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Combination of Basal Insulin Analogues and GLP-1 Receptor Agonists in the Treatment of Obese Subjects with Type 2 Diabetes: Presentation of Clinical Cases

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ABSTRACT

We present the cases of 7 obese subjects with type 2 diabetes (age 58+3 years, BMI 37+1.6Kg/m2, HbA1c 9.1+0.3%, fasting blood glucose 191+20mg/dl) treated with combinations of metformin (850 or 1000mg twice daily), insulin (premixed insulin preparations twice or three times daily or basal-bolus regimens with insulin glargine-U100 plus pre-meal rapid-acting insulin analogues; total insulin dose 106+20 units/day) and sulfonylureas (glimepiride or gliclazide once or twice daily). All patients reported frequent hypoglycemic episodes. According to the ADA/EASD 2018 treatment algorithms, all subjects started a combination with metformin (1000mg twice daily), insulin glargine-U100 20 units at bed time with gradual up-titration targeting fasting blood glucose 100mg/dl) and liraglutide (0.6mg up-titrating to 1.8-2.4mg). Three to 6 months after the triple combination therapy, BMI (33+1Kg/m2), HbA1c (6.57+0.3%), fasting blood glucose (114+9mg/dl) and total units of insulin (42+5 units/day) were all reduced ($p<0.05$); no hypoglycemic episodes were reported. In subjects with obesity and type 2 diabetes, therapeutic options which aggravate the already existing hyperinsulinemia/insulin resistance should be avoided, since they increase body weight and risk for hypoglycemia, deteriorating glucose control. A triple combination with metformin, long-acting basal insulin analogues and GLP-1 receptor agonists is a safe option for metabolic regulation without side-effects.

INTRODUCTION

Obesity is a well-established risk factor for the development of type 2 diabetes [1]. In this condition, insulin resistance in the liver and peripheral tissues (skeletal muscle and adipose tissue) is the main pathogenetic mechanism to explain metabolic dysregulation and hyperglycemia, and is compensated by increased insulin secretion from pancreatic β-cells [1-4]. However, as proposed by Nolan et al [5], insulin resistance can also protect tissues (such as the myocardium) from massive entrance of increased amounts of glucose into the cells in the presence of hyperinsulinemia, thus avoiding further oxidative damage [5,6]. In such subjects with type 2 diabetes, therapeutic options which aggravate hyperinsulinemia could: (a) violate the protective barrier, thus increasing glucose flux into the cells, with detrimental consequences [5]; (b) increase body weight and risk for hypoglycemia, deteriorating insulin resistance and glucose fluctuations. Although recent ADA/EASD treatment guidelines clearly suggest individualization of treatment [7], initiation with metformin and sequential

addition of insulin (especially pre-mixed preparations) and sulfonylureas is still a common practice in several parts of the world because of low cost [8,9].

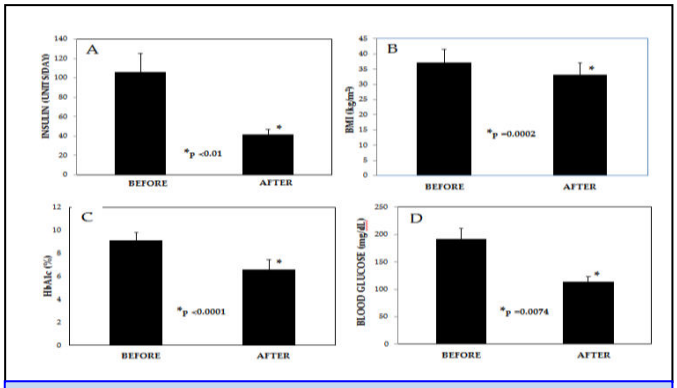

Figure 1: Body mass index (A), HbA1c (B), fasting blood glucose levels (C) and total amount of insulin units administered per day (D) in seven obese subjects with type 2 diabetes, before and 3-6 months after triple combination therapy with metformin, insulin glargine-U100 and GLP-1RAs.

We report cases of seven obese subjects with type 2 diabetes and no comorbidities (mean+SEM, age 58+3 years, BMI 37+1.6Kg/m2, HbA1c 9.1+0.3%, fasting blood glucose 191+20mg/dl), admitted to the diabetes outpatient unit of "Attikon" University hospital, Athens, Greece. All subjects were treated with a combination of metformin (850 or 1000mg twice daily), insulin (intensified regimens with premixed insulin preparations 2-3 injections per day, or basal-bolus with glargine-U100 at bed-time and rapid-acting insulin analogues prior to main meals; total units of insulin were 106+20 units/day) and sulfonylureas (glimepiride or gliclazide, once or twice daily). They all reported frequent hypoglycemic episodes. We performed a C-peptide test to evaluate β-cell reserve, which revealed C-peptide values of 3.54+0.6ng/ml and 5.9+0.6ng/ml at 0 and 6 minutes after administration of 1mg glucagon IV, respectively.

Since all subjects were obese with HbA1c values ~9%, we started a combination of metformin (1000mg twice daily), insulin glargine-U100 (20 units at bed-time SC with gradual titration, targeting fasting blood glucose of 100mg/dl) and liraglutide (initially with 0.6mg/day SC, up-titrating gradually to 1.8-2.4mg/day), according to the ADA/EASD treatment guidelines [7]. All subjects self-monitored their blood glucose levels 4 times daily (prior to three main meals and before sleep). Three to 6 months after the triple combination therapy, the units of insulin required for glucose control were reduced by more than 60%, while BMI, fasting blood glucose levels and HbA1c were all significantly improved (Figure 1); no hypoglycemic episodes were reported.

DISCUSSION/CONCLUSIONS

Insulin resistance is the main pathogenetic mechanism responsible for hyperglycemia and metabolic dysregulation in obese subjects with type 2 diabetes. Insulin resistance is compensated by increased insulin secretion from the β-cells. Furthermore, at the clinical diagnosis of type 2 diabetes, 40-50% of the β-cell mass has already been lost [1-4].

Insulin is the cornerstone of diabetes treatment. Ninety eight years after its discovery, although there are many new categories of anti-diabetes medications, insulin still remains the most effective way to reduce HbA1c [10]. However, in obese subjects with type 2 diabetes, due to already existing hyperinsulinemia, administration of insulin should be initiated with caution [5].

Appropriate adaptations of substrate handling are necessary to maintain tissue energy balance under various metabolic conditions; insulin coordinates glucose, lipid and protein metabolism to satisfy energy needs [11]. However, the amount of insulin required for this purpose depends exclusively on the sensitivity of the liver and peripheral tissues to insulin: if insulin sensitivity is increased (such as after lifestyle interventions), less insulin would be required for the same metabolic effect, thus minimizing the risk for hyperinsulinemia and its side effects [11,12]. A common logic when initiating insulin treatment in obese subjects with type 2 diabetes and high HbA1c values is to combine basal insulin with agents that increase insulin sensitivity, in order to minimize hyperinsulinemia. This has been clearly stated in the recent ADA/EASD guidelines, which highlight the individualization of treatment [7]. Long-acting GLP-1 receptor agonists (GLP-1RAs), along with metformin, are first choice options in the treatment algorithms when weight management is considered a priority, since they: (a) decrease fasting and postprandial hyperglycemia, body weight and risk for hypoglycemia, (b) increase insulin sensitivity, facilitating a reduction in the amount of administered insulin, thus decreasing glucose variability, (c) decrease β-cell apoptosis helping

substantially to maintain β-cell mass, (d) improve endothelial function and protect from cardiovascular complications [13-17]. The use of pre-mixed insulin preparations should be avoided in such subjects, since they dramatically increase weight gain and risk for hypoglycemia [18]. Sulfonylureas should also be avoided since they stimulate insulin secretion aggravating hyperinsulinemia, thus increasing body weight, risk for hypoglycemia and glucose variability, finally forcing the remaining β-cells to apoptosis and total failure [2,19,20]. In our subjects, the combination of metformin, insulin glargine and liraglutide decreased body weight, obliterated hypoglycemia and improved metabolic regulation.

We conclude that, in obese subjects with type 2 diabetes, therapeutic options which aggravate the already existing hyperinsulinemia and insulin resistance should be avoided: they increase body weight and risk for hypoglycemia, deteriorating glucose control. A combination of metformin with long-acting basal insulin analogues [21] and GLP-1RAs [14,16] is a safe option for metabolic regulation without side-effects.

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