Diabetes Mellitus and Glucose Metabolism

CLINICAL TRIALS IN DIABETES AND METABOLIC DISEASE

Improving Glycemic Control of Diabetic Patients in an Outpatient Practice

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Diabetes Mellitus (DM) is a devastating condition with premature mortality, poor quality of life, & vast economic cost contributing to substantial societal burden. More resources are allocated to DM than any other condition, & with an estimated worldwide prevalence of 350 million people by 2025, it remains an urgent epidemic. Providing standardized, high quality care (HQC) to improve DM control is a matter of utmost importance. Our residents receive primary care training in a federal funded healthcare system, with yearly reports from Medicare addressing compliance with current accepted standards, including but not limited to DM management. In this Quality Improvement (QI) project, we sought to directly address deficiencies in their management.

A retrospective chart review was conducted over 1 year. Patients with uncontrolled (UC) DM were identified & a root cause analysis conducted. It was noted that over 40% of diabetics were UC, with a hemoglobin A1c (HbA1c) >8%; 60% of whom did not have appropriate escalation of management (AEOM) in further encounters. A QI intervention was developed aiming to improve AEOM in patients. Plan-Do-Study-Act cycles focused on the creation of a standardized documentation system (SDS) for UC DM encounters, a tracking system & a designated "DM manager", who ensured electronic prescription delivery & early follow-up (F/U) appointments. Clear metrics of AEOM were established & clinicians underwent small group educational sessions emphasizing each intervention, with review of updated ADA guidelines. Although prospective biweekly chart review is ongoing, Fisher's exact test was used for statistical analysis of initial post interventional data.

A total of 33 UC DM patient encounters were analyzed thus far. In January 2020, 31% of all encounters used the newly created SDS; of which 69% had AEOM. In February 2020, 57% of all encounters used the SDS; 71% of providers had AEOM. Of the encounters using the SDS, 83% had AEOM compared to 67% in those without (p:0.42). Average F/U time per patient was 6 weeks.

Delivering standardized & HQC in DM patients presents a challenge dependent on a variety of system & patient factors. This becomes more apparent in rural & low-income populations as in our clinic. Although HbA1c is a well-established method of monitoring glycemic control, we propose that other uniform performance measures be used to dynamically assess overall DM management. Our metrics include standardized, replicable documentation, early F/U time & defined AEOM parameters such as timely addition of new medication, dose adjustments, & utilization of resources such as DM educators. Thus far, there appears to be a non-statistically significant trend towards improved standardization of provider documentation, F/U visits & AEOM. Further data is needed. We hope to see these measures translate into overall improved glycemic control.

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Long-Term Effectiveness and Safety of Once Weekly Dulaglutide as Add-on to Metformin or Metformin Plus Insulin Secretagogues in Obesity and Type 2 Diabetes

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Aim of this monocentric retrospective observational study was to evaluate the 18-month effectiveness and safety of once weekly 1.5 mg GLP-1 receptor agonist (GLP-1 RA) dulaglutide (DU) as add-on to metformin (MET) or MET plus conventional insulin secretagogues (SFU/glinide) in a study cohort with excess body weight (BW) and type 2 diabetes (T2D). Comparative efficacy versus once daily 1.2/1.8 mg liraglutide (LIRA) in a study sample naïve to GLP-1 RAs, matching for age, gender, BMI, T2D duration, cardiovascular comorbidities and medications, was addressed as a secondary aim. Clinical and biochemical data for efficacy outcomes and information on drug discontinuation due to adverse events (AEs) were collected from digital records. Initial analysis included 126 overweight and obese T2D patients (48.4% females). Out of these, 13 discontinued DU due to moderate-severe gastrointestinal AEs after a median follow-up of 6 (3 to 8) months, while 65 completed 18 months of continuous therapy. At 6 months, there was a significant median HbA1c reduction of -0.9 (-1.50 to -0.20) % with respect to baseline values (p<0.001), which remained stable during 18 months of follow-up. These results were accompanied by a moderate BW loss sustained over time, with a median reduction of -1.16 (-4,29 to 0.45) % at 6 months and -1.47 (-4.2 to 0.72) % at 18 months (p=0.048). At univariate Spearman analysis, a negative correlation between baseline BMI and risk of drug discontinuation due to gastrointestinal AEs was observed. The protective effect of obesity (BMI ≥ 30kg/m^2) against drug discontinuation was confirmed by an exploratory logistic regression analysis, while adjusting for confounders [OR 0.211 (95%CI 0.058–0.771), p=0.019]. Neither gender, nor age, nor T2D duration, nor concomitant SUF/glinide use, nor shifting to DU from other GLP-1 RAs influenced its long-term effectiveness. However, higher baseline HbA1c values emerged as predictors of clinically relevant efficacy outcomes, either in form of HbA1c reduction ≥ 0.5% [OR 2.961 (95%CI 1.394–6.290), p=0.005] or BW loss ≥ 5% [OR 2.571 (95%CI 1.171–5.644), p=0.019]. The efficacy outcomes were corroborated by head-to-head comparison with LIRA, a GLP-1 RA with durable beneficial effects on glycemic control and BW in real word scenarios (1). With the advantage of once weekly administration, at 18-month follow-up, a significant larger fraction of patients on DU therapy reached glycemic targets (HbA1c ≤ 7.0%) when compared to those on

LIRA: from 14.8% at baseline (both groups) to 64.8% with DU and 42.6% with LIRA (p=0.033). Although limited by a retrospective design and lack of constant up-titration for LIRA to the highest dose, these findings indicate that the beneficial glycometabolic responses to DU on a background of MET or MET plus SFU/glinide are durable, especially in presence of obesity and greater HbA1c impairment.
(1) **Ref**: Mirabelli et al. IJERPH. 2019;17(1):207.

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Real-World Safety and Effectiveness of iGlarLixi in People With Type 2 Diabetes who Fast During Ramadan: Results From Wave 1 of the SOLIRAM Study

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Background: People with type 2 diabetes (T2D) are at an increased risk of severe hypoglycaemia when fasting. SOLIRAM is an international, prospective, observational study evaluating the safety and effectiveness of the fixed-ratio combination (FRC) of insulin glargine 100 U/mL and lixisenatide (iGlarLixi) in people with T2D who fast during Ramadan. **Methods:** SOLIRAM will be performed in two waves. Here, we present the interim results, using descriptive statistics, from participants who fasted during Ramadan in 2020 (Wave 1). Adults with T2D who had taken iGlarLixi for ≥3 months before inclusion and who planned to fast for ≥15 days during Ramadan, were enrolled from 5 countries. During the study, iGlarLixi treatment was adjusted as per routine practice by the treating physician. **Results:** Overall, 155 people with T2D (54.2% male) were eligible. Mean±SD age was 58.4±9.5 years, body mass index was 30.5±6.0 kg/m² and 64.5% of people had ≥1 diabetes-related complications. Proportion of patients with ≥1 macro- and microvascular complications were 11.0% and 48.4%, respectively. Mean±SD duration of diabetes was 14.0±6.6 years and duration of iGlarLixi treatment prior to study participation was 5.7±3.3 months. Mean±SD length of fasting was 28.7±3.3 days and only 9/153 people (5.9%) broke the fast during Ramadan. Reported reasons for breaking the fast were travel, pre-existing conditions, adverse events (AEs; not related to iGlarLixi), hypoglycaemia, and menses. Change in antihyperglycaemic treatment class was minimal during the study with 79.4% and 54.2% of people taking biguanides and sulfonylureas during Ramadan, respectively. The mean±SD iGlarLixi dose changed from 24.8±11.6 U (pre-Ramadan) to 23.8±10.5 U (Ramadan period) and 24.9±11.6 U (post-Ramadan). During Ramadan, 137/153 (89.5%) and 11/153 (7.2%) of people took iGlarLixi at Iftar (evening) and before Suhur (morning), respectively. The number of participants reporting ≥1 severe and/or symptomatic documented hypoglycaemia (plasma glucose [PG] ≤70 mg/dL; primary endpoint) was 2/151 (1.3%) during pre-Ramadan, 3/148 (2.0%) during Ramadan, and none during post-Ramadan. No participant reported hypoglycaemia with PG <54 mg/dL and there were no severe or serious hypoglycaemia events. The rate of severe and/or symptomatic documented hypoglycaemia (PG ≤70 mg/dL) was 0.02 per patient-month. Improvements were observed for mean±SD HbA_{1c} and fasting PG (pre-Ramadan, 8.4±1.1% and 146.9±32.1 mg/dL to post-Ramadan, 7.5±0.8% and 122.5±28.8 mg/dL) with an average reduction of -0.8±1.1% and -24.4±32.6 mg/dL, respectively. AEs were low (5.8%) and were not considered related to iGlarLixi, and there were no serious AEs. **Conclusion:** In a real-world setting, people with T2D treated with FRC iGlarLixi were able to fast for most of the month of Ramadan; the incidence of hypoglycaemia was low and glycaemic control was improved.

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COVID-19 AND DIABETES

A Case Series of Hyperglycemic Hyperosmolar State During the Global COVID-19 Pandemic

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Hyperglycemic hyperosmolar state (HHS) is rare in pediatrics, particularly in patients with antibody positive diabetes mellitus (DM). Recent literature has implicated COVID-19 in the reported increase in new-onset DM cases, as well as mixed diabetic ketoacidosis (DKA) and HHS cases, however a rise in HHS cases alone has not been well reported [1,2]. We noted an anecdotal increase in the frequency of HHS cases in our pediatric tertiary care center following the onset of the global COVID-19 pandemic. To investigate further, a retrospective chart review evaluating all patients with DM admitted in the first 6 months of 2019 and the first 6 months of 2020 was conducted. A diagnosis of HHS was defined as a blood glucose over 600 mg/dL with a serum osmolality (calculated or measured) greater than 320 mOsm/kg on initial laboratory evaluation. Patients with DKA, defined as a serum bicarbonate level less than 16 mmol/L with evidence of significant ketosis (serum ketones greater than 3 mmol/L), were excluded from the study. During the first 6 months of 2019, 1 patient met inclusion criteria. However, the diagnosis of HHS was complicated by a concurrent diagnosis of diabetes insipidus, which may have contributed to the hyperosmolar state, and a nonketotic lactic acidosis. Five HHS cases were noted in the first 6 months of 2020, 4 of which occurred in May and June. For the 2020 HHS cohort, the average patient age ± SD was 12 ± 3.34 years. The mean ± SD laboratory values included bicarbonate 18.2 ± 1.64 mmol/L, serum blood glucose 776.8 ± 30.75 mg/dL, calculated serum