ARTIGO ORIGINAL

Liraglutida como Coadjuvante no Tratamento da Obesidade

Liraglutideas Adjunct Therapy in the Management of Obesity

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ABSTRACT

The obesity epidemic has reached a new level with some impressive numbers recently published in the United States of America. Even more alarming is the rapid increase in childhood obesity, which has been universally documented over the past few decades. The reasons underlying the problem of obesity can be simplified into three categories: i) routine consumption of bigger portion size meals; ii) confusing messages from food industry to consumers; and iii) physical inactivity is the “new normal”. Considering that the medical consequences of obesity are serious and directly affect morbidity and mortality, it has become necessary to act concomitantly to prevent and treat the increase in body weight and fat excess accumulation. The prevention of obesity is a formidable task that can only be accomplished with a concerted effort put together by several governmental agencies, especially those interested in agriculture, health and education, the food industry and health care providers, including physicians and nutrition specialists. Treatment of obesity with behavioral management, nutritional manipulations (“diets”) and, even bariatric surgery has had some success, but these strategies are accompanied by limited benefits and only to a select group of individuals. More importantly, the overall impact of these on the growing obesity pandemic is disappointing, at best. Some dietary recommendations with caloric restriction and adjustments in nutrient intake combined to pharmacotherapy have expanded our ability to manage obese patients.The recent approval by the U.S. Food and Drug Administration (FDA) agency of the Glucagon-Like-Peptide-1 (GLP-1) receptor analog liraglutide, at the dose of 3.0 mg once daily, has provided us with an additional tool to combat the disease and minimize its complications. In this particular study, a significant reduction in the conversion ratesfrom pre-diabetes to diabetes was also shown and represents an important findingof the trial. Despite the fact that nausea, vomiting and diarrhea were frequently reported during the 1-year period of observation, tolerance was acceptable and most subjects completed the study.These data clearly indicate that combination drug therapy with dietary adjustments can be successful in promoting weight reduction and further support routine utilization of adjuvant pharmacotherapy in the management of obesity.

KeyWords:

Obesity, GLP-1 RA, Liraglutide, Pre-Diabetes

INTRODUCTION

The obesity epidemic has reached a new level with some impressive numbersrecently published in the United States of America (1,2). According to a recent survey, there are currently approximately 26.4% of adult people met the criteria for the diagnosis of Obesity. A Body Mass Index (BMI = weight in kilograms divided by the square of the body height in centimeters) above 30.0 kg/m2was used to define obesity (3). These studies (1,2) also revealed that an additional 30-35% of the U.S. population was overweight, with BMI between 25.0 and 29.9 kg/m2. In contrast, only one–third of individuals was found to have a BMI value in the normal range, i.e., between 18.5-24.9 kg/m2. Amongst all adults, 16.9% were in the obese class 1 (BMI = 30.0-34.9 kg/m2), 6.0% in the obese class 2 (BMI = 35.0-39.9kg/m2) and 3.5% in the obese class 3 (BMI = 40.0kg/m2 or greater). The report acknowledges the fact that obese and overweight persons in general have lower social-economic status, largely represented in poor communities. Moreover, a direct and inverse linear relationship between the degree of personal education and obesity was also documented. Although individuals in the obese class 1 are equally distributed among ethnic groups of Whites (16.4%) and Hispanics (17.9%), there is a slightly higher prevalence inBlacks (20.8%). The same is true for Blacks in the obese class 2 (8.8%) and class 3 (6.0%), as compared to Hispanics, 6.3% and 3.4% and Whites, 5.6% and 3.1%, respectively. Of interest, Asians living the U. S. are affected the least, with 7.6%, 2.1% and 1.0%, respectively categorized in obese class 1,2and 3. These data provide additional evidence for the relentless growth of the obesity pandemic globally, assuming these data reflect, at least to some extent, the body habitus of the vast majority of the current world's population. In critical analyses of these observations, we can accept the facts as they are and then take for granted that "heavier-larger" people are now the "new norm" and live with the consequences. Alternatively, we can look atthe global obesity as a "gigantic problem" and, make an effort to better understand the reasons why people have deviated so much from previous standards. This would be an important and critical step in the direction of finding better solutions to obesity problem.

In taking the second option, one must realize thatobesity as medical problem is likely to continue into this and even perhaps, the next century. This is further substantiated by the rapid increase in childhood obesity, which has been documented over the past few decades. One in three children between the ages of 2 and 19 years fits the criteria for overweight and obesity (4).So, why are people living in the U.S. obese? The answer is very complex even controversial andbeyond the scope of this review. Nonetheless, we propose that reasons underlying the growing obesity epidemic fall into three categories, (also summarized in Table 1below):

I) Consumption of bigger portions: various observations have repeatedly pointed out that an excessive amount of calories, as well as of specific nutrients are ingested by a given person, regularly. Recent data (1,4) indicates that in the last 50 years, the intake of meat and processed meats, fat products and sugared grains has skyrocketed, which may account for large portion sizes consumed;

II) To achieve reasonable profits and maintain/ enhance sales, the food industry has eluded the consumers by false advertisement, at large and by printing confusing messages in food labels. It is usually not very easy to discern the exact nutrient and calorie content of a "diet" vs. a 'low fat" or a "low carb" product. Most food labels are incomprehensible to the average consumer, who cannot understand, for example, that "low fat" means "high carb". Moreover, serving sizes vary from product to product, even within those in the same category. This makes comparisons between products very difficult as there is often a suggestion that one product may have a lower content of, for instance, carbohydrates, when in fact the serving size noted in the label is smaller than the competitor's product. There is also a substantial difference in the cost of products labeled as "dietary" as compared to "regular" food products. Tactics of the food industry to entice children and distracted or innocent consumers in public advertisements are well-known;

III) Inactivity is the "new normal". Recent obser-vations (1,4) revealed that only 20% of jobs offered today actually require some form of physical activity and, people walk much less to move around. Everything everywhere is essentially automated, such as escalators, elevators, motorized, on wheels, etc… and it has become so

easy to choose not to walk or to carry weight. Many communities and neighborhoods have no adequate space for walking and, there are sparse or no children playgrounds or open fields to stimulate physical activity. In strong contrast, there are plenty of available means that foster sedentary lifestyle, such as time spent sitting, watching TV, playing videos, games and surfing the web, most of which have taken over and now occupy people'sfree time. There are numerous observational studies that confirm these and some estimates (1,4) haveconcluded that people burn nearly 140 calories per day less today,compared to the 60's, i.e. 50 years ago.

The medical complications associated with obesity and physical inactivityhaslong been recognized. Insulin resistance and the cardio-metabolic syndrome with accompanying accelerated atherosclerotic cardiovascular disease, glucose intolerance, type 2 diabetes, hypertension, dyslipidemia and non-alcoholic liver disease are fairly prevalent in obese subjects. This is true formost countries and contributes significantly to overall morbidity and mortality rates (5,6).Sleep apnea and sudden death (7) are commonly seen in overweight and obese individuals, just as are osteo-articular disorders (8). The adverse psycho-social consequences of obesity are enormous and this is especially difficult for young overweight children of school age (9).The simple fact that obese people have a shorter lifespan and carry higher mortality than age- and gender-matched individuals with normal weight (10) raises sufficient concern and calls for more effective interventions. In this regard,one must consider not just aggressive therapies but also strategies designed to "prevent" the future development of obesity (Table 2).

The prevention of obesityrequires multi-disciplinary efforts combining a series of consensual decisions with effective actions involving government officials, the food industry, health care providers and the consumers.The implementation of these must be aimed primarily at improving the affordability and transparency of healthy nutritional food products and simultaneously enhance the level of understanding of the consumers. The latter is particularly relevant to local school systems and to families who are responsible for the nutritional well-being of children and young individuals (11). In addition, promoting education in nutrition among physicians and health care providers during formal trainingand thereafter should becomea priority. Government leaders, both in local and federal agencies must ascertain that the health, education and agriculture branches, for example are in agreement with the policies intended to provide more adequate nutrition to the people. This is necessary in order to avoid the financial disputes and confrontations that usually erupt between policies defended by these departments. The hope is that as a result of honest and frank dialogue overall economic growthconcomitant with a superior nutritional status for most people will emerge.

In addition to measures proposed to prevent obesity, there is equal need and interest in developing more effective therapies that might curb and decrease the accumulated excess body fat described in obese individuals.

Several strategies have been put in practice to control body weight gain and fat excess,though none has met with overwhelming success. Behavioural management can be helpful and tends to provide greater benefits when it is geared towards families and includes pre-pubertal children (12). Numerous nutritional manipulations have been suggested to accomplish body weight and fat reduction (13-15), but nearly all impose unattainable changes in food intake habits and the results are thus, short-lived. In our experience (16) and of others (13-15), most sustainable body weight reductions are achieved with low-calorie and low-carbohydrate dietary regimens. These are especially efficacious if the overweight or obese subjects are allowed to choose whatever they want to eat, as long as they decrease the portion size of each meal, for instance to one-half of previous intake. Initiation of a routine of regular exercises and becoming more physically active is usually associated with better maintenance of any weight reduction that is reached with specific dietary recommendations (17). For those individuals categorized as obese class 2 and 3, bariatric surgery and/or the use of novel gastro-intestinal devices that block calorie absorption have shown some promising results (18-20). In long-term follow-up study of morbidly obese patients who underwent different forms of bariatric surgery has demonstrated that the clinical benefits are preserved, even though mean percent weight decrease was attenuated from 5 versus 15 years, respectively from 31% to 25% (Roux-en-Y Gastric Bypass), from 17% to 14% (Lap Band Gastroplasty) and from 17% to 16% (Vertical Band Gastroplasty). One must keep in mind, however, that these are extreme cases of obesity and the results cannot be generalized and

applied to all obese individuals. Moreover, it is not feasible or scientifically justifiable that all obese patients should undergo bariatric surgery to improve clinical outcomes and quality of life. To this end, an alternativeapproach to the management of obesity is the use of medications currently availableas adjunct therapy to dietary recommendations. Many studies have shown that the use of drugsin addition to calorie restriction and nutritional manipulations tend to yield better results than those observed with dietary measures alone (21-24). Of particular interest, are the recently released findings of a study (25) with Glucagon-Like Peptide-1 receptor analogue (GLP-1 RA), liraglutide used in obese patients with the exclusive goal of promoting weight reduction.

In this study, the use of liraglutide at the dose of 3.0 mg injected once daily was given to a group (n~3,600) of adult obese patients (BMI>30.0 Kg/m2) and overweight subjects (BMI>27.0% who had either hypertension and/or dyslipidaemia). Patients with type 1 or type 2 diabetes were excluded, but those with impaired glucose tolerance, as defined by a standard oral glucose tolerance test were included. Subjects were randomly assigned to receive either liraglutide or placebo injections and were instructed to follow a 500 calorie/day restriction diet. Regular physical activity was also recommended but, not enforced. At the end of 56 weeks, liraglutide was associated with clinically meaningful weight loss of 8.4 kg vs. 2.8 kg in the placebo group. There were also improvements in glycaemic indices, risk factors, and in quality of life. These data areimportant additional evidence that when used in combination with dietary restrictions, the GLP-1 RA liraglutide is accompanied by reduced food intake and maintenance of weight reduction, as long as the medication continues to be injected. Having used GLP-1 RA therapy in type 2 diabetes, these results are not entirely surprising. GLP-1 RA drugs are capable of slowing down gastric emptying, augmenting the uptake and storage of glucose in the liver (26) and of reducing the appetite, possibly via a central nervous system mechanism (27). Of considerable interest, however, was the significant decrease attained in the conversion rate of pre-diabetes to diabetes and, from non-diabetes to pre-diabetes in subjects who received the liraglutide injection.

Approximately 60% of subjects enrolled in each group met the criteria for the diagnosis of impaired glucose tolerance, a pre-diabetes condition. In the placebo injection group full diabetes developed in 14.0%, whereas in the liraglutide group the conversion rate was only 4.0%. This represents a decrease in the yearly conversion rate from pre-diabetes to diabetes of 72%, which is comparable to most of previously reported interventions using pharmaceutical agents and/or nutritional manipulations (28-31). After 56 weeks of therapy, 20.7% of the normal glucose tolerant individuals in the placebo group were classified as pre-diabetes vs. 7.2% in the liraglutide group. In the end, there was a mild increase in the percent of subjects classified as pre-diabetes from before (60.9%) to after (67.3%) placebo injection therapy. In contrast, the percent of subjects with pre-diabetes prior to liraglutide (61.4%) decreased significantly to 30.8%. These changes can be largely attributed to the substantial weight loss and improvements in glycaemic indices,with lower fasting and post oral challenge plasma glucose concentrations following liraglutide injection. In addition, decreased glucotoxicity effect on insulin-mediated peripheral glucose metabolism and, perhaps a direct stimulation of the GLP-1 receptors on islet cells of the pancreas are likely to further contribute to the delay in the appearance of diabetes. In fact, it seems safe to speculate that if these obese and overweight subjects continue to use liraglutide injection for many years, the degree of improvement in outcomes might be comparable to that described in obese class 2 and 3 subjects' post-bariatric surgery (32).

The report also includes some important, though anticipated adverse effects of the liraglutide injection. Nausea and diarrhea occurred in 40.2% and 20.9% of patients on liraglutide, whereas only in 14.0% and 9.7%, respectively in the placebo injection group. Vomiting, dyspepsia and abdominal pain was also 2- to 3-fold more common with liraglutide than with placebo injections. Despite the fact that the nausea subsided a few months into the study, subjects using liraglutide injections continued to have greater loss of appetite that those on placebo. Of note, 14 patients were diagnosed with breast cancer (vs. only 3 in the placebo group) and 4 had acute pancreatitis while taking liraglutide but, in view of the small number of cases the cause-and-effect relationship could not be firmly established. As expected, with body weight loss blood pressure and lipid serum levels decreased. Also, the was a mild and sustained increase in pulse rate of ~6-8 bpm in subjects receiving liraglutide, which returned to baseline a few weeks after the drug was discontinued.Although the benefits of weight reduction are well documented, the significan-

ce of these latter findings on cardiovascular disease and events outcome remains uncertain.

This study demonstrates that 3.0 mg of liraglutide injection daily, as an adjunct to diet and exercise in obese and overweight non-diabetic individuals is associated with reduced body weight and improved metabolic control. This new agent was recently approved by the U.S. Food and Drug Administration office and is indicated in combination with nutritional manipulations and regular physical activity in patients with BMI>30.0 or >27.9 kg/m2and co-morbidities in order to aid in weight management. The drug is now commercially available with the name of Saxenda® and should not be used in patients with a past history of pancreatitis or medullary thyroid cancer. In addition to weight loss, a delay in the development of type 2 diabetes is anticipated, as long as the drug is injected regularly. Similar to all other means (drugs and diets) utilized to reduce body weight, when the liraglutide injection is interrupted, for whatever reason, body weight re-gain and further deterioration of metabolic profile, including the appearance of type 2 diabetes is inevitable.

In conclusion, considering that obesity has now reached pandemic proportions and that most results with nutrition manipulations and regular exercise programs alone have been disappointing, the introduction of novel strategies is welcome. Behavioural management and bariatric surgery are reserved for a few and select group of obese individuals. Bariatric surgery also provides beneficial effectsbut at increased risk and with some complications. Widespread low-calorie and low carbohydrate dietary recommendations have the potential to offer clinically important outcomes, but only in rare motivated and adherent individuals. Modifications in lifestyle and eating habits are very difficult, if not impossible, to accomplish in the majority of adult subjects. The utilization of adjuvant pharmacotherapy in the management of obesity has been shown to be more successful than dietary changes alone. Albeit at a higher cost, these pharmacological interventions when used in combination with caloric restriction and nutritional manipulations raise some expectations and may result in superior outcomes. Practical strategies for eating less and moving more are urgently needed in order to undo the detrimental influences of the new environment. Even modest body weight reductions of 5-10% can make medical issues more manageable.The ultimate solution to the growing obesity pandemic however still rests on the will and power of leaders, who are determined to implement the known necessary changes to create sustained healthier nutritional conditions and effectively prevent excess body fat accumulation.

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Table 1 - Principal Causes of Exogenous Obesity

1. CONSUMPTION OF BIGGER PORTION SIZES

I) Meat & related processed food

II) Fat products

III) Sugared grains & drinks

2. CONFUSING MESSAGES TO CONSUMERS & MARKETING STRATEGIES

For example, ''Diet vs. Low Fat'' labels do not properly address specific calorie content for serving sizes

There are significant cost differences for adding nutritional or healthier ingredients

3. PHYSICAL INACTIVITY IS THE ''NEW NORMAL''

Studies have shown that only 20% of jobs today require some physical activity

Less walking to move around (people burn 140cal/day less vs. 1960's)

Table 2 - Management of Exogenous Obesity

1. PREVENTION STRATEGIES

Require multi-disciplinary combined effort with a series of consensual decisions & effective actions involving government officials, food industry, health care providers, particularly nutrition specialists, consumers & advocates

2. TREATMENT OPTIONS

I) Behavioural Modifications: family-based are more effective & children show greater benefit

II) Nutritional Manipulations: low-calorie, low-carbohydrate diets tend to provide best results; higher maintenance with regular exercise

III) Bariatric Surgery (Obesity Class 2 & 3 only)*: mean weight reduction at 5 & 15 years with RYGB (31% & 25%); LABG (17% & 14%); and VBG (17% & 16%), respectively

IV) Adjunct Pharmacotherapy: always useful, more effective when used in combination with any one of the above

* RYGB = Roux-en-Y Gastric Bypass, LABG = Lap Band Adjustable Gastroplasty; VBG = Vertical Band Gastroplasty [Refs # 18,19,20]