Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications(MECSJ)
Issues 66 (2023)
ISSN: 2616-9185

Safety and efficacy of glucagon-like peptide-1 receptor agonists and their effect on weight loss

عبدالعزيز عبدالله العنزي
Pharmacist/ Abdulaziz Abdullah Alanazi
aaal-onazi@moh.gov.sa

زياد محمد النصر
Pharmacist/Ziyad Mohammad Alnasr
zalnasr@moh.gov.sa

داليا فايز العنزي
Pharmacist/Dalya Fayez Alenazi
dfalenazi@moh.gov.sa

Abstract

Obesity can substantially harm human health, increasing the risk of diabetes mellitus (DM) and other negative effects. To lose weight, successful therapy methods and drugs have been developed. Glucagon-like peptide-1 receptor agonists (GLP-1Ras) are indicated for weight loss in obese persons with or without type 2 diabetes (T2DM). The aim of this research to provide an overview of the safety and efficacy of glucagon-like peptide-1 receptor agonists and to determine whether treatment with a glucagon-like peptide-1 receptor leads to weight loss in overweight or

Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications(MECSJ)
Issues 66 (2023)
ISSN: 2616-9185

obese patients with or without type 2 diabetes. The current research offers evidence that GLP-1R agonist medication results in weight loss in overweight or obese people with or without type 2 diabetes mellitus. Given its potential benefits in lowering weight in addition to glycemic management, GLP-1 agonists may soon be used to treat obesity in both diabetic and non-diabetic persons. However, further research investigations, namely big clinical trials, are necessary to extend and fully explain the beneficial effects and potential negative effects of GLP-1 agonists. Obesity therapies based on glucagon-like peptide-1 (GLP-1) agonism are now being used and further developed. GLP-1 RA as an addition to LSI is effective and safe in adolescents with obesity who do not react well to lifestyle interventions. Since of the scarcity of data, a general advice is to favor long acting GLP-1 RA over short acting GLP-1 RA since they are licensed for the treatment of obesity and have greater tolerability, safety, and therapeutic response impact.

Keywords: Safety, Efficacy, Glucagon-like peptide-1 receptor agonists; Obesity; Weight Loss.

1. Introduction

Obesity and overweight can substantially harm human health, increasing the risk of type 2 diabetes mellitus (T2DM) and other negative effects such as insulin resistance at the cellular level, hyperlipidemia, and heart disease (Wu & Ballantyne, 2020). According to the World Health

Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications(MECSJ)
Issues 66 (2023)
ISSN: 2616-9185

Organization, around 1.5 billion persons were classified as overweight in 2011, and approximately 2.8 million deaths among adults are attributable to overweight or obesity each year (WHO, 2011). Obesity or overweight affects more than 80% of T2DM patients, and about three-fourths of DM patients may develop complications such as vascular diseases and other DM-related problems as a result of obesity (Eeg-Olofsson et al, 2009). Many doctors and patients seek to reduce or gain weight while regulating their patients' glucose levels. Both doctors and patients want to lose weight and lessen the negative consequences of T2DM, as well as control their glucose levels (Shin, 2012).

Successful therapy alternatives and drugs, both pharmacological and non-pharmacological, have been devised to reduce weight, primarily among patients with diabetes, in order to lower the risk of a variety of obstacles (Bailey et al, 2020). However, it has been shown that drugs used to control diabetes, such as sulphonylureas, insulin, and thioglitazones, cause weight gain. Metformin, dipeptidyl peptidase 4 inhibitors (DPP4is), sodium-glucose cotransporter-2 (SGLT-2) inhibitors, and glucagon-like peptide receptor agonists (GLP-1RAs) decrease weight while also controlling blood sugar levels. As a result, there is a propensity to select solutions that maintain glycemic control while not increasing weight. One of these alternatives is glucagon-like peptide-1 receptor agonists (GLP-1Ras), which are prescribed to obese people with or without T2DM to help them lose weight. GLP-1Ras is a hormone that is released from the

Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications(MECSJ)
Issues 66 (2023)
ISSN: 2616-9185

stomach (intestine) after a meal, which in turn induces the creation of insulin and suppresses the release of glucagon (Maula et al, 2020). This hormone suppresses hunger, slows stomach emptying, and stimulates satiation, and so plays an important role in regulating blood glucose and reducing weight in obese people. Furthermore, by binding to its receptor on neurons in the hypothalamus, GLP-1Ras may increase satiation and decrease caloric consumption by delaying stomach emptying (Kanoski et al, 2012). There is evidence that GLP-1Ras have the ability to decrease weight in people with or without diabetes via the processes described above. However, there is a need to analyze and combine the data of both observational and experimental investigations in order to better understand the function of GLP-1Ras in weight loss and the extent to which these GLP-1Ras may do so emptying (Moher et al, 2010). Therefore, this research will focus on the safety and efficacy of glucagon-like peptide-1 receptor agonists and to determine whether treatment with a glucagon-like peptide-1 receptor leads to weight loss in overweight or obese patients with or without type 2 diabetes (Aldahash et al., 2021).

2. Glucagon-like peptide-1 receptor and Obesity

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are a medication class principally created for the treatment of individuals with type 2 diabetes (T2DM), and they are the cornerstone therapy method for this condition today (Vilsbøll et al., 2012). GLP-1 (glucagon-like peptide-1) is a gut hormone that is produced from the intestine in response to meal

Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications(MECSJ)
Issues 66 (2023)
ISSN: 2616-9185

consumption and promotes insulin production while inhibiting glucagon release in a dose-dependent manner (van Valkenhoef et al., 2012). GLP-1 can reduce food intake and appetite, as well as slow stomach emptying and produce satiety, and hence plays a significant role in blood glucose homeostasis. However, the quick inactivation of GLP-1 in vivo, as well as the resulting short half-life, precludes its therapeutic application. Long-acting GLP-1 receptor agonists (GLP-1 RAs) that may be given once or twice a day, or even once a week, have been created. Exenatide, liraglutide, albiglutide, taspoglutide, lixisenatide, and LY218926 are examples of GLP-1 RAs. GLP-1 RA treatment improves insulin resistance and glucose homoeostasis in Type 2 DM patients (Lu & Ades, 2004). Because of their manner of action, they also have a minimal risk of hypoglycemia. Exenatide and liraglutide are now being used effectively in the treatment of Type 2 diabetes (Salanti et al., 2011).

Overweight or obesity may raise the risk of cardiovascular problems while also causing significant psychological anguish in the majority of Type 2 DM patients (Chaimani et al., 2013).Effective weight-loss therapies are an important aspect of Type 2 DM cares to avoid the development of microvascular and macrovascular problems. However, several diabetes medications (insulin, thiazolidinediones, and sulfonylureas) cause weight gain as a side effect. By attaching to its receptor on hypothalamic neurons, GLP-1 can increase satiety and reduce calorie intake by delaying stomach emptying (Sun et al., 2015).

Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications(MECSJ)
Issues 66 (2023)
ISSN: 2616-9185

Obesity has been linked to an increased risk of diabetes and its consequences, such as insulin resistance, dyslipidemia, and cardiovascular disease (Buse et al., 2013). Overweight or obese people account for more than 80% of Type 2 diabetics. It is appealing to both doctors and patients to avoid Type 2 DM weight gain during glycemic control medication. GLP-1 RAs are a novel family of glucose-lowering medications that have been found in clinical investigations of Type 2 DM patients to enhance glycemic control and increase weight reduction. The first long acting stable GLP-1 RA was licensed by the US Food and Drug Administration in 2005. The drugs exenatide (Byetta; EliLilly) and liraglutide (Victoza; NovoNordisk) are now accessible. Both treatments can be used in conjunction with oral diabetes medications such as metformin, thiazolidinediones, or sulfonylureas. The medicines are approved for Type 2 diabetes patients who have not achieved acceptable glycemic control after therapy with standard diabetes medications (Seino et al., 2015).

(Ard et al., 2021) indicated that obesity is a chronic disease associated with many complications. Weight loss of 5-15% can improve many obesity-related complications. Despite the benefits of losing weight, there are many challenges with losing weight and maintaining weight loss over the long term. In a study by Baden et al., (2023), glucagon-like peptide-1 receptor agonists showed potential for treating obesity and reducing the risk of developing type 2 diabetes, but there is a lack of studies comparing adverse events across different populations, and compare

Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications(MECSJ)
Issues 66 (2023)
ISSN: 2616-9185

indirect adverse events of pharmaceutical preparations agonists of glucagon-like peptide-1 receptors for the treatment of overweight or obesity in adults, adolescents, and children.

3. Safety and efficacy of glucagon-like peptide-1 receptor in the Management of Obesity

Obesity is a chronic and progressive condition; hence weight control must be maintained throughout one's life (Hope et al., 2018). Obesity treatment is accomplished in three stages: (1) LSI with behavioral therapy, physical activity, and food modification; (2) medication; and (3) bariatric surgery. The intervention is decided based on the BMI, waist circumference, comorbidities, and response to previous anti-obesity therapy (Davies et al., 2021).

LSI alone has been linked to mild weight reduction that is eventually restored. It produces a large number of poor responders in both the adult and pediatric populations (Wadden et al., 2021). Although bariatric surgery is regarded as the most successful treatment, it comes at the expense of irreversibility, surgery-related problems, and significant late complications. Although pharmacotherapy can supplement lifestyle treatment and bariatric surgery, the duration of such intervention is unknown (Jepsen et al., 2021).

Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications(MECSJ)
Issues 66 (2023)
ISSN: 2616-9185

Maintaining weight reduction achieved with any treatment method is particularly difficult due to adaptation, which is defined by changes in appetite-regulating hormone levels and a drop in resting metabolic rate. Some research suggests that even momentary weight loss may have long-term advantages, although the evidence is inadequate to justify short-term anti-obesity therapies (Nauck et al., 2021).

3.1 GLP-1 RA for the Treatment of Obesity

GLP-1 agonism in combination with existing GLP-1 RA and novel anti-obesity drugs would probably serve as a model for future pharmacological anti-obesity therapy. GLP-1 receptors of functional significance can be found in the pancreas, gut, and hypothalamus. The activation of neuronal pathways producing decreases in appetite-regulating areas of the hypothalamus causing reductions in hunger and food intake and so promoting weight loss is most significant for the weight-reducing capabilities (Lau et al., 2015).

Liraglutide was the first long-acting GLP-1 RA licensed for the treatment of obesity by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). It was found to be effective in lowering body weight in people with and without diabetes, as well as in youngsters. Following then, further work focuses on boosting efficacy and extending benefits through several critical structural alterations. With these characteristics in mind, semaglutide, a novel long acting GLP-1 RA, has

Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications(MECSJ)
Issues 66 (2023)
ISSN: 2616-9185

been created (Pi-Sunyer et al., 2015). Liraglutide is a polypeptide with 97% similarity to human GLP-1 with a fatty acid side chain connected through a linker molecule. Semaglutide is structurally similar to liraglutide, but with slight differences in the GLP-1 moiety, with 94% homology to human GLP-1 and another fatty acid side chain (Wadden et al., 2013). The improved pharmacokinetic characteristics of semaglutide allow for once-weekly dosage rather than once-daily delivery of liraglutide (Le Roux et al., 2017).

The alteration leads to increased effectiveness, which was initially seen in a phase 2 study in people with obesity, where patients achieved a mean weight reduction from baseline of 13.8% compared to 7.8% for liraglutide at week (wk) 52 (Blackman et al., 2016). The FDA authorized injectable semaglutide as the newest anti-obesity medicine in the United States in June 2021. The recommended dosages for both medications for weight reduction are higher than those for glycemic control: 3.0 mg against 1.8 mg for liraglutide and 2.4 mg versus 1.0 mg for semaglutide. The difficulties in losing weight in persons with type 2 diabetes mellitus compared to people without diabetes are well established. Smaller weight reductions with both GLP-1 RA have been confirmed in treating individuals with type 2 diabetes mellitus vs those without (Garvey et al., 2020).

Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications(MECSJ)
Issues 66 (2023)
ISSN: 2616-9185

3.2 GLP-1 RA for Pediatric Obesity

At the moment, the only two GLP-1 RA drugs with pediatric evidence are the short acting GLP-1 RAs exenatide and liraglutide. From 2016 to 2019, a randomized, double-blind, placebo-controlled phase 3 study was conducted to assess the effectiveness and safety of subcutaneous liraglutide 3.0 mg as an addition to lifestyle treatment for weight management in adolescents with obesity (Tamborlane et al., 2019). The experiment included a 12-week run-in period, a 56-week treatment period, and a 26-week no-treatment follow-up period. They enrolled people aged 12 to 18 with obesity and a poor response to lifestyle changes alone. There were 125 individuals in the liraglutide group and 126 in the placebo group (O'Connor et al., 2017). Liraglutide outperformed placebo in terms of change from baseline in the BMI standard deviation score at week 56, with an estimated difference of 0.22 points. A 5% reduction in BMI was reported in 43.3% of individuals in the liraglutide group and 18.5% of people in the placebo group; a 10% reduction in BMI was recorded in 33% and 9% of participants, respectively. Liraglutide was shown to be more effective than placebo in terms of BMI, with an estimated difference of 4.64 percentage points, and body weight, with an estimated difference of 4.5 kg for absolute change and 5.01% for relative change. After cessation, liraglutide caused a larger rise in the BMI standard deviation score than placebo (Tamborlane et al., 2019).

Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications(MECSJ)
Issues 66 (2023)
ISSN: 2616-9185

The observed reduction in BMI standard deviation score with liraglutide (0.22) was bigger than differences seen in US Preventive Service Task Force trials of lifestyle treatment (0.17) and a summary of Cochrane reviews (0.13). Despite some changes in the weight loss trajectory, the treatment difference in body weight seen with liraglutide was similar to the treatment effect observed in the analogous study of liraglutide in adults (Kushner et al., 2020). The weight gain seen throughout the 26-week follow-up period was consistent with findings from placebo-controlled studies of liraglutide 3.0 mg in adults (Wilding et al., 2021).

The liraglutide group reported more gastrointestinal adverse events (64.8% vs. 36.5%) and adverse events that resulted to trial treatment discontinuation (10.4% vs. 0%). There were few significant adverse events in either group (2.4% vs. 5 [4%]). Additional significant adverse events occurred in 1 person who got liraglutide (1 incident) and 4 individuals who received placebo (5 occurrences) throughout the 26-week follow-up period. Psychiatric illnesses were experienced by 13 participants (10.4%) in the liraglutide group and 18 participants (14.3%) in the placebo group. There were no clinically significant changes between treatment groups in terms of mental health questionnaire scores. However, one suicide occurred in the liraglutide group about 340 days after treatment began, and two patients (1 from each treatment group) reported a suicide attempt during the 26-week follow-up period. These three incidents were assessed unlikely to be connected to the study

Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications(MECSJ)
Issues 66 (2023)
ISSN: 2616-9185

therapy by the site investigators. Liraglutide caused more hypoglycemia episodes than placebo (26 vs. 18), however none were classified as severe by the American Diabetes Association-International Society for Paediatric and Adolescent Diabetes criteria. There were no discernible variations in growth or pubertal development between treatment groups (Tamborlane et al., 2019).

Adverse events that resulted in trial treatment discontinuation occurred in 13 patients (10.4%) in the liraglutide group and none in the placebo group (p 0.001). Ten competitors dropped out owing to stomach issues. Adherence was >80%, which was higher than in many prior studies including obese adolescents (about 70%). However, as the treatment period progressed, the fraction of samples acquired for pharmacokinetics analysis with liraglutide values below the lower limit of quantification rose (Riesenberg, 2019).

In conclusion, liraglutide 3.0 g as an addition to lifestyle treatment resulted in a higher decrease in BMI than placebo in adolescents with obesity. The increased occurrence of gastrointestinal side effects with liraglutide shows that this medication may not be appropriate for all individuals (Tamborlane et al., 2019). From 2012 to 2018, another bigger trial was done in kids with type 2 diabetes to determine if liraglutide 1.8 mg added to metformin with or without basal insulin therapy is safe and effective. The weight loss was reported but not classified as a primary or secondary outcome (Abuzzahab, 2013).

Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications(MECSJ)
Issues 66 (2023)
ISSN: 2616-9185

Patients aged 10 to 17 were randomly randomized to receive subcutaneous liraglutide or placebo during a 26-week double-blind period, followed by a 26-week open-label extension term. A BMI more than the 85th percentile and a glycated hemoglobin level between 7.0 and 11.0% if the patients were treated with diet and exercise alone or between 6.5 and 11.0% if they were treated with metformin with or without insulin, were the inclusion criteria. During the experiment, all participants were given metformin. After 26 weeks, the major end point was the change in glycated hemoglobin level. The change in fasting plasma glucose level was a secondary end objective (Schwarzenberg, 2012). The trial's safety was monitored at all times. A total of 135 patients were randomly assigned to receive at least one dosage of liraglutide (66 patients) or placebo (68 patients) (Jensterle & Janež, 2021).

4. The effect of glucagon-like peptide-1 receptor on weight loss

More over two-thirds of the population in the United States is overweight (BMI 25-29.9) or obese (BMI 30). This share is lower in Europe, but it is growing (Finucane, 2011). According to the World Health Organization, 1.5 billion persons worldwide are overweight, with 500 million obese. Every year, about three million Americans die as a result of being overweight or obese. These weight issues are responsible for an estimated 44% of the diabetes burden, as well as 23% and 7-41% of the burdens for

Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications(MECSJ)
Issues 66 (2023)
ISSN: 2616-9185

ischemic heart disease and certain malignancies, respectively (WHO, 2011).

Weight reduction is difficult to achieve and maintain. Meta-analyses of clinical studies on non-pharmacological weight loss techniques found 1-6 kg weight loss that was difficult to sustain (Pronk, 2007). Meta-analyses of sibutramine and orlistat studies show average weight loss of 3 to 5 kg, but some of the included trials had attrition rates of up to 50%, which might be attributable to adverse events, suggesting that the therapies may be less successful in practical practice (Gourlan et al., 2011). Meta-analyses have revealed that bariatric surgery improves long-term mortality in obese patients, but the safety concerns and costs restrict its usage in broad patient groups.

Diabetes risk increases with excess body weight, increasing thrice with a body mass index of 25.0 to 29.9, and 20-fold with an index of 35 or above compared to a healthy value of 18.5-24.9. The low number (50%) of patients treated to treatment objectives reflects the challenges faced in the management of type 2 diabetes (Padwal et al., 2011). Bodyweight gain (thiazolidinediones, sulphonylureas, and insulin), hypoglycemia (sulphonylureas, repaglinides, and insulin), and gastrointestinal side effects (metformin and alpha glucosidase inhibitors) are some of the problems with current treatment management (Pontiroli & Morabito, 2011).

GLP-1 (glucagon-like peptide-1) is a gut hormone produced from the intestine in response to meal consumption. GLP-1-based therapy was

Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications(MECSJ)
Issues 66 (2023)
ISSN: 2616-9185

recently announced as a new therapeutic option for people with type 2 diabetes. GLP-1 treatment increases endogenous insulin release caused by meal intake while inhibiting glucagon secretion, promoting glucose homoeostasis. Notably, it reduces food intake and appetite. Trials in type 2 diabetes patients reveal that agonists of the GLP-1 receptor (GLP-1R) have favorable effects on metabolic control and may result in weight reduction (Bolen et al., 2007).

The rapid rise in obesity rates poses a serious danger to public health. In European Union nations, 30-70% of adults are overweight, while 10-30% is obese. Since 1980, the incidence has increased in several European regions. Furthermore, the prevalence of overweight and obesity among children and adolescents has increased drastically from 4% in 1975 to slightly more than 18% in 2016. In 2016, nearly 340 million children and adolescents aged 5 to 19 were overweight or obese. In 2019, 38.2 million children under the age of five were expected to be overweight or obese (Styne et al., 2017).The estimated percentage of obese adolescents who become overweight/obesity adults ranged from 24% to 90% (Singh et al., 2008).

At the age of two, extremely obese children have a 20% chance of not becoming fat by the age of 35, and by the age of five, the likelihood has reduced to 10%. The permanence of heightened risk is striking: a fat 2-year-old is more likely to be obese at 35 than an overweight 19-year-old

Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications(MECSJ)
Issues 66 (2023)
ISSN: 2616-9185

(Ward et al., 2017). If present trends continue, more than 1.1 billion people will be obese by 2030, which is about 2.5 times the number of adults currently living with diabetes (Jepsen et al., 2021).

As a result of the obesity epidemic, a significant cardiometabolic, oncological, psychological, and economical burden will continue to grow (Di Cesare et al., 2017). Obesity increases the risk of developing early puberty in children and adolescents (De Leonibus et al., 2012), menstrual irregularities in adolescent girls [67, 68], obstructive sleep apnea [69], and cardiovascular risk factors such as prediabetes, type 2 diabetes mellitus, high cholesterol levels, hypertension, nonalcoholic fatty liver disease, and metabolic syndrome. Furthermore, obese children and adolescents have psychological problems such as sadness, anxiety, low self-esteem, body image and peer interactions, and eating disorders. Obesity, with its increased all-cause morbidity and death, reduced quality of life, and decreased national production, should be characterized as one of the key initiatives to battle the growing noncommunicable disease epidemic across the lifespan beginning in infancy (Rankin et al., 2016).

Recognizing obesity as a chronic progressive disease by relevant organizations is a critical first step in advocating for effective obesity healthcare management and treatment. The primary aims of adult obesity treatment are to prevent problems by keeping the patient metabolically fit, to prevent or cure comorbidities if they already exist, to combat stigma, and to restore well-being, positive body image, and self-esteem.

Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications(MECSJ)
Issues 66 (2023)
ISSN: 2616-9185

Body weight reduction is not seen as a top concern. Treatment objectives should be adjusted to the complications. Adults should always be offered predicted weight loss as a signal of what may be accomplished to reduce cardiometabolic risks (Frühbeck et al., 2016).

It is more difficult to identify such immediate therapy goals customized to the difficulties in the juvenile population. A change in the standard deviation score of the body mass index (BMI) of at least 0.2 has been indicated to be clinically relevant in children and adolescents, but the data are sparse and ambiguous (Grossman et al., 2017). The US Preventive Services Task Force reported that complete intensive lifestyle treatment that resulted in a 0.17 change in the mean BMI standard deviation score did not result in concomitant improvements in cardiometabolic indicators (Ells et al., 2017). Exenatide, on the other hand, resulted in improvements in glucose and cholesterol levels despite a minor reduction in the BMI standard deviation score difference of 0.09 (Wiegand et al., 2015). To further establish clinically relevant treatment goals in the juvenile population, the particular relevance of different weight management techniques and long-term follow-up regarding risk reduction for obesity-related comorbidities should be examined.

Governments and communities should prioritize public health strategies that optimize lifestyle intervention (LSI) and reduce responsible environmental exposures for the prevention and treatment of childhood obesity (Bergsten et al., 2020). However, LSI is frequently insufficient in

Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications(MECSJ)
Issues 66 (2023)
ISSN: 2616-9185

the treatment of obesity. There is still a subset of children and adolescents that are resistant to lifestyle interventions. The need for safe and efficient weight-loss medications is obvious for these poor responders. Recognizing that aberrant satiety and eating signals inside the brain contributes to successful treatment methods that target central nervous system processes via glucagon-like peptide-1 (GLP-1) agonism (Cardel et al., 2020). Following the encouraging findings in the adult population with and without type 2 diabetes, evidence on the efficacy and safety of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in juvenile obesity have been accumulating over the last decade (Jensterle et al., 2021).

4.1 The Current Position of GLP-1 RA for the Weight Management

GLP-1 RA for overweight and obesity should be used as an addition to lifestyle therapy rather than as a stand-alone treatment, with the goal of producing higher weight reduction and weight loss maintenance as compared to lifestyle therapy alone (Garvey et al., 2016). Pharmacotherapy is appropriate for adult patients with a BMI more than 30 kg/m2 or a BMI greater than 27 kg/m2 with comorbidities. Anti-obesity medications have responders and nonresponders. After three months of therapy, nondiabetic individuals should lose 5% of their body weight and diabetic patients should lose more than 3%. If this is not the case, the anti-obesity medication should be discontinued. Weight loss

Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications(MECSJ)
Issues 66 (2023)
ISSN: 2616-9185

medications should be avoided during pregnancy, breastfeeding, and childhood (Durrer Schutz et al., 2019). Clinicians should consider differences in efficacy, side effects, cautions, and warnings that characterize medications approved for chronic management of obesity, as well as the presence of weight-related complications and medical history, when selecting the optimal weight loss medication for each patient; these factors are the basis for individualized weight loss pharmacotherapy; and a generalizable hierarchical algorithm for medication preferences that would be applicable to all patients (Jensterle et al., 2021).

Obesity prevention and lifestyle weight management therapies, such as instructional exercise and nutritional education, promotion of healthy alternatives, and behavioral counseling, are the cornerstones of obesity management in children. Rather than addressing obesity as an individual problem, it is critical to approach this issue through the lens of the family unit (Kansra et al., 2021).

Although these interventions have the potential to be extremely beneficial in select individuals in the right situation, they have evident limits and may benefit from additional techniques or therapies (Ryan et al., 2021). Adolescents are only offered bariatric surgery if they are severely obese, and it is performed seldom (Bolling et al., 2019). Liraglutide, the first and so far only class of GLP-1 RA, was approved by the FDA in 2020 for use in children aged 12-17 years with obesity (weight >60 kg and BMI >30 kg/m2 according to international criteria 10/95th percentile). Currently,

Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications(MECSJ)
Issues 66 (2023)
ISSN: 2616-9185

the EMA has not authorized any pharmacotherapeutic medicines for childhood obesity. A double-blind placebo-controlled phase 3 study is under underway to assess the effectiveness and safety of liraglutide 3.0 mg on weight management in children aged 6-12 years (Clinicaltrials.gov ID: NCT04775082). A phase 2 trial evaluating the efficacy of liraglutide in adolescents (12-20 years) with obesity after sleeve gastrectomy is also underway, as is a double-blind placebo-controlled phase 3 trial evaluating the efficacy and safety of semaglutide 2.4 mg once weekly in the treatment of adolescents with overweight and obesity (Jensterle et al., 2021).

Taha et al (2022) conducted a study discussing the role of GLP-1RAs in obesity management. Two subcutaneous GLP-1RAs, liraglutide and semaglutide, have been evaluated in several weight loss clinical trials. Liraglutide achieves an average weight loss of 4-7 kg, and over 50% of treated individuals achieve 5% or greater weight loss. Semaglutide has a greater effect on weight loss, with the average weight loss being 9-16 kg, and over 50% of treated individuals achieving 10-15% or greater weight loss. These results led to regulatory approval of these agents for weight loss in obese individuals, regardless of diabetic status. In addition to weight loss, the benefits of GLP-1RAs extend to other risk factors, such as controlling blood sugar and blood pressure. Gastrointestinal symptoms are the most frequently encountered adverse events with a frequency of between 5 and 30%. Finally, cost remains one of the most important

Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications(MECSJ)
Issues 66 (2023)
ISSN: 2616-9185

challenges limiting the use of GLP-1RAs. The study showed that GLP-1RAs have powerful benefits in weight loss and are expected to have a critical role in the management of obesity in the coming years. Upcoming studies will evaluate the durability of weight loss achieved with GLP-1RAs and the effect on cardiovascular outcomes (Taha et al., 2023).

Both GLP-1RAs and SGLT-2is are recommended as medication options in type 2 diabetes mellitus patients with overweight or obesity Semaglutide 2.4mg showed the greatest effects on losing body weight, controlling glycaemic level and reducing blood pressure while it was associated with high risk of adverse events. In terms of serious adverse events GLP-1RAs were associated with a higher risk of SAEs compared to placebo in a network metaanalysis, but there was no significant difference between SGLT-2RAs and placebo. In obese patients or with no diabetes, major reduction of body weight, HgA1c and FPG has been observed for both GLP-1RAs and SGLT2Is (Ma et al., 2023).

Based on the Look AHEAD (Action for health in diabetes; ClinicalTrials.gov Identifier: NCT00017953) trial, which showed that weight loss of more than 5 % is associated with improvements in different surrogate markers for cardiovascular disease such as blood pressure and lipids. Look ARG, Wing RR. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: Four-year results of the Look AHEAD trial (Williamset al., 2022).

Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications(MECSJ)
Issues 66 (2023)
ISSN: 2616-9185

The results of the network meta-analysis by Alkhezi et al. also showed that tirzepatide produced better weight loss in non-diabetic patients compared with liragrutide and semaglutide, and the safety results were similar with no difference. Alkhezi O.S., et al., Comparative effectiveness of glucagon-like peptide-1 receptor agonists for the management of obesity in adults without diabetes: A network meta-analysis of randomized clinical trials (Lin et al., 2023).

5. Conclusion

GLP-1RAs appear to be an effective therapy option for weight control in persons with antipsychotic-related obesity, improving glycemia and lipid profile parameters. Given its potential benefits in lowering weight in addition to glycemic management, GLP-1 agonists may soon contribute to the treatment of obesity in both diabetic and non-diabetic persons. However, further research investigations, namely big clinical trials, are necessary to extend and fully explain the beneficial effects and potential negative effects of GLP-1 agonists. Current therapies for type 2 diabetes patients include flaws (weight gain, hypoglycemia, and other side effects) that restrict the number of patients who achieve acceptable therapeutic goals. The current meta-analysis offers solid evidence that GLP-1R agonists have clinically relevant positive effects on body weight when administered to obese people with or without diabetes .

Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications(MECSJ)
Issues 66 (2023)
ISSN: 2616-9185

There is considerable interest in the present usage and continuing development of obesity therapies based on GLP-1 agonism, which have been shown to reduce morbidity and mortality in the adult population. Obesity prevention and LSI within the family unit are the cornerstones of anti-obesity treatment in children. Pediatricians now have nothing to give patients who are resistant to lifestyle changes. GLP-1 RA seems to be safe and mildly beneficial in lowering weight and improving cardiometabolic profile in children with obesity who do not respond to LSI alone.

Although this comprehensive analysis discovered that GLP-1 agonists have a good effect on weight loss, physicians must write prescriptions with caution to avoid potential adverse effects of the GLP-1 agonists while providing an opportunity for the general health of obese persons with or without diabetes. Additional benefits to blood pressure and total cholesterol may be obtained. Patients with diabetes who are fat or overweight should consider the intervention. More research is needed to determine the impact of GLP-1R agonists in the treatment of obese persons who do not have diabetes. Since of the scarcity of data, a general advice is to favor long acting GLP-1 RA over short acting GLP-1 RA since they are licensed for the treatment of obesity and have greater tolerability, safety, and therapeutic response impact. New studies are being conducted to collect pediatric data, including long acting GLP-1

Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications(MECSJ)
Issues 66 (2023)
ISSN: 2616-9185

RA semaglutide. Future semaglutide studies are being planned in order to offer conclusive answers to this intriguing and demanding therapy topic.

Reference

- Aldahash, R. (2021). Efficacy of glucagon-like peptide-1 receptor agonists in the weight loss among obese individuals: A systematic review. Journal of Endocrinology and Metabolism, 11(5), 95-107.
- Ard, J., Fitch, A., Fruh, S., & Herman, L. (2021). Weight loss and maintenance related to the mechanism of action of glucagon-like peptide 1 receptor agonists. Advances in therapy, 38(6), 2821-2839.
- Baden, C. S., Andersen, J. T., Christensen, M. B., & Gade, C. (2023). Safety of glucagon-like peptide-1 receptor agonists for weight management in adults, adolescents, and children with obesity: a scoping review. Adverse Drug Reaction Bulletin, 339(1), 1315-1318.
- Bailey, C., Skouteris, H., Teede, H., Hill, B., De Courten, B., Walker, R., ... & Ademi, Z. (2020). Are lifestyle interventions to reduce excessive gestational weight gain cost effective? A systematic review. Current Diabetes Reports, 20, 1-16.
- Blackman, A., Foster, G. D., Zammit, G., Rosenberg, R., Aronne, L., Wadden, T., ... & Mignot, E. (2016). Effect of liraglutide 3.0 mg in individuals with obesity and moderate or severe obstructive

Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications(MECSJ)
Issues 66 (2023)
ISSN: 2616-9185

sleep apnea: the SCALE Sleep Apnea randomized clinical trial. International journal of obesity, 40(8), 1310-1319.

- Bolen, S., Feldman, L., Vassy, J., Wilson, L., Yeh, H. C., Marinopoulos, S., ... & Brancati, F. L. (2007). Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. Annals of internal medicine, 147(6), 386-399.
- Bolling, C. F., Armstrong, S. C., Reichard, K. W., Michalsky, M. P., Haemer, M. A., Muth, N. D., ... & Gow, K. W. (2019). Metabolic and bariatric surgery for pediatric patients with severe obesity. Pediatrics, 144(6).
- Buse, J. B., Nauck, M., Forst, T., Sheu, W. H., Shenouda, S. K., Heilmann, C. R., ... & Schernthaner, G. (2013). Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. The Lancet, 381(9861), 117-124.
- Cardel, M. I., Atkinson, M. A., Taveras, E. M., Holm, J. C., & Kelly, A. S. (2020). Obesity treatment among adolescents: a review of current evidence and future directions. JAMA pediatrics, 174(6), 609-617.
- Chaimani, A., Higgins, J. P., Mavridis, D., Spyridonos, P., & Salanti, G. (2013). Graphical tools for network meta-analysis in STATA. PloS one, 8(10), e76654.
- Davies, M., Færch, L., Jeppesen, O. K., Pakseresht, A., Pedersen, S. D., Perreault, L., ... & Lingvay, I. (2021). Semaglutide 2· 4 mg

Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications(MECSJ)
Issues 66 (2023)
ISSN: 2616-9185

once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. The Lancet, 397(10278), 971-984.

- De Leonibus, C., Marcovecchio, M. L., & Chiarelli, F. (2012). Update on statural growth and pubertal development in obese children. Pediatric reports, 4(4), e35.
- Di Cesare, M., Sorić, M., Bovet, P., Miranda, J. J., Bhutta, Z., Stevens, G. A., ... & Bentham, J. (2019). The epidemiological burden of obesity in childhood: a worldwide epidemic requiring urgent action. BMC medicine, 17, 1-20.
- Durrer Schutz, D., Busetto, L., Dicker, D., Farpour-Lambert, N., Pryke, R., Toplak, H., ... & Schutz, Y. (2019). European practical and patient-centred guidelines for adult obesity management in primary care. Obesity facts, 12(1), 40-66.
- Eeg-Olofsson, K., Cederholm, J., Nilsson, P. M., Zethelius, B., Nunez, L., Gudbjörnsdóttir, S., & Eliasson, B. (2009). Risk of cardiovascular disease and mortality in overweight and obese patients with type 2 diabetes: an observational study in 13,087 patients. Diabetologia, 52, 65-73.
- Ells, L. J., Rees, K., Brown, T., Mead, E., Al-Khudairy, L., Azevedo, L., ... & Demaio, A. (2018). Interventions for treating children and adolescents with overweight and obesity: an overview

Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications(MECSJ)
Issues 66 (2023)
ISSN: 2616-9185

of Cochrane reviews. International journal of obesity, 42(11), 1823-1833.

- Finucane, M. M., Stevens, G. A., Cowan, M. J., Danaei, G., Lin, J. K., Paciorek, C. J., ... & Ezzati, M. (2011). National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9· 1 million participants. The lancet, 377(9765), 557-567.
- Franz, M. J., VanWormer, J. J., Crain, A. L., Boucher, J. L., Histon, T., Caplan, W., ... & Pronk, N. P. (2007). Weight-loss outcomes: a systematic review and meta-analysis of weight-loss clinical trials with a minimum 1-year follow-up. Journal of the American Dietetic association, 107(10), 1755-1767.
- Frühbeck, G., Sbraccia, P., Nisoli, E., Woodward, E., Yumuk, V., Farpour-Lambert, N. J., ... & Carruba, M. O. (2016). 2015 Milan declaration: a call to action on obesity-an EASO position statement on the occasion of the 2015 EXPO. Obesity Facts, 9(4), 296-298.
- Garvey, W. T., Birkenfeld, A. L., Dicker, D., Mingrone, G., Pedersen, S. D., Satylganova, A., ... & Mosenzon, O. (2020). Efficacy and safety of liraglutide 3.0 mg in individuals with overweight or obesity and type 2 diabetes treated with basal insulin: the SCALE insulin randomized controlled trial. Diabetes care, 43(5), 1085-1093.

Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications(MECSJ)
Issues 66 (2023)
ISSN: 2616-9185

- Garvey, W. T., Mechanick, J. I., Brett, E. M., Garber, A. J., Hurley, D. L., Jastreboff, A. M., ... & Plodkowski, R. (2016). American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. Endocrine Practice, 22, 1-203.
- Gourlan, M. J., Trouilloud, D. O., & Sarrazin, P. G. (2011). Interventions promoting physical activity among obese populations: a meta-analysis considering global effect, long-term maintenance, physical activity indicators and dose characteristics. Obesity Reviews, 12(7), e633-e645.
- Grossman, D. C., Bibbins-Domingo, K., Curry, S. J., Barry, M. J., Davidson, K. W., Doubeni, C. A., ... & US Preventive Services Task Force. (2017). Screening for obesity in children and adolescents: US Preventive Services Task Force recommendation statement. Jama, 317(23), 2417-2426.
- Hope, D. C., Tan, T. M., & Bloom, S. R. (2018). No guts, no loss: toward the ideal treatment for obesity in the twenty-first century. Frontiers in endocrinology, 9, 442.
- https://doi.org/10.1080/14728214.2021.1947240
- Jensterle, M., & Janež, A. (2021). Glucagon-like peptide-1 receptor agonists in the treatment of obesity. Hormone Research in Pædiatrics, 1-10.

Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications(MECSJ)
Issues 66 (2023)
ISSN: 2616-9185

- Jensterle, M., & Janež, A. (2021). Glucagon-like peptide-1 receptor agonists in the treatment of obesity. Hormone Research in Pædiatrics, 1-10.
- Jepsen MM, Christensen MB. Emerging glucagon-like peptide 1 receptor agonists for the treatment of obesity. Expert Opin Emerg Drugs. 2021 Sep;26(3):231–43.
- Jepsen, M. M., & Christensen, M. B. (2021). Emerging glucagon-like peptide 1 receptor agonists for the treatment of obesity. Expert opinion on emerging drugs, 26(3), 231-243.
- Kanoski, S. E., Rupprecht, L. E., Fortin, S. M., De Jonghe, B. C., & Hayes, M. R. (2012). The role of nausea in food intake and body weight suppression by peripheral GLP-1 receptor agonists, exendin-4 and liraglutide. Neuropharmacology, 62(5-6), 1916-1927.
- Kansra, A. R., Lakkunarajah, S., & Jay, M. S. (2021). Childhood and adolescent obesity: A review. Frontiers in pediatrics, 8, 866.
- Kelly, A. S., Metzig, A. M., Rudser, K. D., Fitch, A. K., Fox, C. K., Nathan, B. M., ... & Schwarzenberg, S. J. (2012). Exenatide as a weight-loss therapy in extreme pediatric obesity: a randomized, controlled pilot study. Obesity, 20(2), 364-370.
- Kelly, A. S., Rudser, K. D., Nathan, B. M., Fox, C. K., Metzig, A. M., Coombes, B. J., ... & Abuzzahab, M. J. (2013). The effect of glucagon-like peptide-1 receptor agonist therapy on body mass

Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications(MECSJ)
Issues 66 (2023)
ISSN: 2616-9185

index in adolescents with severe obesity: a randomized, placebo-controlled, clinical trial. JAMA pediatrics, 167(4), 355-360.

- Kushner, R. F., Calanna, S., Davies, M., Dicker, D., Garvey, W. T., Goldman, B., ... & Rubino, D. (2020). Semaglutide 2.4 mg for the treatment of obesity: key elements of the STEP trials 1 to 5. Obesity, 28(6), 1050-1061.
- Lau, J., Bloch, P., Schäffer, L., Pettersson, I., Spetzler, J., Kofoed, J., ... & Kruse, T. (2015). Discovery of the once-weekly glucagon-like peptide-1 (GLP-1) analogue semaglutide. Journal of medicinal chemistry, 58(18), 7370-7380.
- Le Roux, C. W., Astrup, A., Fujioka, K., Greenway, F., Lau, D. C., Van Gaal, L., ... & Farrell, J. (2017). 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. The Lancet, 389(10077), 1399-1409.
- Lin, F., Yu, B., Ling, B., Lv, G., Shang, H., Zhao, X., ... & Li, Y. (2023). Weight loss efficiency and safety of tirzepatide: A Systematic review. Plos one, 18(5), e0285197.
- Lu, G., & Ades, A. E. (2004). Combination of direct and indirect evidence in mixed treatment comparisons. Statistics in medicine, 23(20), 3105-3124.
- Ma, H., Lin, Y. H., Dai, L. Z., Lin, C. S., Huang, Y., & Liu, S. Y. (2023). Efficacy and safety of GLP-1 receptor agonists versus SGLT-2 inhibitors in overweight/obese patients with or without

Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications(MECSJ)
Issues 66 (2023)
ISSN: 2616-9185

diabetes mellitus: a systematic review and network meta-analysis. BMJ open, 13(3), e061807.

- Mastrandrea, L. D., Witten, L., Carlsson Petri, K. C., Hale, P. M., Hedman, H. K., & Riesenberg, R. A. (2019). Liraglutide effects in a paediatric (7-11 y) population with obesity: A randomized, double-blind, placebo-controlled, short-term trial to assess safety, tolerability, pharmacokinetics, and pharmacodynamics. Pediatric obesity, 14(5), e12495.
- Maula, A., Kai, J., Woolley, A. K., Weng, S., Dhalwani, N., Griffiths, F. E., ... & Kendrick, D. (2020). Educational weight loss interventions in obese and overweight adults with type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. Diabetic Medicine, 37(4), 623-635.
- Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & Prisma Group. (2010). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. International journal of surgery, 8(5), 336-341.
- Nauck, M. A., & Meier, J. J. (2019). Management of endocrine disease: are all GLP-1 agonists equal in the treatment of type 2 diabetes?. European journal of endocrinology, 181(6), R211-R234.
- O'Connor, E. A., Evans, C. V., Burda, B. U., Walsh, E. S., Eder, M., & Lozano, P. (2017). Screening for obesity and intervention for weight management in children and adolescents: evidence

Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications(MECSJ)
Issues 66 (2023)
ISSN: 2616-9185

report and systematic review for the US Preventive Services Task Force. Jama, 317(23), 2427-2444.

- Padwal, R., Klarenbach, S., Wiebe, N., Birch, D., Karmali, S., Manns, B., ... & Tonelli, M. (2011). Bariatric surgery: a systematic review and network meta-analysis of randomized trials. Obesity reviews, 12(8), 602-621.
- Pi-Sunyer, X., Astrup, A., Fujioka, K., Greenway, F., Halpern, A., Krempf, M., ... & Wilding, J. P. (2015). A randomized, controlled trial of 3.0 mg of liraglutide in weight management. New England Journal of Medicine, 373(1), 11-22.
- Pontiroli, A. E., & Morabito, A. (2011). Long-term prevention of mortality in morbid obesity through bariatric surgery. A systematic review and meta-analysis of trials performed with gastric banding and gastric bypass. Annals of surgery, 253(3), 484-487.
- Rankin, J., Matthews, L., Cobley, S., Han, A., Sanders, R., Wiltshire, H. D., & Baker, J. S. (2016). Psychological consequences of childhood obesity: psychiatric comorbidity and prevention. Adolescent health, medicine and therapeutics, 125-146.
- Ryan, P. M., Seltzer, S., Hayward, N. E., Rodriguez, D. A., Sless, R. T., & Hawkes, C. P. (2021). Safety and efficacy of glucagon-like peptide-1 receptor agonists in children and adolescents with obesity: a meta-analysis. The Journal of Pediatrics, 236, 137-147.
- Salanti, G., Ades, A. E., & Ioannidis, J. P. (2011). Graphical methods and numerical summaries for presenting results from

Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications(MECSJ)
Issues 66 (2023)
ISSN: 2616-9185

multiple-treatment meta-analysis: an overview and tutorial. Journal of clinical epidemiology, 64(2), 163-171.

- Seino, Y., Yabe, D., Takami, A., Niemoeller, E., & Takagi, H. (2015). Long-term safety of once-daily lixisenatide in Japanese patients with type 2 diabetes mellitus: GetGoal-Mono-Japan. Journal of Diabetes and its Complications, 29(8), 1304-1309.
- Shin, S. J. (2012). Glucagon-like peptide-1 receptor agonists and their effects on weight reduction. Journal of Diabetes Investigation, 3(6), 490.
- Singh, A. S., Mulder, C., Twisk, J. W., Van Mechelen, W., & Chinapaw, M. J. (2008). Tracking of childhood overweight into adulthood: a systematic review of the literature. Obesity reviews, 9(5), 474-488.
- Styne, D. M., Arslanian, S. A., Connor, E. L., Farooqi, I. S., Murad, M. H., Silverstein, J. H., & Yanovski, J. A. (2017). Pediatric obesity—assessment, treatment, and prevention: an Endocrine Society clinical practice guideline. The Journal of Clinical Endocrinology & Metabolism, 102(3), 709-757.
- Sun, F., Chai, S., Li, L., Yu, K., Yang, Z., Wu, S., ... & Zhan, S. (2015). Effects of glucagon-like peptide-1 receptor agonists on weight loss in patients with type 2 diabetes: a systematic review and network meta-analysis. Journal of diabetes research, 2015.

Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications(MECSJ)
Issues 66 (2023)
ISSN: 2616-9185

- Taha, M. B., Yahya, T., Satish, P., Laird, R., Agatston, A. S., Cainzos-Achirica, M., ... & Nasir, K. (2022). Glucagon-like peptide 1 receptor agonists: a medication for obesity management. Current Atherosclerosis Reports, 24(8), 643-654.
- Tamborlane, W. V., Barrientos-Pérez, M., Fainberg, U., Frimer-Larsen, H., Hafez, M., Hale, P. M., ... & Barrett, T. (2019). Liraglutide in children and adolescents with type 2 diabetes. New England Journal of Medicine, 381(7), 637-646.
- van Valkenhoef, G., Lu, G., de Brock, B., Hillege, H., Ades, A. E., & Welton, N. J. (2012). Automating network meta-analysis. Research synthesis methods, 3(4), 285-299.
- Vilsbøll, T., Christensen, M., Junker, A. E., Knop, F. K., & Gluud, L. L. (2012). Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials. Bmj, 344.
- Wadden, T. A., Bailey, T. S., Billings, L. K., Davies, M., Frias, J. P., Koroleva, A., ... & STEP 3 Investigators. (2021). Effect of subcutaneous semaglutide vs placebo as an adjunct to intensive behavioral therapy on body weight in adults with overweight or obesity: the STEP 3 randomized clinical trial. Jama, 325(14), 1403-1413.
- Wadden, T. A., Hollander, P., Klein, S., Niswender, K., Woo, V., Hale, P. M., & Aronne, L. (2013). Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-

Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications(MECSJ)
Issues 66 (2023)
ISSN: 2616-9185

induced weight loss: the SCALE Maintenance randomized study. International journal of obesity, 37(11), 1443-1451.

- Ward, Z. J., Long, M. W., Resch, S. C., Giles, C. M., Cradock, A. L., & Gortmaker, S. L. (2017). Simulation of growth trajectories of childhood obesity into adulthood. New England Journal of Medicine, 377(22), 2145-2153.
- Weghuber, D., Forslund, A., Ahlström, H., Alderborn, A., Bergström, K., Brunner, S., ... & Bergsten, P. (2020). A 6-month randomized, double-blind, placebo-controlled trial of weekly exenatide in adolescents with obesity. Pediatric Obesity, 15(7), e12624.
- Wiegand, S., Keller, K. M., Lob-Corzilius, T., Pott, W., Reinehr, T., Röbl, M., ... & Holl, R. W. (2015). Predicting weight loss and maintenance in overweight/obese pediatric patients. Hormone research in paediatrics, 82(6), 380-387.
- Wilding, J. P., Batterham, R. L., Calanna, S., Davies, M., Van Gaal, L. F., Lingvay, I., ... & Kushner, R. F. (2021). Once-weekly semaglutide in adults with overweight or obesity. New England Journal of Medicine, 384(11), 989-1002.
- Williams, D. M., Staff, M., Bain, S. C., & Min, T. (2022). Glucagon-like peptide-1 receptor analogues for the treatment of obesity. touchREVIEWS in Endocrinology, 18(1), 43.
- World Health Organization (2011). Obesity and overweight. Available at: www.who.int/mediacentre/factsheets.

Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications(MECSJ)
Issues 66 (2023)
ISSN: 2616-9185

- Wu, H., & Ballantyne, C. M. (2020). Metabolic inflammation and insulin resistance in obesity. Circulation research, 126(11), 1549-1564.