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Research Article

Effectiveness of Insulin Degludec/Insulin Aspart (Ryzodeg®) in Comparison with Insulin Aspart/Aspart Protamine (Novomix®) in Adult Patients with Type 2 Diabetes Mellitus in a Tertiary Care Hospital

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Abstract

Our study compares the use of ARNI plus Carvedilol or ARNI plus Bisoprolol in real-world settings to assess suboptimal ARNI use due to hypotension.

Abbreviations: DM: Diabetes Mellitus; BG: Blood Glucose; T2DM: Type 2 Diabetes Mellitus; FPG: Fasting Plasma Glucose; SGLT-2: Sodium-Glucose Cotransporter-2; GLP-1RAs: Glucagon-Like Peptide-1 Receptor Agonists; HbA1C: Glycated Hemoglobin; IDegAsp: Insulin Degludec/Insulin Aspart; BIAsp: Biphasic Insulin Aspart; IDeg: Insulin Degludec; IAsp: Insulin Aspart; BIAs: Biphasic Insulin Aspart; PK: Pharmacokinetic; PD: Pharmacodynamic; BMI: Body Mass Index; WHO: World Health Organization; IDF: International Diabetes Federation; SFH: Security Forces Hospital; MRN: Medical Record Number; NCBE: National Committee of Bio Ethics

Introduction

Diabetes Mellitus (DM) is a metabolic disorder characterized by an increase in Blood Glucose (BG) associated with carbohydrate, fat, and protein abnormal metabolism, results in impaired secretion of insulin or insulin resistance and can be both [1,2]. The patients with DM are classified into two broad categories: type 1 DM and type 2 DM [3]. Type 1 DM, formerly known as insulin dependent diabetes, affects 5% to 10% of cases and is typically caused by an autoimmune attack on pancreatic β-cells, which leading to absolute insulin deficiency [4]. It is commonly present in children and adolescents, but it can occur at any age [5]. The condition initiated when a genetically individual is exposed to an unknown environmental trigger [5]. Saudi Arabia is among the top ten countries with the highest incidence rates of type 1 DM in children [6]. A new diagnosis of type 1 DM has an incidence rate of 33.5 cases per 100,000 population per year [7]. It is estimated 35,000 children with type 1 DM in Saudi Arabia with 3900 new cases per year [6,7].

Type 2 DM accounts for 90% to 95% of cases as a result of β-cell dysfunction characterized by increasing deficiency in insulin secretion and insulin resistance [2]. Most individuals with type 2 DM are overweight or obese, and abdominal adiposity is a major contributor to insulin resistance [8]. Saudi Arabia is among the top ten countries with the highest prevalence of type 2 DM [6]. According to the World Health Organization (WHO), Saudi Arabia reported as a second highest rate of diabetes in the Middle East and is seventh in the world, approximately seven million of the population diagnosed with diabetes and almost around three million have pre-diabetes [6,9]. According to International Diabetes Federation (IDF) Atlas, the worldwide prevalence of DM in adults (20-79 years) was 8.8% (7.2-11.3%) in 2017, the number of people with DM worldwide in 2017 was 425 million [6].

Most patients who develop type 2 DM is characterized by multiple defects including; (1) impaired insulin secretion is β-cell mass and function are both reduced, and β-cell failure is progressive; (2) deficiency and resistance to incretin hormones in patients with type 2 DM; (3) insulin resistance is manifested by decreased skeletal muscle uptake of glucose, and increased lipolysis and free fatty acid production; (4) excess glucagon secretion; (5) increased hepatic glucose production; (6) Sodium-Glucose Cotransporter-2 (SGLT-2) upregulation in the kidney; (7) systemic inflammation; and (8) diminished satiety [10].

Moreover, in some cases of type 2 diabetes patients, as the disease progresses, the pancreatic β-cell's capacity to secrete insulin declines, and the patients required insulin administration [2]. Type 2 diabetes is treated using a stepwise approach, starting with lifestyle management, and progressing to oral anti-diabetic treatments and injectable Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RAs) or insulin, to prevent microvascular and macrovascular tissue damage caused by chronic hyperglycemia [11]. Insulin therapy is required for patients with

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T2DM who are unable to achieve glycemic control with oral anti-diabetic medications, the next treatment options include adding prandial insulin to basal insulin (basal - bolus insulin regimen) [7,12].

Basal insulin products are utilized for the remaining endogenous insulin secretion throughout the day and improve Fasting Plasma Glucose (FPG), whereas bolus insulins are used to meet prandial insulin needs and limit postprandial hyperglycemia [10,13]. Basal-bolus regimens, in which basal and bolus insulins are injected separated or in combination can be used the premixed insulins, which contain a protaminated, and non protaminated insulin in a single injection [10].

Premixed insulin comprises both basal and bolus components, provides stable FPG and postprandial glycemic control, and is alternative to classical basal–bolus therapy as fewer daily injections are required [14]. The biphasic insulin aspart (BIAsp; NovoMix®), containing 30% soluble insulin aspart and 70% protamine-crystallized insulin aspart, one of the most used premixed insulins [15]. Premixed insulin formulations have some limitations, including the need for adequate resuspension for accurate dosing, the fact protaminated insulins still have a shorter duration and higher glycemic variability than basal insulin analogues [16]. When compared to rapid-acting insulins, this results in prolonged and excessive peak glucose-lowering since the two components absorption kinetics are not clear [16]. In recent years, fixed-ratio co-formulation products have been created in response to the aforementioned limitations [17]. These are composed of two antihyperglycemic medicines that maintain their unique Pharmacokinetics (PK) and Pharmacodynamic (PD) properties despite being delivered as a co-formulation, these can provide a comparatively simple insulin regimen with fewer injections and more dosage timing flexibility than basal-plus/basal-bolus therapy [17]. Available fixed-ratio co- formulations include insulin degludec/insulin aspart (IDegAsp) [18].

The degludec is assembling dihexamers into a very stable structure, held together by side chain zinc contacts [19]. In the injectable depot, there is probably little or no association between degludec monomers and monomers of the co-formulated insulin aspart (IAsp) at high zinc concentrations [19,20]. Since the resulting soluble product has a better PK profile than conventional premixed insulins due to the degludec component, there are flat and prolonged stable levels of basal insulin levels and a clear separation of the bolus component, thus there is no observed 'shoulder effect' with insulin degludec/insulin aspart (IDegAsp) [19].

IDegAsp (Ryzodeg®) is the first co-formulation of ultra-long-acting basal (70%, insulin degludec) and rapid-acting bolus (30%, insulin aspart) providing basal and prandial insulin cover when administered, unlike Biphasic Insulin aspart (BIAsp) 30/70 (NovoMix®) [18,21]. The Ryzodeg compared with NovoMix component produces a flat and stable glucose lowering action profile that exceeds 24 hours, enabling a flexible injection schedule [22]. Insulin degludec with insulin aspart, provides postprandial control of glycemia, this co-formulation therapy is delivered in a single injection [23], and is therefore expected to improve adherence to treatment while providing long-term, stable glycemic control with fewer hypoglycemic episodes than traditional premixed insulins [24,25].

Considering the characteristics of IDegAsp, it can be expected to be more effective than other basal-bolus insulins for blood glucose control [26]. However, a study conducted in China by Wenying and his colleagues to evaluate efficacy and safety of insulin degludec/insulin aspart versus biphasic insulin aspart in Chinese adults with type 2 diabetes [27]. This study has demonstrated non-inferiority in terms of change from baseline to week 26 in HbA1c, on the other hand IDegAsp twice daily was superior when compared to BIAsp twice daily for a change in FPG, with the hypoglycemic episodes was demonstrated [28]. Patients on IDegAsp twice daily were more likely to achieve the HbA1c goal of <53 mmol/mol (<7.0%) compared to patients on BIAsp twice daily, participants (7.0%) without hypoglycemia [28]. Another study meta-analysis was done by Shinje Moon et al. in 2021 to evaluate the efficacy and safety of insulin Degludec/Insulin Aspart basal insulin or premixed insulin. [27] The aim of this meta-analysis was to compare the safety and efficacy of IDegAsp with the usual premixed insulin, such as biphasic insulin aspart 30 (BiAsp30), or basal insulin, such as insulin glargine or insulin degludec. They found that both once-daily and twice-daily IDegAsp regimens improved glycemic control when compared to twice-daily premixed insulin when compared to other insulin regimens [27].

Therefore, we preliminarily investigated 451 adults with type 2 diabetes who had switched to insulin degludec/insulin aspart (Ryzodeg®) from insulin aspart/insulin aspart crystallized protamine (NovoMix®) from 2017 to 2022. This study was performed to evaluate the long-term efficacy of insulin degludec/insulin aspart (Ryzodeg®) compared to insulin aspart/insulin aspart crystallized protamine (NovoMix®) BIAsp in adults with type 2 diabetes mellitus.

In conclusion, our aim is to compare the efficacy of IDegAsp (Ryzodeg®) co-formulation with biphasic insulin aspart (BIAsp) 30/70 (NovoMix®). To evaluate the benefits of the IDegAsp regimen, we analyzed the FPG and HbA1c levels and investigated potential areas for improvement in patient outcomes, increasing the awareness of clinicians and pharmacists of the importance of adherent to the guidelines.

Methods

Study Design and Setting

This is a retrospective cohort observational study, which was conducted in a tertiary care military hospital, Security Forces Hospital (SFH) in Riyadh, Saudi Arabia. The data were confined between 2017 to 2022 for patients that were treated with Novomix and then switched to Ryzodeg.

Participants

Patients who were eligible to be recruited were those with type two Diabetes Mellitus who had been treated with Novomix before switching to Ryzodeg, the patients were adults with age older than 18 years. The patients had to be diagnosed with type two Diabetes Meletus for ≥1 year before enrollment, patients who were switched to Ryzodeg need at least 3 months before enrollment with or without metformin or another type of anti-diabetic agents.

The excluded patients were those with type 1 diabetes mellitus, patients who were not on Novomix and then switching to Ryzod.

Data Collection

The data was collected using an electronic health record of the hospital system, the Medical Record Number (MRN) of many patients with diabetes were provided to the research

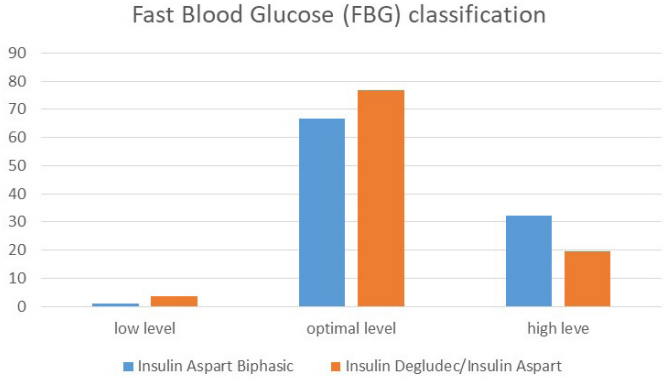

Figure 1:

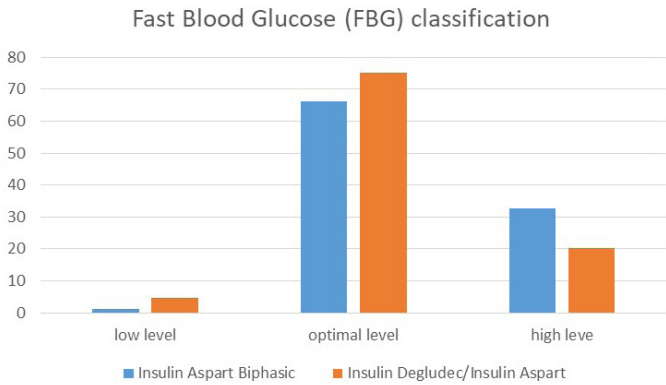

Figure 2: FBG for similar medication and dose.

group through excel sheets, and 1858 patients were scanned to check if they fit the criteria, according to the inclusion criteria participants who were included in the trial were a total of 448 patients that were included. 178 of those patients were having the similar medication and the similar dose. The statistical analyses have been done for both group (448, and 178 patients).

Statistical Analysis

Our primary objective in this study is to compare (Ryzodeg®) with (NovoMix®) in terms of efficacy for long term use, by comparing and analyzing the effect of the different insulin formulations on HbA1c and fasting blood glucose in patients who had been using Novomix and then switched to Ryzodeg. Data were statistically analyzed using descriptive analysis and one sample T-test for quantitative data and Q Squared for qualitative data. The SPSS program for data analysis was version 28.

Ethical Statement

The study protocol was reviewed and approved by the research committee in Security Forces Hospital, which is constituted and functions in accordance with the National Committee of Bio Ethics (NCBE) in Saudi Arabia, accreditation number (H-01-R-069). The confidentiality of patients was maintained by coding them with numbers and using their file number as an identifier.

Results

In our study, the number of patients included was 448 patients. The demographic details of patients are presented in (Table 1). The results showed that 53% of the patients were female. The mean age of our sample was 65.61 years with mean Body Mass Index (BMI) of 32.28.

The study showed a significant difference between Insulin Aspart Biphasic and Insulin Degludec/Insulin Aspart that the HbA1C was 8.6 (SD+1.69) for Aspart Biphasic and post switching, 8.09 (SD+1.4) with significant P value of <0.0001 (Table 2).

Also the mean of Fast Blood Glucose (FBG) with patient on Insulin Degludec/Insulin Aspart is lower than Insulin Aspart Biphasic (8.49±3.65 vs 9.4±3.85) with p value <0.0001 (Table 2).

Table 1: Baseline Characteristics for all patients.

Demographic	
Total number	448
Age — yr. Mean+SD	65.61±11.132
Gender	
Female	239(53.3)
Male	209(46.7)
BMI (kg/m^2) Mean+SD	32.28±6.09

Table 2: Compare HbA1c and glucose fasting between 2 groups for all patients.

	Insulin Aspart Biphasic	Insulin Degludec/Insulin Aspart	P value
HbA1c %	8.6±1.7	8.09±1.5	<0.0001
Fast Blood Glucose (FBG)	9.4±3.85	8.49±3.65	<0.0001
Fast Blood Glucose (FBG) classification	low glucose: 5(1.1) optimal level: 299(66.7) high level: 144(32.2)	low glucose: 16(3.6) optimal level: 344(76.8) high level: 88(19.6)	0.000362

Fast Blood Glucose (FBG) has been classified into 3 categories which were high, optimal, and low FBG. Low blood sugar: 4mmol/L or lower, optimal blood sugar >4mmol/l and <11.1mmol/L, high blood sugar: >11.1mmol/l. The classification of FBG have been found significant different between the 2 groups. The optimal FBG with patient on Insulin Degludec/ Aspart higher than patient on Aspart Biphasic (75%vs 65%). Also, the percentage of high FBG for patients on Insulin Degludec/ Insulin Aspart lower than those on insulin Aspart Biphasic (19% vs 32%) (Table 2) (Figure 1).

The total number among the patients who were using similar medications and similar dose were 178. 51% of them were male. The average age is 65 year. The mean of BMI is 32kg/m^2.

The level of HbA1C before switching (insulin Aspart Biphasic) among the patients who were using similar medications and similar dose before and after switching, was 8.6%. While HbA1C changed to 8.2% after switching (Insulin Degludec/ Aspart) with P value of <0.0001. Also, FBG level have been changed from 10 with insulin Aspart Biphasic to 8.1 with Insulin Degludec/Insulin Aspart (p value <0.0001). Finally, it has been found the level of FBG were more optimal with Insulin Degludec/Insulin Aspart 75% while the level of FBG was 65% with insulin Aspart Biphasic. On the other hand, patients who were uncontrolled blood glucose were more with insulin Aspart Biphasic than those with Insulin Degludec/Insulin Aspart (32% vs 20%) (Table 4) (Figure 2).

Table 3: Baseline Characteristics for similar dose and medications.

Demographic	
Total number	178
Age — yr. Mean+SD	65.3±10.67
Gender	
Male	92(51.7)
Female	86(48.3)
BMI (kg/m^2) Mean + SD	32.1±6.2

Table 4: Compare HbA1c and glucose fasting between 2 similar dose and medications.

	Insulin Aspart Biphasic	Insulin Degludec/ Insulin Aspart	P value
HbA1c %	8.62±1.708	8.093±1.56	<0.0001
Fast Blood Glucose (FBG)	10.038±3.659	8.14±3.32	<0.0001
Fast Blood Glucose (FBG) classification	low glucose: 2(1.1) optimal level: 118(66.3) high level: 58(32.6)	low glucose: 8(4.5) optimal level: 134(75.3) high level: 36(20.2)	0.000075

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