patients who achieved the target HbA_{1c} increased from 1.7% at baseline to 26.9% after 24 weeks of treatment with insulin analogues. The change in the mean body weight after 24 weeks of treatment was 1.3 kg in the Levemir® group, 0.9 kg in the NovoMix®30 group, 0.1kg in the NovoRapid® group, and 0.7kg in the combination group. The change in major hypoglycemia was as follows: In the detemir group 2.9% at baseline to 0.2% at week 24, in the BIAsp30 group was 2.9% at baseline to 0.2% at week 24, in the aspart group 3.1% at baseline to 0% at week 24 (p < 0.0001).Switching to insulin Aspart (NovoRapid® FlexPen®), insulin detemir (Levemir® FlexPen®), biphasic insulin aspart 30 (NovoMix® 30 FlexPen®), or the combination of any of them resulted in significant lowering in HbA_{1c}, fasting blood sugar, postprandial blood sugar, postprandial glucose increment, and the number of major hypoglycemic attacks. The percentage of patients attaining the required HbA_{1c} below 7% was 26.9%. The body weight was reduced in all treatment groups.

Keywords: *insulin analogues, insulin detemir, insulin aspart, biphasic insulin aspart, observational study*

Introduction

Despite the extensive research that has been done on diabetes, it still remains one of the most important causes of morbidity and mortality in the world. It is also likely that its impact worldwide is likely to accelerate.[1] According to WHO estimates, the prevalence of diabetes mellitus was around 177 million people in the year 2000. The number is going to increase to around 300 million individuals by 2025.[2] There is a rising trend in the incidence of diabetes in Saudi Arabia in recent decades.[3] A community-based national epidemiological health survey done in Saudi Arabia between 1995 and 2000 reported a 23.7% prevalence of diabetes among Saudi adults between the age of 30 to 70 years.[3,4] A large number of Saudi diabetics are unaware of the diagnosis despite the availability of medical care. The delay will eventually result in complications of the disease.[4] The most frequent complications in type 2 Saudi diabetics are related to cardiovascular and renal systems.[3] In the Sultanate of Oman, the incidence rates of type 1 diabetes were 2.45 and 2.62 per 100,000 person per year during 1993 and 1994, respectively in 0 to 14-year-old children.[5]

Type 1 diabetes mellitus (T1DM) is caused by absolute insulin deficiency and is characterized by a presence of T-lymphocytes and autoantibodies against the antigen structure of β-cells. The incidence of T1DM is 25 per 100,000. However, ethnic differences have been found; the

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lowest incidence is found in China and Japan (0.4 and 1.6 per 100,000, respectively) and the highest incidence is in Finland (40 per 100,000). The only therapeutic option for T1DM is the substitution of missing insulin using an intensified regimen of basal-bolus therapy.[6] Basal-bolus insulin regimens try to mimic the insulin secretion profile in the body; the normal insulin secretion has two components: low basal levels secreted between meals, through the night, and during fasting, and very high levels secreted postprandially. Basal-bolus insulin regimens in diabetes consist of one or two injections per day of intermediate or long-acting insulins (basal) and multiple mealtime (bolus) injections of rapid-acting or regular insulins.[7]

Type 2 diabetes (T2DM) is a heterogeneous metabolic disorder. Relative insulin deficiency is characteristic to T2DM. This is due to reduced sensitivity of tissues to insulin and impaired insulin secretion from pancreatic β cells. T2DM represents more than 80% of the DM cases. The prevalence of T2DM is growing more than expected. In order to prevent the well documented complications in type 2 DM, early initiation of insulin therapy is required before the development of co-morbidities. This therapeutic approach may protect the β cells from functional impairment as a result of long-term hyperglycemia.[6] Insulin therapy has been recommended by the International Diabetes Federation and the American Association of Clinical Endocrinologists in the treatment initiation regimens, especially when HbA_{1c} levels are high (>10%).[8]

Management of diabetes has greatly improved recently with newer strategies for aggressive glucose control(1). The treatment of type 1 DM and advanced type 2 DM usually includes basal-bolus insulin regimen in order to achieve better glycemic control targets (HbA1c, fasting plasma glucose, and postprandial glucose).[9,10] The benefits of insulin are well documented but are limited by hypoglycemic attacks and the risk of weight gain. Due to these limitations, a patient may not cooperate in titrating and intensifying the insulin therapy.[9] Insulin analogues are replacing the traditional insulin products as the insulin analogues have improved pharmacokinetics which result in either more rapid or prolonged pharmacodynamic effects. The improved pharmacokinetic and pharmacodynamic effects of the insulin analogues allow them to mimic the physiologic insulin more closely.[1] Traditional human insulin products are unable to provide pharmacokinetic PK/ pharmacodynamic PD profiles that match the physiological insulin need. This may lead to increased incidence of hypoglycemia; postprandial hypoglycemia (in case of bolus human insulin) or nocturnal hypoglycemia or high fasting blood sugar (in case of bedtime basal human insulin). It has been shown in randomized clinical trials, the safety and the efficacy of modern insulin and how it is time for real life experience on modern insulin application to look at the safety and efficacy of modern insulin in normal clinical physician practice.

Insulin Therapy

Subcutaneous insulin preparations differ in the shape of their serum time-concentration profiles due to their different absorption patterns and their effects on glucose levels. It is also important to maintain reproducible and non-variable activity, which is the main limitation with traditional insulin products.[1]

Insulin Aspart

Insulin aspart is a rapid-acting recombinant insulin analogue. Its structure differs from human insulin at position 28, where proline is substituted with charged aspartic acid. This modification allows insulin aspart to be absorbed twice as fast as human insulin. When administered before meals, it provides a better postprandial glycemic control in patients with type 1 or type 2 diabetes mellitus.[2,11,12] Furthermore, the pharmacokinetic and pharmacodynamic variability of insulin aspart was found to be lower than human insulin by 10 to 20%.[1]

Insulin Detemir

Insulin detemir is a long-acting basal insulin analogue modified from human insulin structure through the addition of a C14 fatty acid side chain at position B29 through acylation of myristic acid to lysine residue.[1,12] It provides consistent, relatively flat, and protracted insulin levels. These insulin levels are achieved by delayed absorption due to increased self-association at the injection site (hexamer stabilization) and a high degree of reversible albumin binding within the subcutaneous tissue as well as because albumin binding causes buffering of plasma concentration.[1,12] These modifications will also contribute to lower within subject variability than NPH and insulin glargine.[3] Detemir is also expected to provide a more consistent and reliable basal insulin supply compared to NPH insulin and insulin glargine as the absorption of determir does not depend on the appropriate re-suspension before injection and the dissolution of crystals in the subcutaneous tissue.[13]

Detemir also significantly reduces the rate of hypoglycemia and no or less weight gain than NPH insulin.[6] Some studies even observed a slight weight loss with detemir, which may be attributed to slightly lower food intake due to less hypoglycemic episodes and less defensive snacking.[13]

Biphasic insulin aspart

Biphasic insulin aspart 30 contains 30% soluble insulin aspart fraction and 70% protamine-crystallized fraction of insulin aspart. Incorporation of insulin aspart into a premixed formulation should combine the advantages of the rapid-acting analogue with the advantage or a premixed formulation where the insulin aspart is rapidly absorbed while the protamine insulin aspart has a longer duration of action.[15]

The fast absorption of soluble insuln aspart in biphasic insulin aspart 30 have indication to improve postprandial glucose control as peak concentrations of insulin after subcutaneous injection of premixed insulin are similar to the desired endogenous serum insulin. This will allow the biphasic insulin aspart 30 to be administered immediately before meals rather than 30 minutes before meals.[15]

The product used in this study names for insulin aspart

(NovoRapid®), insulin detemir (Levemir®) and biphasic insulin aspart 30 (NovoMix® 30) are used throughout the text.

Materials and Methods

Study Design

This study was a prospective, multicenter, open label, non-controlled, observational study in patients with type 1 and type 2 diabetes in the Gulf countries (Saudi Arabia, Oman, Kuwait, United Arab Emirates, Qatar, and Bahrain). The aim of the study was to reflect the post-authorization experience with all three insulin analogue preparations in FlexPen® (NovoMix® 30, Levemir®, and/or NovoRapid®). No direct comparison was intended between NovoMix® 30, Levemir®, and/or NovoRapid® treatment groups. The study focused on safety parameters and changes in glycemic control when using these insulin analogues.

The study was conducted in accordance with the Declaration of Helsinki[16] and the Guidelines for Good Pharmacoepidemiology Practice.[17] Local regulations in regards to Ethics Committee, informed consent, health authority requirements were followed.

Data was collected from patients visiting specialist physicians who prescribed insulin. Data was collected at baseline and at approximately 12 weeks (interim visit) and again at approximately 24 weeks (final visit) after starting NovoMix® 30, Levemir®, and/or NovoRapid®. The study medication was prescribed by the physician as a result of clinical evaluation. The physician was to determine the starting dose and frequency, as well as later changes to either dose or frequency, if any. At all visits, the physician was to gather information from patients. In case of termination of Levmir®, NovoMix® 30, and/or NovoRapid® therapy it is according to the discretion of the physicians, based upon their clinical evaluation.

NovoMix® 30, Levemir®, and/or NovoRapid® were commercially available and were administered by subcutaneous injection. Dose alterations and frequency of dosing were made at the discretion of the physician. NovoMix® 30, Levemir®, and/or NovoRapid® were available as 3ml FlexPen® devices (100 U/ml, 5 FlexPen® devices/package). NovoFine® disposable needles were designed for use with the mentioned devices.

Patient Population

Any patient with type 1 to type 2 diabetes, who was treated with any diabetes treatment other than NovoMix® 30, Levemir®, and/or NovoRapid® was eligible for the study. The selection of the patients was done at the discretion of the individual physician. Particular attention was paid to drug interactions that were listed within the product label. Patients could withdraw at any time.

Patients with any of the following were not included in the study:

- Patients currently being treated with Levemir®, NovoMix® 30, and/or NovoRapid®
- Patients with hypersensitivity to Levemir®, NovoMix® 30, and/or NovoRapid® or to any of the excipients
- Women who are pregnant, breast-feeding or have the intention of becoming pregnant within the next 6 months
- Patients who were previously enrolled in the study

Sample Size and Statistical Analysis

The sample size was based on the primary objective to evaluate the incidence of major hypoglycemic events reported as severe adverse reactions and the change in glycemic control measured by HbA_{1c} after approximately 12 and 24 weeks of treatment compared to baseline. A sample size of 5,000 patients was to provide a probability of 95% of detecting major hypoglycemic events with the incidence of 75 in 100,000 patients with an estimated dropout rate of 20%.

Summary statistics (N, mean with standard deviation, median, minimum, and maximum) were presented for continuous variables. Discrete ordinal variables, e.g. number of hypoglycemic events were summarized in frequencies and percentages. Percentages were presented based on the number of responders with valid data. The numbers of non-responders were reported where applicable. Missing data was not replaced in general.

Paired t-test was used to assess the absolute and relative change in body weight at the final visit (week 24) from baseline, to assess the absolute and relative change in HbA1c at the final visit (week 24) from baseline by treatment group, and to compute and compare the absolute and relative changes in fasting blood sugar, postprandial blood sugar, and postprandial glucose increment. The change in the number of all, diurnal, nocturnal hypoglycemic and major hypoglycemic and major hypoglycemic episodes in the last 4 weeks before each visit was compared using the Wilcoxon signed Rank tests, if adequate number of such episodes were observed. The number of treatment emergent adverse events, adverse reactions, and severe adverse events were summarized by severity, relation, changes to products and outcome and also classified by System Order Class and Preferred Team according to the Medical Dictionary for Regulatory Activities (MedDRA).

The significance level for the two-sided statistical testing was set at 5%. No correction for multiplicity was used. Statistical programming and analyses of this study were performed using SAS® version 9.1 for Windows.

Treatment regimen

Patients were divided into the following groups for analysis:

- NovoRapid® insulin therapy (with/without oral-antidiabetic drugs)
- NovoMix® insulin therapy (with/without oral-antidiabetic drugs)
- Levemir® insulin therapy (with/without oral-antidiabetic drugs)
- NovoRapid®, NovoMix®, and/or Levemir® Combination therapy (with/without oral antidiabetic drugs)

- Other insulin therapy ('other' in combination with NovoRapid®, NovoMix®, and/or Levemir® therapy) (with/without oral antidiabetic drugs)
- All therapies

Efficacy Variables

Efficacy was assessed through the evaluation of the primary and secondary outcome variables including HbA_{1c}, fasting blood glucose (FBG), and postprandial blood glucose (PPBG).

The primary efficacy variable was the change in HbA_{1c} from baseline, while the secondary variables were the percentage of subjects achieving HbA_{1c} less than 7.0% after approximately 12 and 24 weeks compared to baseline, change in fasting blood sugar after approximately 12 and 24 weeks of treatment compared to baseline, and the change in postprandial blood sugar after approximately 12 and 24 weeks compared to baseline.

Primary and Secondary Safety Endpoints

The primary safety endpoint was the incidence of major hypoglycemic events reported during the 24 weeks of using the study medications. Major hypoglycemic events are defined as events with severe central nervous system symptoms consistent with hypoglycemia in which the subject was unable to treat himself/herself and has one of the following characteristics: blood glucose less than 3.1 mmol/L and reversal of symptoms was observed after either food intake or glucagon or intravenous glucose administration. Nocturnal hypoglycemic event was defined as individualized symptomatic events consistent with hypoglycemia, that occur while the participant is asleep, between bedtime after the evening insulin injection and before getting up in the morning (if relevant, before morning determination of fasting blood sugar and before morning injection).

The secondary safety endpoints were: change in body weight after approximately 12 and 24 weeks compared to baseline, change in number of hypoglycemic event n the last 4 weeks before routine visits at approximately 12 and 24 weeks compared to the last 4 weeks before baseline, change in the number of nocturnal hypoglycemic events in the past 4 weeks before routine visits at approximately 12 and 24 weeks compared to the last 4 weeks before baseline, and number of adverse drug reactions after 12 and 24 weeks of treatment.

Results

The data presented throughout the article represent the full analysis set/FAS, which is defined as all patients with a baseline visit and who used NovoMix® 30, Levemir® or NovoRapid® at least once (sum of total NovoMix® 30, Levemir®, and NovoRapid® dosage at baseline, interim and final visit is larger than 0U).

Patient characteristics

Patient flow chart and baseline characteristics are present in figure 1 and table 1, respectively. In total, more male patients (61.7%) were enrolled than female patients (38.3%). Patients were on average 47.1 (± 13.4) years old with a mean height of 1.66 (±0.11) m, mean body weight of 82.0 (± kg), mean body mass index of 29.7(±5.9) kg/m^2, and mean duration of diabetes of 9.8 (±5.9) years. The majority (84.9%) were diagnosed with type 2 diabetes mellitus.

In the Levemir® group, the mean daily dose of insulin at baseline was 24.4 U (0.26 U/kg) and increased to 32.4 U (0.36 U/kg) at the end of the treatment (week 24). In the NovoMix® 30 group, the mean daily dose of insulin at baseline was 49.3 U (0.31 U/kg) and increased to 58.6 U (0.36 U/kg) at the end of the treatment (week 24). In the NovoRapid® group, the mean daily dose of insulin at baseline was 38.5 U (0.23 U/kg) and decreased to 35.7 U (0.26 U/kg) at the end of the treatment (week 24). In the combination group, the mean daily dose of insulin at baseline was 53.5 U (0.23 U/kg) and increased to 70.5 U (0.26U/kg) at the end of the treatment (week 24). In the other group, the mean daily dose of insulin at baseline was 56.0 U (0.26 U/kg) and increased to 75.1 U (0.28 U/kg) at the end of the treatment (week 24).

As for the reasons for starting new therapy by the physicians, the major reason for starting a new therapy was to improve glycemic control (93.5%), followed by the aim to reduce blood glucose variability (34.8%) and change due to insulin pen (28.4%). Other reasons include: improve weight control (25.8%), patient dissatisfaction with current therapy (27.2%), reduce the risk of hypoglycemia (22.2%), try new insulin (26.0%), and unstable diabetes (23.3%).

Primary efficacy variable

The primary efficacy objective was the change in glycemic control measured by HbA_{1c} after approximately 12 and 24 weeks of treatment with NovoMix® 30, Levemir®, and/or NovoRapid® compared to baseline.

The changes of HbA_{1c} from baseline to week 24 by treatment group are presented in table 2 for patients in the full analysis set.

Secondary efficacy variables

The percentage of patients reaching the target HbA_{1c} (less than 7.0%) increased from 1.7% at baseline to 26.9% after 24 weeks of treatment. In the Levemir® group, the proportion of patients who achieved the target of HbA_{1c} less than 7.0% was increased from 1.0% at baseline to 27.1% after 24 weeks. As for the NovoMix® 30 group, the increase in the number of patients was from 1.6% at baseline to 24.4% after 24 weeks. The greatest increase was observed in the NovoRapid® group where such an increase was from 5.3% at baseline to 56.4% after 24 weeks of treatment. In the combination group, the proportion of patients who achieved the target HbA_{1c} levels was increased from 2.4% at baseline to 29.7% after 24 weeks. In the other group, the increase was from 2.5% at baseline to 13.2% after 24 weeks of treatment.

The values of fasting blood glucose by treatment group throughout the study period and the change from baseline to the end of the study (week 24) are presented in table 3 and figure 2 for the full analysis group.

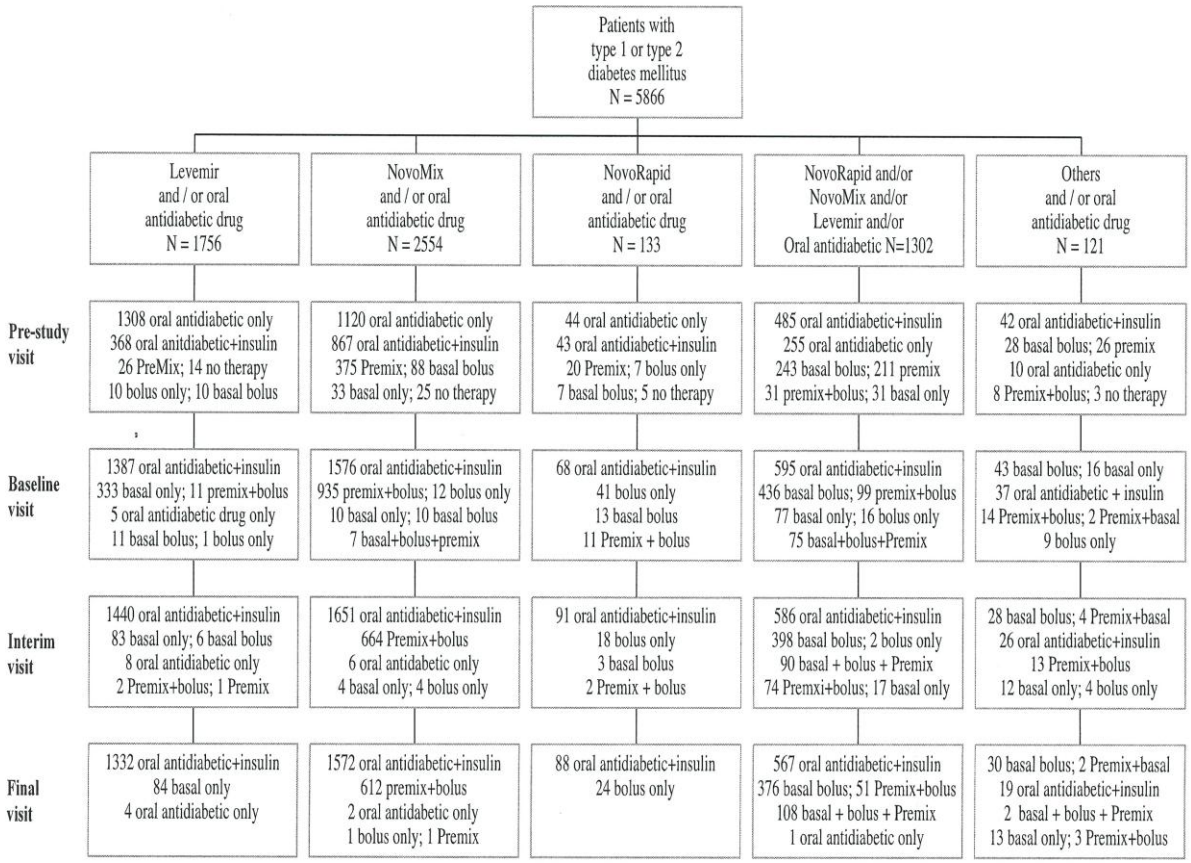

Figure 1: Patient flow chart of the patients selected from the Gulf countries

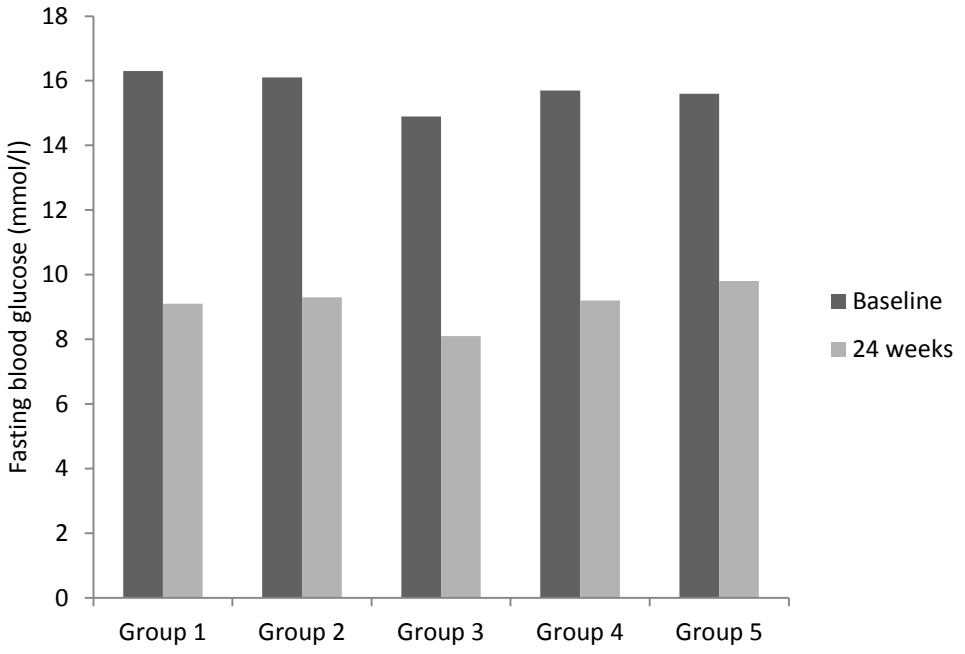

Figure 2: Change in fasting blood glucose from baseline to the end of the study

Table 1: Summary of Baseline characteristics

	Levemir +/- OAD	**NovoMix +/- OAD**	**NovoRapid +/- OAD**	**NovoRapid +/- NovoMix +/- Levemir +/- OAD**	**Others +/- OAD**	**Total**
Full Analysis Set	1756	2554	133	1302	121	5866
Gender, N (%)						
N	1744	2537	133	1296	121	5831
Male	1088 (62.4)	1639 (64.6)	66 (49.6)	744 (57.4)	59 (48.8)	3596 (61.7)
Female	656 (37.6)	898 (35.4)	67 (50.4)	552 (42.6)	62 (51.2)	2235 (38.3)
Age (years)						
N	1696	2458	129	1210	118	5611
Mean (SD)	49.8 (10.3)	48.2 (11.9)	46.4 (16.4)	42.2 (17.0)	38.0 (19.3)	47.1 (13.4)
Type of Diabetes Mellitus, N (%)						
N	1736	2531	129	1283	118	5797
Type 1	40 (2.3)	326 (12.9)	24 (18.6)	425 (33.1)	55 (46.6)	870 (15.0)
Type 2	1696 (97.7)	2204 (87.1)	105 (81.4)	856 (66.7)	62 (52.5)	4923 (84.9)
Height (m)						
N	1530	1969	122	1138	95	4854
Mean (SD)	1.67 (0.09)	1.67 (0.09)	1.63 (0.12)	1.64 (0.14)	1.58 (0.18)	1.66 (0.11)
Weight (kg)						
N	1533					
Mean (SD)	85.5 (16.9)	82.6 (17.0)	123	1150	99	4893
BMI (kg/m^2)						
N	1529	1969	122	1138	95	4853
Mean (SD)	30.7 (5.5)	29.7 (5.5)	29.2 (6.5)	28.6 (6.6)	26.3 (6.6)	29.7 (5.9)
Duration of diabetes (years)						
N	1707	2471	127	1264	120	5689
Mean (SD)	9.0 (5.4)	10.1 (5.9)	9.8 (5.7)	10.3 (6.4)	11.7 (7.4)	9.8 (5.9)

SD: standard Deviation; BMI: Body Mass Index; OAD: Oral antidiabetic Drugs; +/-: with/without

Table 2: Summary of change in HbA_{1c} from baseline to end of the study

	Group 1	**Group 2**	**Group 3**	**Group 4**	**Group 5**
Study Regimen	Levemir +/- OAD	NovoMix +/- OAD	NovoRapid +/- OAD	NovoRapid +/- NovoMix +/- Levemir +/- OAD	Others +/- OAD
Baseline HbA_{1c} (%)					
N	1620	2271	122	1215	105
Mean (SD)	9.7 (1.6)	9.9 (1.8)	9.1 (1.8)	9.7 (1.7)	9.8 (1.9)
24-week HbA1c (%)					
N	1325	1940	105	1063	67
Mean (SD)	7.3 (1.1)	7.5 (1.2)	6.6 (1.0)	7.5 (1.2)	8.0 (1.4)
Absolute change from baseline					
N	1264	1818	100	1008	59
Mean (SD)	-2.4 (1.6)	-2.3 (1.6)	-2.5 (1.6)	-2.3 (1.7)	-2.2 (1.9)
p-value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

The values of the postprandial blood glucose by treatment group throughout the study period and then change from baseline to week 24 (end of study) are summarized in table 4 and presented in figure 3. Mean bodyweight at baseline, at 24 weeks and change from baseline is presented in table 5 and figure 4.

Hypoglycaemia

In total, the proportion of patients who reported major hypoglycemic episodes decreased from 4.2% at baseline to 0.4% after 24 weeks of treatment. Major daytime episodes decreased from 3.3% at baseline to 0.3% after 24 weeks where major nocturnal episodes decreased from 2.3% at

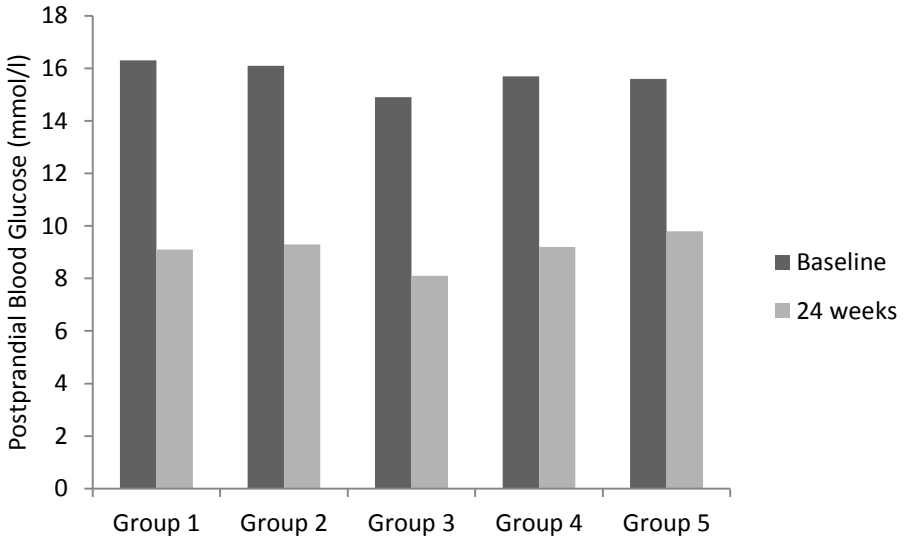

Figure 3: changes in postprandial blood glucose from baseline to the end of the study

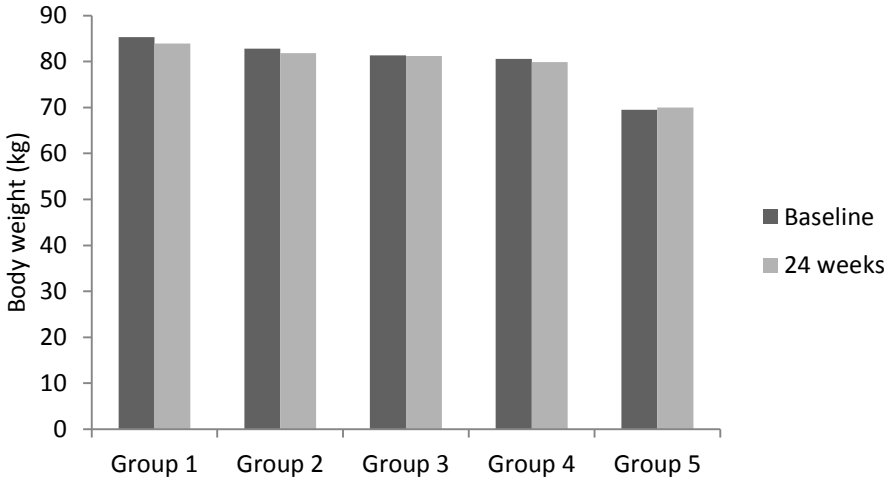

Figure 4: Changes in body weight from baseline to the end of the study

baseline to 0.2% after 24 weeks. After the 24 weeks of treatment, the percentage of major hypoglycemic events was similar in the other group and the combination group and was slightly higher than the rest of groups. According to the Wilcoxon Signed Rank test, the reduction observed in the overall and major nocturnal and daytime hypoglycemic episodes was considered to be highly significant ($p < 0.0001$).

The frequencies of hypoglycemic episodes were calculated as events per patient year. The rate of overall hypoglycemic episodes was reduced from 5.7 episodes per patient year at baseline to 1.6 episodes per patient year after 24 weeks of treatment. The same pattern was observed for daytime hypoglycemic episodes (from 3.9 episodes per patient year at baseline to 1.2 episodes per patient year at week 24) and for nocturnal hypoglycemic episodes (from 1.8 episodes per patient year at baseline to 0.4 episodes per patient year at week 24). A similar reduction was observed for the rate of major hypoglycemic episodes. In total, the rate of major hypoglycemic episodes was reduced from 1.1 episodes per patient year at baseline to 0.1 episodes per patient year at week 24. The same pattern was observed for daytime hypoglycemic episodes (from 0.6 episodes per patient year at baseline to 0.1 episode per patient year at week 24) and for nocturnal hypoglycemic episodes (from 0.4 episodes per patient year at baseline to 0.0 episodes per patient year at week 24).

Adverse Drug Reactions

The severe adverse reactions occurred in the combination group (0.46%) and the other group (2.48%). No severe adverse reactions were reported in the Levemir® group, NovoMix® 30 group and NovoRapid® group. In order to deal with the severe adverse reactions, some patients adjusted the insulin dose. All patients recovered. One death occurred after the study period due to myocardial infarction after the patient was treated with the Levemir® for diabetes.

Table 3: Summary of change in fasting blood glucose (FBG) from baseline to end of the study

Study Regimen	Group 1 Levemir +/- OAD	Group 2 NovoMix +/- OAD	Group 3 NovoRapid +/- OAD	Group 4 NovoRapid +/- NovoMix +/- Levemir +/- OAD	Group 5 Others +/- OAD
Baseline FBG (mmol/l)					
N	1589	2265	116	1130	98
Mean (SD)	11.5 (3.0)	11.5 (3.4)	11.3 (3.6)	10.9 (3.4)	10.5 (3.5)
24-week FBG (mmol/l)					
N	1339	2000	107	994	58
Mean (SD)	6.7 (1.6)	6.9 (1.9)	6.3 (1.2)	6.8 (1.7)	6.7 (1.7)
Absolute change from baseline					
N	1256	1878	102	936	48
Mean (SD)	-4.7 (2.8)	-4.6 (3.3)	-5.1 (3.0)	-4.3 (3.2)	-4.0 (3.3)
p-value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Table 4: Summary of change in postprandial blood glucose (PPBG) from baseline to end of the study

Study Regimen	Group 1 Levemir +/- OAD	Group 2 NovoMix +/- OAD	Group 3 NovoRapid +/- OAD	Group 4 NovoRapid +/- NovoMix +/- Levemir +/- OAD	Group 5 Others +/- OAD
Baseline PPBG (mmol/l)					
N	1394	1926	105	1021	93
Mean (SD)	16.3 (4.3)	16.1 (4.5)	14.9 (4.9)	15.7 (4.6)	15.6 (4.8)
24-week PPBG (mmol/l)					
N	1126	1655	91	909	53
Mean (SD)	9.1 (2.1)	9.3 (2.5)	8.1 (2.4)	9.2 (2.6)	9.8 (3.6)
Absolute change from baseline					
N	1027	1441	88	797	45
Mean (SD)	-6.9 (4.1)	-6.8 (4.7)	-7.0 (4.8)	-6.6 (4.6)	-6.3 (5.0)
p-value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Table 5: Summary of change in bodyweight (kg) from baseline to end of the study

Study Regimen	Group 1 Levemir +/- OAD	Group 2 NovoMix +/- OAD	Group 3 NovoRapid +/- OAD	Group 4 NovoRapid +/- NovoMix +/- Levemir +/- OAD	Group 5 Others +/- OAD
Baseline bodyweight (kg)					
N	1235	1814	105	959	60
Mean (SD)	85.3 (15.8)	82.8 (17.0)	81.3 (21.8)	80.6 (21.6)	69.5 (28.4)
24-week bodyweight (kg)					
N	1235	1814	105	959	60
Mean (SD)	83.9 (14.7)	81.8 (15.6)	81.2 (19.4)	79.9 (20.1)	70.0 (26.8)
Absolute change from baseline					
N	1235	1814	105	959	60
Mean (SD)	-1.3 (4.7)	-0.9 (4.8)	-0.1 (4.9)	-0.7 (4.0)	0.5 (5.3)
Median	-0.7	0.0	0.0	0.0	0.5
Min ; Max	-20.0; 19.0	-20.0; 20.0	-18.0; 14.0	-20.0; 19.1	-19.8; 17.2
p-value	<0.0001	<0.0001	0.8156	<0.0001	0.4423
Relative change from baseline					
N	1235	1814	105	959	60
Mean (SD)	-1.2 (5.4)	-0.6 (6.3)	1.2 (7.9)	-0.2 (5.4)	3.2 (12.4)
p-value	<0.0001	<0.0001	0.1185	0.3529	0.0487

Discussion

In this study, it was observed that there was a significant reduction (p-value < 0.0001) in HbA_{1c} in all treatment groups after 24 weeks irrespective of the previous insulin regimen. The reduction in HbA_{1c} (about 2%) was similar in all treatment groups. The observed reductions in fasting blood glucose and postprandial blood glucose after 24 weeks of treatment were considered highly significant and were similar in all treatment groups. In total, fasting blood glucose was reduced by 4.5 mmol/l after 24 weeks of treatment from 11.3 mmol/l at baseline to 6.8 mmol/l after 24 weeks. In total, postprandial blood glucose was reduced by 6.8 mmol/l after 24 weeks of treatment from 16.1 mmol/l at baseline to 9.1 mmol/l at the end of the study (week 24).

Body weight was reduced in all groups except the Others group as other insulin products apart from the insulin analogues were used in that group In which a mean of 0.5 kg weight increase from baseline by the end of the study. The change in body weight after 24 weeks of treatment was 1.3 kg in the Levemir® group, 0.9 kg in the NovoMix® 30 group, 0.1 kg in the NovoRapid® group, 0.7kg in the combination group and 0.5 kg in the other group. The most significant weight reductions occurred in the Levemir® and NovoMix® 30 groups.

Insulin doses continued to be increased during the study, accompanied by reduced HbA_{1c} levels and modest weight loss. This suggests that further optimization of insulin would be possible and could lead to further improvement in glycemic control.

The benefits of insulin in type 1 and type 2 diabetes mellitus are well established. The risk of developing hypoglycemia and the risk of weight gain pose major limitations to traditional insulin products.[9] Hypoglycemia increases the risk of accident, coma, or death and remains a major physiological obstacle to aggressive tight glycemic control. Moreover, the risk of severe hypoglycemia increases with traditional insulin products as the monthly HbA1c values declines[(1)]. Due to these drawbacks, the patient may be unwilling to titrate and intensify insulin therapy thus the glycemic control achieved is limited.[9] The risk of hypoglycemia that often occurs with human insulin can be a limiting factor in the pursuit of intensive glycemic control in diabetes and increased weight is a problematic issue during insulin therapy. The results from this study confirm that the treatment with Levemir®, NovoMix® 30 and/or NovoRapid® insulin lead to an improvement of glycemic control as reflected by the decreased levels of HbA_{1c}, fasting blood glucose, and postprandial blood glucose and the higher proportion of patients attaining the target value of HbA_{1c} with a low risk of hypglycemia and modest weight control.

The impact of insulin therapy on the quality of life is an important factor to consider. Parameters that may deteriorate quality of life include the patient's concerns about needles, frequent injections, severe hypoglycemia, and weight gain. On the other hand, improved glycemic control itself enhances the patient's state of mind and improves all aspects of everyday activities, therefore motivating treatment compliance.[19]

Limitations

As any observation study, the major limitation in this study were the design which is non controlled study that doesn't allow any control over their prescribing habits of the physician. On the other hand as any observational study, this design is giving a clear view and reflection for the routine clinical practice of physicians.

In routine clinical practice in Gulf countries, treatment with Levemir®, NovoMix® 30, and/or NovoRapid® was considered as safe as the proportion of patients who reported major and total hypoglycaemic episodes decreased throughout the study. Improvement in the glycaemic control included a significant reduction in HbA_{1c}, fasting blood glucose, and postprandial blood glucose along with a modest weight loss.

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References

1. Hartman I. Insulin analogues. Impact on Treatment Success Satisfaction, Quality of Life, and Adherence. Clin Med Res 2008; 6: 54-67.
2. Reynolds NA, Wagstaf AJ. Insulin Aspart A Review of its Use in the Management of Type 1 or 2 Diabetes Mellitus. Drugs 2004; 64: 1957-1974.
3. Alwakeel JS, Sulimani R, Al-Asaad H, Harbi A, Tarif N, Al-Suwaida A, Al-Mohaya S, Isnani AC, Alam A, Hammad D. Diabetes Complications in 1952 type 2 diabetes mellitus patients managed in a single institution. Ann Saudi Med 2008; 28: 260-266.
4. Al-Nozha M, Al-Maatouq MA, Al-Mazrou Y, Al-Harthi S, Arafah MR, Khalil MZ, Khan NB, Al-Khadra A, Al-Marzouki K, Nouh MS, Abdullah M, Attas O, Al-Shahid MS, Al-Mobeireek A. Diabetes Mellitus in Saudi Arabia. Saudi Med J 2004; 25: 1603-1610.
5. Soliman AT, Al-Salmi IS, Asfour MG. Epidemiology of childhood insulin-dependent diabetes mellitus in the Sultanate of Oman. Diabet Med 1996; 13: 582 -586.
6. Raslova K. An Update on the treatment of type 1 and type 2 diabetes mellitus: focus on insulin detemir, a long acting human insulin analogue. Vasc Health Risk Manag 2010; 6: 399- 410.
7. Soran H, Younis N. Insulin detemir: a new basal insulin analogue. Diabetes Obes Metab 2006; 8: 26- 30.
8. Shah S, Benroubi M, Borzi V, Gumprecht J, Kawamori R, Shaban J, Shestakova M, Weying Y, Valensi P. Safety and effectiveness of biphasic insulin aspart

30/70 (NovoMix® 30) when switching from human premix insulin in patients with type 2 diabetes: subgroup analysis from the 6-month IMPROVE™ observational study. Int J Clin Pract 2009; 63: 574-582.

9. Hermansen K, Dornhorst A, Sreenan S. Observational, open label study of type 1 and type 2 diabetes patients switching from human insulin to insulin analogue basal-bolus regimen: insights form the PREDICTIVE study. Curr Med Res Opin 2009; 25: 2601 -2608.
10. Halmi S, Raskin P, Liebl A, Kawamori R, Fulcher G, Yan G. Efficacy of Biphasic Insulin Aspart in Patients with Type 2 Diabetes. Clin Therap 2005; 27 Suppl. B: S57- 74.
11. Chapman TM, Noble S, Goa KL. Spotlight on Insulin Aspart in Type 1 and 2 Diabetes Mellitus. Treat Endocrinol 2003; 2: 71- 76.
12. Home PD, Lindholm A, Riist A. Insulin aspart vs. human insulin in the management of long-term blood glucose control in type 1 diabetes mellitus: a randomized controlled trial. Diabet Med 2000; 17: 762 -771.
13. 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: 4534-4539.
14. Vague P, Selam J, Keie S, Deleeuw I., Elte JWF, Haahr H, Kristensen A, Draeger E. Insulin Detemir is Associated with more predictable glycemic control and reduced risk of hypoglycemia than NPH insulin in patients with type 1 diabetes on a basal-bolus with premeal insulin aspart. Diabetes Care 2003; 26: 590-596.
15. Jacobsen LV, Sogaard B, Riis A. Pharmacokinetics and pharmacodynamics of a premixed formulation of soluble and protamine – retarded insulin aspart. Eur J Clin Pharmacol 2000; 56: 399- 403.
16. World Medical Association. Declaration of Helsinki. Ethical Principles for Medical Research involving Human Subjects. 52nd WMA General Assembly, Edinburgh, Scotland, October 2000. Last amended with Note of Clarification on Paragraph 29 by the WMA General Assembly, Washington 2002, and Note of Clarification on Paragraph 30 by the WMA General Assembly, Tokoyo 2004.
17. International Conference on Harmonization. ICH Harmonized Tripartite Guideline. Good Clinical Practice. 01-May-1996.
18. Davidson J, Vexiau P, Cucinotta D. Vaz J, Kawamori R. Biphasic Insulin Aspart 30: Literature Review of Adverse Events Associated with Treatment. Clin Ther 2005; 27 Suppl. B: S75- S88.
19. Valla V. Therapeutics of Diabetes Mellitus: Focus on Insulin Analogues and Insulin Pumps. Exp Diabetes Res 2010; 178372