زانکۆی سەلاحەدین-هەولێر
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A study of the role of saxenda in female weight loss, with a study of the most important side

Research Project
Submitted to the Department of (Chemistry) in partial fulfillment
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بِسْمِ اللَّـهِ الرَّحْمَـٰنِ الرَّحِيمِ

يَا أَيُّهَا الَّذِينَ آمَنُوا إِذَا قِيلَ لَكُمْ تَفَسَّحُوا فِي الْمَجَالِسِ فَافْسَحُوا يَفْسَحِ اللَّهُ لَكُمْ وَإِذَا قِيلَ انْشُزُوا فَانْشُزُوا يَرْفَعِ اللَّهُ الَّذِينَ آمَنُوا مِنْكُمْ وَالَّذِينَ أُوتُوا الْعِلْمَ دَرَجَاتٍ وَاللَّهُ بِمَا تَعْمَلُونَ خَبِيرٌ ﴿١١﴾

صدق الله العظيم

سورة المجادلة \ لأية 11

AKNOLDGMENT

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Abstract

The main purpose of this study to investigate whether to lose weight and keep the weight off, it is used together with diet and exercise.

Obesity is a chronic disease universally defined as an excess of adipose tissue resulting in body mass index (BMI) > 30.0 kg/m2. Over the past few years, the concept of prevention has gained increased awareness, thus lead- ing to the development of additional pharmaceutical op- tions for the treatment of obesity since 2012. Treating obesity revolves around an individualized, multi-disci- plinary approach with additional focus on a healthy and supportive lifestyle to maintain the weight loss. Saxenda® (liraglutide) injection 3 mg is an injectable prescription medicine used for adults with excess weight (BMI ≥27).

KEYWORDS: obesity, Saxenda(liraglutide), overweight, anti-obesity therapies, weight-loss medications

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BMI = body mass index

GLP-1 = Glucagon-like peptide-1

PCOS = polycystic ovarian syndrome

Chapter one Introduction

1.1 Obesity

-Is an epidemic disease that threatens to inundate health care resources by increasing the incidence of diabetes, heart disease, hypertension, and cancer. These effects of obesity result from two factors: the increased mass of adipose tissue and the increased secretion of pathogenetic products from enlarged fat cells. This concept of the pathogenesis of obesity as a disease allows an easy division of disadvantages of obesity into those produced by the mass of fat and those produced by the metabolic effects of fat cells. In the former category are the social disabilities resulting from the stigma associated with obesity, sleep apnea that results in part from increased Para pharyngeal fat deposits, and osteoarthritis resulting from the wear and tear on joints from carrying an increased mass of fat. The second category includes the metabolic factors associated with distant effects of products released from enlarged fat cells. The insulin-resistant state that is so common in obesity probably reflects the effects of increased release of fatty acids from fat cells that are then stored in the liver or muscle. When the secretory capacity of the pancreas is overwhelmed by battling insulin resistance, diabetes develops. The strong association of increased fat,

Figure 1: obese man

especially visceral fat, with diabetes makes this consequence particularly ominous for health care costs. The release of cytokines, particularly IL-6, from the fat cell may stimulate the pro-inflammatory state that characterizes obesity. The increased secretion of prothrombin activator inhibitor-1 from fat cells may play a role in the procoagulant state of obesity and, along with changes in endothelial function, may be responsible for the increased risk of cardiovascular disease and hypertension. For cancer, the production of estrogens by the enlarged stromal mass plays a role in the risk for breast cancer. Increased cytokine release may play a role in other forms of proliferative growth. The combined effect of these pathogenetic consequences of increased fat stores is an increased risk of shortened life expectancy. (Bray,2004)

1.2 Obesity and epidemic

Several environmental factors contribute to the obesity epidemic that is now being observed among children: the sustained excess of energy-dense foods with refined carbohydrates and high saturated fat (the age groups between 0 and 19 years are those with the highest intake of saturated fats per total calories consumed), as well as insufficient consumption of fruit and vegetables. The impact of these nutritional factors is further aggravated by an increasingly sedentary lifestyle attributed in part to urbanization, which limits the opportunities for physical activity, and the predominance of electronic entertainment over

physical activity. In addition to these external influences, a genetic predisposition for obesity has often been discussed as a contributing factor for the increasing prevalence of overweight. However, it is unlikely that genetic background would explain the growing obesity epidemic of the past several years; a population gene pool does not change significantly within a decade. Twin studies suggest that only a minor proportion of the tendency toward obesity is inherited, and the primary genetic disorders presenting with childhood obesity (PraderLabhart-Willi syndrome, Bardet-Biedl syndrome, etc.) are extremely rare.(Gielen and hanbrecht,2004)

1.3 Obesity and disease

Obesity in women is associated with alterations in the reproductive cycle with a reduction in fertility, as well as an increased risk of polycystic ovarian syndrome (PCOS) and infrequent or no ovulation. Overweight women with PCOS have a tendency towards insulin resistance and are prone to developing diabetes, particularly in later life. All these issues make the treatment of infertility more complicated and less successful. Furthermore, the tendency toward menstrual and ovarian disturbances associated with obesity may predispose to an increased risk of ovarian, breast and endometrial cancer. In fact, it is now clear the incidence of all gynaecological cancer increases with increasing BMI. Maternal obesity during pregnancy is also fraught with risks to both the mother and baby. Adverse maternal outcomes associated with obesity include an increased risk of spontaneous miscarriage, gestational diabetes, hypertensive disease of pregnancy including gestational protein uric hypertension with multi-system consequences. Pregnancy is more likely to be prolonged, while labour is more likely to be difficult requiring operative delivery which brings increased risk of infection, Maternal obesity also confers an elevated risk of congenital abnormalities, particularly congenital heart disease and neural tube defects.

Figure 2: Pregnant women

- The obese woman is also less likely to succeed in breastfeeding, requiring resort to artificial feeding which in itself increases the risk of childhood obesity. Thus maternal obesity has been shown to have significant short and long term consequences for both mother and child and it is now clear that timely lifestyle interventions introduced before becoming pregnant and maintained throughout pregnancy may help to mitigate complications in both. By improving the intrauterine nutritional milieu of the developing foetus, it may be possible to improve the child’s general health and thereby reduce the risk in later life of health problems associated with obesity, including circulatory and respiratory disease as well as mental health. All providers of maternity care and women’s health services should have advice available for all women and particularly those planning pregnancy. Lifestyle advice, particularly on dietary habits and

physical activity, should be available particularly to all overweight and obese women. The importance of these issues for the health of the next generation needs particular emphasis.

1.3.1 Diabetes and obesity

The term diabetes describes a group of metabolic disorders characterized and identified by the presence of hyper glycaemia in the absence of treatment. The heterogeneous aetio-pathology includes defects in insulin secretion, insulin action, or both, and disturbances of carbohydrate, fat and protein metabolism. The long-term specific effects of diabetes include retinopathy, nephropathy and neuropathy, among other complications. People with diabetes are also at increased risk of other diseases including heart, peripheral arterial and cerebrovascular disease, obesity, cataracts, erectile dysfunction, and nonalcoholic fatty liver disease. They are also at increased risk of some infectious diseases, such as tuberculosis. There are two major types: type 1 diabetes (T1DM) and type 2 diabetes (T2DM). There are several reasons for revisiting the diabetes classification. Firstly, the phenotypes of T1DM and T2DM are becoming less distinctive with an increasing prevalence of obesity at a young age, recognition of the relatively high proportion of incident cases of T1DM in adulthood and the occurrence of T2DM in young people. Secondly, developments in molecular genetics have allowed clinicians to identify growing numbers of subtypes of diabetes. (Khera et all.,2016) The World Health Organization in 2008 reported that more than 1.4 billion adults were overweight, BMI > 25 kg/m2, and more than half a billion were obese. This global epidemic has led to growing concerns, for adults, and for the increased rate in childhood obesity that predisposes them to become obese adults. Prevention is imperative regardless of age. (Curry,2017) Obesity is a significant concern in the United States, affecting approximately 35% of the population. Comorbidities, such as diabetes, hypertension, and hyperlipidemia, significantly increase one's risk of heart attack, stroke, and even death. Liraglutide, a medication originally used to treat diabetes, has been approved for the treatment of obesity. Clinical trials have shown significant improvements in body weight and body mass index (BMI) at a dose of up to 3.0 mg daily. The most common adverse effects are gastrointestinal in nature, however, these often subside with time. Safety concerns with regards to thyroid tumors and pancreatitis should be carefully considered prior to use of this agent. Liraglutide should be considered an additional tool in the treatment of obesity, especially in patients with concomitant diabetes. Although obesity rates do not appear to have significantly increased overall in the past decade, the rate of obesity in women over the age of 60 has increased significantly. This increased rate of obesity in older women corresponds to the two-fold increase in diabetes in persons aged 65 or older since 1980. The association between obesity and diabetes has been well studied, with obese men having a seven times greater chance of developing diabetes and obese women having a twelve fold increased risk. However, other comorbidities such as hypertension, hyperlipidemia, asthma, arthritis and general poor health have also been associated with obesity making it one of leading causes of preventable death. (Onge et all.,2016) The present 56-week randomized, double-blind, placebo controlled trial examined the efficacy of liraglutide for maintaining prior weight loss achieved with a low-calorie diet (LCD). Liraglutide, an analog of the incretions hormone glucagon-like peptide-1, is currently approved for the treatment of type 2 diabetes (T2D) at 1.2 or 1.8mg per day (once-daily subcutaneous injection). Liraglutide at the higher dose of 3.0 mg per day is currently under development for chronic weight management. In patients with T2D, treatment with liraglutide 1.8mg per day over 26 weeks resulted in weight losses up to 2.6 kg greater than placebo. In obese individuals without T2D, treatment with liraglutide (Finkelstein and vedghese,2018).0mg per day over 20 weeks resulted in a 4.4 kg greater mean weight loss than placebo and a 3.0 kg greater weight loss than Orlistat. Weight losses with liraglutide were sustained for up to 2 years with continued use of the medication. The present trial

provides the first evaluation of liraglutide for maintenance of prior weight loss achieved by treatment with a LCD in obese/overweight individuals without T2D. (Wadden et all.,2013)

1.4 Obesity and drug

Obesity is one of the world's most important public health problems, but the approved anti-obesity drugs are extremely limited. Currently, only two types of anti-obesity drugs for long term weight loss are on the market, pancreatic lipase inhibitors and central nervous system appetite suppressants. Those that can increase energy consumption and metabolism were withdrawn due to side effects. Until now, there are five drugs (Orlistat, phentermine/topiramate, lorcaserin, naltrexone/bupropion and liraglutide) approved for long-term use and four sympathomimetic drugs approved for short-term treatment of obesity by the US FDA. Medical treatment of obesity can be traced to the late 19th and early 20th century. Between 1887 and 1940 thyroid hormone, dinitrophenol and amphetamine were used to treat obesity. All of them were finally stopped due to side effects. Neuropathy and cataracts induced by dinitrophenol and trityl alcohol were named as one of the disasters caused by medicine in the 20th century. In the early 1950s, amphetamine and its congener methamphetamine, became widely abused street drugs. The side effects and addictive effect of them lead to the search for safer alternatives. Serotonergic agents like fenfluramine opened a new area of anti-obesity drugs, although the side effects like primary pulmonary hypertension lead to withdrawal later. Combination therapy for treatment of obesity was popular between 1973 and 1996, and one of the most popular combination drugs was d, l-fenfluramine and phentermine. However, they were removed from the market worldwide in 1997 because more than 30% of patients have the potential to develop valvular heart disease. (Chan,2019)

Table 1: currently approved anti-obesity drug

Name	Mechanism of Action	Average weight lost at 1 year (kg) vs.for placebo	Percentage of patients achieving > 5% loss of body weight at 1 year vs. for placebo	Safety warning	Contraindications
Liraglutide 3.0 mg	GLP-1 receptor agonist	7.4% (*vs*. 3.0% for placebo)	62.3% (*vs*. 34.4% for placebo)	Boxed warning: thyroid c-cell tumorsin rodents. Warnings: acute pancreatitis, acute gallbladder disease, serious hypoglycemia if used with insulin secretagogue, heart rate increase, use caution in renal impairment; hypersensitivity reactions can occur, monitor for depression or suicidal	Patients with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia, pregnancy

1.4.1 Liraglutide (Saxenda)

It has long been considered that analogs of naturally occurring gut hormones (GLP-1, oxyntomodulin, PYY) engaged in energy balance regulation may represent a specific and low side-effect approach in the treatment of obesity. Liraglutide is a GLP-1 receptor agonist that has 97% homology to native GLP-1. After approval by US FDA to treat type 2 diabetes at a 1.5 mg dosage in 2010, the 3.0 mg dosage of liraglutide (marked name Saxenda) was approved to treat obesity in December 2014. Phase III studies have shown that compared with placebo and cognitive behavioral intervention, Saxenda treatment can achieve more weight loss, in the range of 26% to 28%. Data confirm that after using Saxenda,

patients have shown improvements in systolic and diastolic blood pressure, LDL and triglycerides reduction, HDL cholesterol increasing and waist circumference reduction. Besides, Saxenda can improve glycemic control in a weight loss independent manor. As to the side effects, some patients have shown transient nausea and vomiting. Of note is that Saxenda can increase heart rate slightly, which is opposed by its cardio protective properties. A black box warning of Saxenda said it may increase the risk of thyroid C-cell tumors because Saxenda causes C-cell tumors in rodents but not in humans. Patients with a personal or family history of Multiple Endocrine Neoplasia or medullary thyroid carcinoma should

avoid liraglutide for safety concerns. As with all the other weight loss drugs, Saxenda is contraindicated in pregnancy or hypersensitivity patients. Clinical trials have shown the potential risks of mild or moderate pancreatitis; thus the drug should be stopped if acute pancreatitis is suspected. Phase 3 studies also report cholecystitis and cholelithiasis, but whether it was caused by the drug or weight loss is uncertain. (Chan,2019)

1.4.2 liraglutide properties

Molecular Formula: (C172H265N43O51)

Molecular Weight: 3751 g/mole

Exact Mass: 3749.9498161 g/mole

Figure 3: liraglutide structure

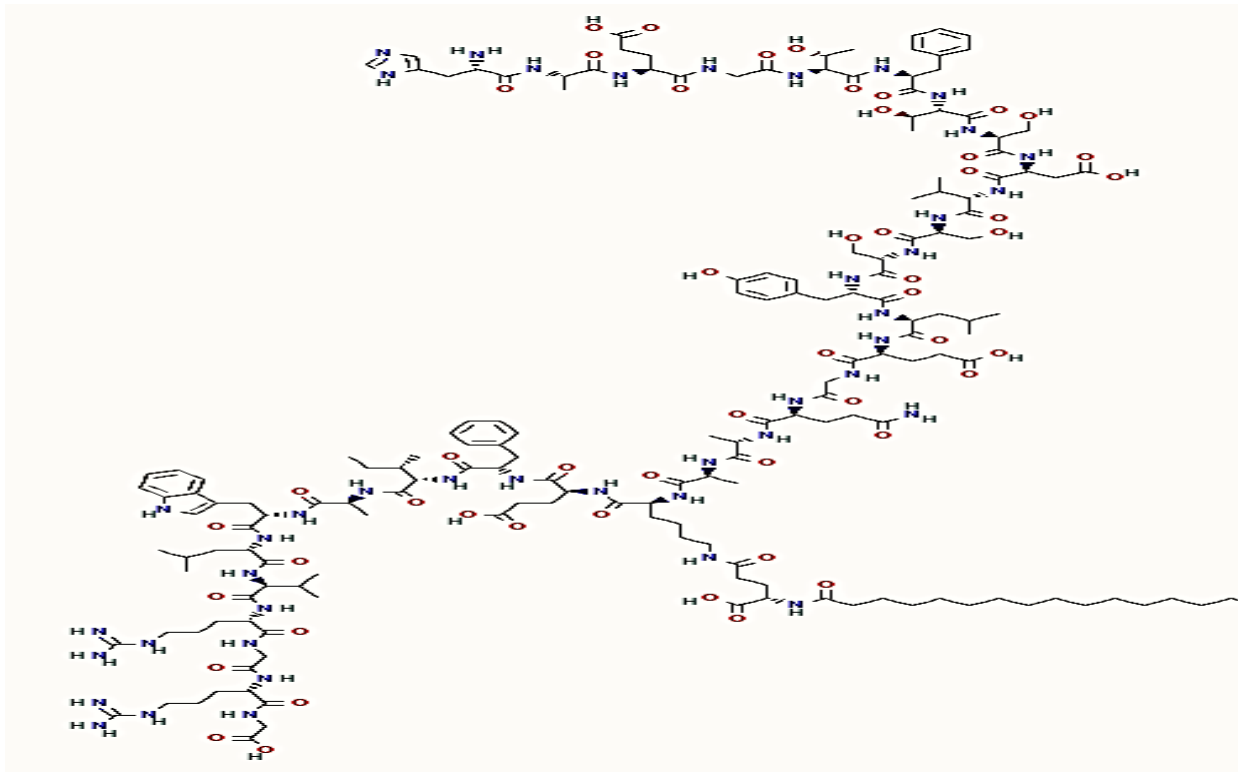

Table 2: Saxenda Properties

Medicine	Saxenda
Therapeutic area	Obesity; Overweight
Active Substance	liraglutide
INN/Common name	liraglutide
Pharmacotherapeutic Classes	Drugs used in diabetes

Chapter two (Material and method)

2.1 Materials

The materials that used in this study are as follow: -

Saxenda drug

Special pen and needle

Sphygmomanometer

BMI Height and Weight Scale Machine

2.2 Methods

2.2.1 Data collection and study design

Data were received from 5 female patients with BMI ≥25 and age between 36-56 year who were prescribed liraglutide for obesity treatment between February 1, 2022, and March 31, 2022, at the Shalel Clinic at erbil city. For enrolled patients, initial height, weight, BMI, age, sex, and diabetes data were collected. Patients were recommended to visit the clinic once a week. Patients' weight data were collected at liraglutide re-prescription dates closest to 7, 14, 21, 28 and 35 days after the first prescription. Final weight loss was measured at the final prescription visit. Then the BMI, early responders and behavioral characteristics were examined. Early responders were defined as weight loss in 7 or 14 days after the first prescription, which was compared with weight loss in later time periods and final weight loss. Behavioral characteristics were measured by lifestyle questions, discussed below.

2.2.2 Dose Schedule of Saxenda (Liraglutide)

Dose of liraglutide was generally recommended as follows: liraglutide was initiated at a dose of 0.6mg. The dose was increased by approximately 0.6mg each week to 1.2mg by 7 days, 1.8mg by 14 days, 2.4mg by 23 days, and 3.0mg by 31 days. Those who continued to visit the clinic after 31 days were treated with 3.0mg daily. This schedule is shown in table (2.1).

Table2.1 Dose injection of liraglutide

Week	Dose injected
1	0.6 mg once a day
2	1.2 mg once a day
3	1.8 mg once a day
4	2.4 mg once a day
5	3.0 mg once a day

2.2.3 Rout of Liraglutide Injection

Saxenda (Liraglutide) is given as injection under the skin (subcutaneous injection), the best places to inject are the front of waist(abdomen), front of thighs or upper arm. It doesn't inject into a vein or muscle. The first dose is 0.6 mg once a day for at least one week after increase the dose 0.6mg usually each week until reach the recommended dose of 3.0 mg once a day.

2.2.4 Data analysis

have numerical values, and the other will describe the types of categories being compared.

The comparison you want to make will help determine whether to display the bars vertical or horizontal. You would Data were analyzed by bar chat A bar chart uses bars to show comparisons between categories of data. These bars can be displayed horizontally or vertically. A bar graph will always have two axes. One axis will generally need to decide whether the data you are trying to represent has an intuitive direction or not. And we used vertical bar chat in our research to compare between to values, in each Weight before and Weight after used liraglutide that can show decrease or increase during this drug used and obviously showed in result.

Table2.2 Data collected

Patients No.	Age	height (cm)	Weight(Kg) Before	BMI	Weight(Kg)-After 1 week	BMI	Weight(Kg)-After 5 week	BMI
1	36	159	101	40	94	37	86	34
2	39	157	84	34	82	33	79	32
3	44	168	109	38	97	34	87	30
4	51	173	95	31	89	29	81	27
5	56	161	114	43	106	40	96	37

Chapter three Results and discussion

3.1 Effect of Saxenda (liraglutide): -

3.1.1 Effect of Saxenda during using

diarrhea,

constipation,

low blood sugar (hypoglycemia),

decreased appetite,

headache,

dizziness,

fatigue,

abdominal or stomach pain or upset,

bloating,

gas,

urinary tract infection,

dry mouth,

changes in taste,

gastroesophageal reflux disease (GERD),

injection site reactions or redness,

lack of energy or weakness,

gastroenteritis,

anxiety, or insomnia.

3.1.2 Effect of Saxenda

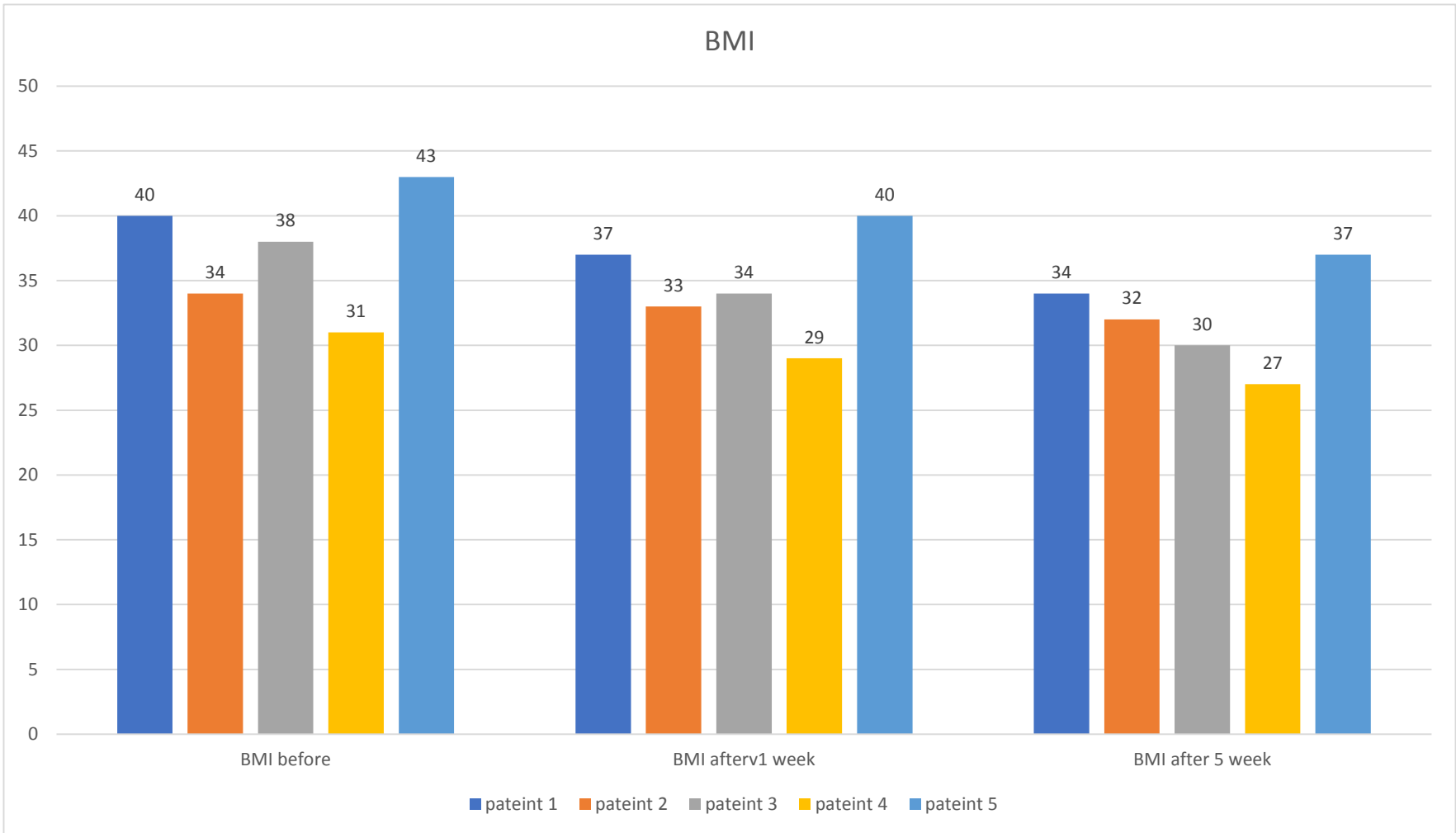

Table2.3 BMI Before and After

The number of patient who were prescribed liraglutide within 7 days after the first prescription was 5 patients within 35 days. In this study weight reduction during liraglutide treatment was significant the international classification of obesity defines BMI ≥ 25 as obese the samples were collected all of patients BMI ≥25 means over weight, in patient 3 the BMI was 38 after the first week of dose injection BMI was 34 means the different was high but the patient felt headache , stomachaches and diarrhea because the weight was decrease too high, but in after dose injection patient 3 don't effected, in last dose injection BMI 30 this was the good result during prescription Saxenda liraglutide .

Another sample was patient number 5 the weight was too high because patient ate high greasy food after one week of dose injection the BMI 40 during the week the patient don't ate greasy food, in last dose injection BMI 37 because patient drank soft water. In patient 2 BMI 34 after 1 week of prescription BMI 33 and last dose injection BMI 32 the weight loss lower than 4 samples because the patient 2 in last dose injection don't use 3.0 mg of drug, she less used of Saxenda liraglutide so she felt at last a lot of food desire. Patient 1 & 4 BMI 40&31 after 1 week of dose injection BMI 37&29 both of patient during first dose injection did exercise and last week of dose injection BMI 34&27, the patient 1 continued to exercise so she lost weight, but patient 4 didn't continue to exercise so she didn't lost enough weight.

Chapter Four Conclusion and Recommendation

4.1 Conclusion

In conclusion, liraglutide treatment led to meaningful weight loss in patients. This study showed that liraglutide can have a positive effect in Asian populations, with patients with relatively small

4.2 Recommendation

1.Drinking water can help with weight loss in a variety of ways. It may suppress your appetite, boost your metabolism, and make exercise easier and more efficient, all of which could contribute to results on the scale.

2. Patients can always lose weight by eating less food. Eating less will help take in fewer calories. When cut calories generally start to lose weight. Whenever eat less want to make sure the foods are eating is nutritious.

3. By replacing carbs and fat with protein, reduce the hunger hormone and boost several satiety hormones. This leads to a major reduction in hunger and is the main reason protein helps you lose weight. It can make you eat fewer calories automatically.

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