AMJ Australasian Medical Journal [AMJ 2023;16(6):661-681]

Glucagon-like peptide 1 receptor agonist and cancer meta-analysis and review

Ahmed Zayed Alotaibi*

Riyadh Elm University, Riyadh, Kingdom of Saudi Arabia

REVIEW

Please cite this paper as: Alotaibi AZ. Glucagon-like peptide 1 receptor agonist and cancer meta-analysis and review. AMJ 2023;16(6): 661-681
https://doi.org/10.21767/AMJ.2023.3757

Corresponding Author:
Ahmed Zayed Alotaibi
Riyadh Elm University,
Riyadh, Kingdom of Saudi Arabia
Email: ahmed.z.alotaibi@student.riyadh.edu.sa

ABSTRACT

Background

Diabetes is a medical condition known and diagnosed when the human body does not use the insulin hormone effectively. This causes blood sugar levels to rise. There are 2 diabetes types. Oral hypoglycaemic drugs are used in the treatment of type 2 diabetes mellitus (T2DM) while insulin used in treatment of type 1 diabetes.

Aims

Evaluating the risk of thyroid and pancreatic cancer associated with GLP 1 R agonists (GLP 1RAs), by carrying out a meta-analysis based on collecting information about cancers associated with GLP 1RAs in patients with type 2 diabetes mellitus (T2DM).

Methods

Medline and Clinical Trials were searched to identify randomized controlled trials that reported cancer events in T2DM patients treated with glucagon like peptide 1 receptor agonists (GLP 1RAs). Odds ratio (OR) with 95 percent Confidence Interval (CI) was calculated for overall cancer (primary outcome), thyroid cancer and compare the results with pancreatitis.

Results

A total of 11 eligible trials were identified. The OR for overall thyroid cancer associated with GLP 1RAs was 0.004 (95 percent CI 0.003–0.005; $p<0.001$) for pancreatitis was 0.027 (95 percent CI 0.022–0.032; $p<0.001$) compared with comparators, and no elevated risk of overall cancer was identified for other GLP 1RAs. No significant differences in the risks of thyroid cancer were disclosed between GLP 1RAs and comparators.

Conclusion

This meta-analysis did not suggest any increased risk of cancers associated with GLP 1RAs use in T2DM. The reduction in the risk of overall cancer associated with GLP 1RAs.

Key Words

GLP 1 receptor agonists, thyroid Cancer, meta-analysis, type 2 diabetes mellitus (T2DM)

What this review adds:

1. What is known about this subject?

Diabetes is a medical condition known and diagnosed when the human body does not use the insulin hormone effectively. This causes blood sugar levels to rise.

2. What new information is offered in this review?

This meta-analysis provides convincing evidence against the presumption that the therapeutic class of GLP1 RAs increases the risk of thyroid cancer and pancreatitis.

3. What are the implications for research, policy, or practice?

There is an urgent need for more large scale RCTs with long term thyroid safety monitoring while administering this group of medications.

Introduction

Diabetes Mellitus (DM)

DM is an illness where the hormone insulin is not used effectively by the human body, leading to sugar levels to rise in the blood[1-3]. There are 2 diabetes types, Type 1, which occurs when no insulin is produced by the human body because the immune system assaults and destroys the pancreatic cells. It's generally found in kids (juvenile diabetes) but sometimes it appears in adults. Type2 diabetes occurs when the body doesn't generate enough insulin or resist the effect of insulin. (Association, 2005).

Blood glucose high level can cause severe health issues that harm the blood vessels, nerves, heart, eyes, and kidneys, Lack of monitoring Type 2 diabetes may also include nausea or vomiting, rapid breathing, ketone odor, weakness, somnolence, confusion, and uncoordinated muscle motion. If diabetes remains untreated, it may even lead to coma and

death. In type 2 diabetes there are many indications of insulin resistance darkening skin around the throat or axes, high blood pressure, cholesterolemia, yeast infections, and disruption periods in teenage girls and females[4-8]. At present, kids at risk of illness are mostly diagnosed because more kids are overweight and less physically active (Tripathi and Srivastava, 2006).

At late stage, the symptoms become more severe, these symptoms frequently include extreme hunger and thirst, frequent urination, weight loss, fatigue, drowsiness, delayed vision, sores, recurrent skin, gum, bladder or vaginal yeast diseases, dry itchy skin and numbness in the fingers or feet. Diabetic Patients are normally diagnosed with HBA1C blood test as a gold standard (Committee, 2009). In addition to fasting blood sugar testing after 8 hours and random blood sugar testing (Association, 2016) (Alberti and Zimmet, 1998).

Pre-diabetes is defined and diagnosed when blood glucose levels are higher than normal but not too high to be formally diagnosed as diabetes. Pre-diabetics are at high risk of developing type 2 diabetes which is defined as Impaired glucose tolerance and impaired fasting glucose, HBA1C of 5.7 percent to 6.4 percent (Ferrannini et al., 2011). Risk variables that cause type 2 diabetes include obesity that increases insulin resistance, alcohol , tobacco and age (especially over 45 years) in addition to race / ethnic background and family history (Grundy, 2012). In women, unbalanced hormone levels called polycystic ovary syndrome (PCOS) and pregnancy (Gestational diabetes) are also risk factor for developing diabetes further in life (Hu et al., 2001). The American Academy of Family Physicists (AAFP) recommends that pregnant females be screened for gestational diabetes after the 24th week of pregnancy. The higher incidence of risk factors the higher the probability of occurrence the type 2 diabetes[9-15]. On the other hand, the use of prevention as exercise for 30 to 60 minutes and weight control with a healthy diet is proven to prevent or delay the occurrence of type 2 diabetes option through lifestyle changes (Grundy, 2012).

Anti-diabetic medications are divided into oral medicine and insulin. Proper use and control of diabetes and glucose blood level is proven to delay serious health problems, these are known as diabetic complications which are divided into two types, Micro-vascular complication Known as diabetic neuropathy (nerve damage) in brain and other parts of the body and losing ability to feel, Diabetic retinopathy (eye problems) and diabetic nephropathy (kidney damage) (Nathan, 1993). As for macro-vascular complications of diabetes will lead to heart disease and stroke (Brownlee, 2001).

Anti-diabetic medications

Insulin

Different types of insulin give several options to control type I and II DM. Such as rapid acting insulin which has a 15 minutes onset, 1 hour peak and 4 hours duration. On the other hand, short acting (regular) insulin has 30 minutes onset, 3 hour peak and 6 hour duration. Furthermore, intermediate acting insulin with 4 hours onset, 12 hours peak and 18 hours duration. The slowest among them is the long acting insulin which has an onset Several hours after injection, does not peak and 24 hours duration (Shah and Shafi, 2019).

Oral Anti-hyperglycaemic Drugs

Biguanides (metformin)

Is the main class of oral type 2 diabetes drugs, which works by decreasing hepatic glucose production, decreasing gastrointestinal glucose absorption, and increasing target cell insulin sensitivity. This group is contraindicated in metabolic acidosis, abnormal creatinine clearance, acute myocardial infarction, septicaemia, renal disease, lactation, and radiologic contrast study within 48 hours (Schäfer, 1983).

Thiazolidinedione (Pioglitazone, rosiglitazone)

It increases insulin receptor sensitivity and influences the production of gene products involved in lipid and glucose metabolism, increases insulin sensitivity of the body cells and reduces the production of glucose by the liver. It is contraindicated in established NYHA class III/IV heart failure. This group might cause swelling due to water retention, weight gain, Pioglitazone increases the risk of bladder cancer while Rosiglitazone increases risk of a non-fatal heart attack (Diamant and Heine, 2003).

Sulfonylureas (Glyburide , glipizide, Gliclazide, glimepiride, tolazamide, tolbutamide)

Works by Stimulating beta cell insulin secretion, decrease hepatic glucose output and increase insulin receptor sensitivity at peripheral target tissues[15-20]. It contraindications include sulfa allergy, type 1 diabetes, diabetic ketoacidosis, concomitant use with risk to hypoglycemia (Diamant and Heine, 2003).

Meglitinides (Repaginate)

Works by Stimulating the pancreas to produce more insulin leading to hypoglycemia (Black et al., 2007).

Alpha glucosidase inhibitors (Acarbose & Miglitol)

It inhibits the upper gastrointestinal enzymes that convert dietary starch and other complex carbohydrates into simple sugars, which can be absorbed. Its contraindications include Diabetic ketoacidosis, cirrhosis, inflammatory bowel disease, colonic ulceration, partial intestinal obstruction,

and renal failure. Might cause bloating, flatulence, and Diarrhea (Lebovitz, 1997).

Dipeptidyl peptidase 4 (DPP 4) inhibitors (Linagliptine, Saxagliptine, Sitagliptine, Alogliptine)

Works by increase of intestinal hormones effect which is involved in the control of blood sugar. This group might Cause Pharyngitis, headache (Elrishi et al., 2007).

Sodium glucose co transporter 2 (SGLT2) inhibitors (Canaglifozine, Dapagliflozine, Empagliflozine, Ertugliflozine)

It helps eliminate glucose in the urine, and it might cause genital and urinary infections, more frequent urination (Jabbour and Goldstein, 2008, Shah and Shafi, 2019).

Glucagon like Peptide 1 receptor agonist (GLP1RA)

Insulin and amylin hormones control glucose homeostasis and are produced by beta cells in the pancreas; glucagon has a role in glucose homeostasis and is produced by alpha cells in the pancreas; and gastrointestinal peptides, including glucagon like peptide 1 (GLP 1) and glucose dependent insulin tropic polypeptide [20-28]. Any disturbance in previous substances may contribute to diabetes (Plum et al., 2006). GLP 1 is produced from the proglucagon gene in small intestine L cells and is secreted in reaction to meals. GLP 1 binds to a particular receptor. GLP 1 stimulates insulin release from the pancreatic islets that is dependent on glucose. It slows gastric emptying, inhibits the unsuitable release of glucagon after the meal, and reduces the consumption of food. GLP 1 also slows gastric emptying (Schjoldager et al., 1989).

Glucagon like Peptide 1 receptor Agonist (GLP1RA)

Exenatide

It is a synthetic analog of extending 4 obtained from the lizard saliva called *Heloderma suspectum*. Approved in 2005 by the U.S. Food and Drug Administration and in 2006 by the European Union for T2DM therapy (Hargrove et al., 2007). The half-life of exenatide is about two hours after subcutaneous administration; therefore, it is administered twice daily beginning at a dose of 5 mcg twice daily, titrating it up to 10mcg twice daily after 1 month [29-35]. It is excreted by the kidney and is associated with a decrease of about 1 percent in HBA1C that affects both fasting (15 to 25mg percent) and post prandial Glucose from plasma (15 to 30 mg percent) (Barnett, 2007).Weight loss over 30 weeks of roughly 1.0 to 2.5kg and over 52 weeks of 3 to 6kg (Buse et al., 2010). The most significant adverse effect is nausea and vomiting (Barnett, 2007). There is a warning that it might cause or induce pancreatitis and it can be strongly argued by most authors that the risk is more theoretical than practical (Denker and Dimarco, 2006).

Exenatide Long Acting Release (LAR)

Approved for use in 2011 by the European Medical Association, it is the first anti Hyperglycemia to be injected once a week. It is authorized for use and has a 4 day plasma half-life. It is renal excreted and shares much of the same exenatide features with a handy dosage once a week and a safer profile of side effects (Copley et al., 2006). The incidence of nausea and vomiting is smaller than twice a day of exenatide and vomiting in one week of preparing. Compared to twice a day exenatide, it is slightly more efficient in decreasing HBA1C and fastening plasma glucose (Sennik et al., 2012, Norris et al., 2009, Dore et al., 2011).

Taspoglutide

It shares a 93 percent homology with the native GLP 1 and is completely resistant to DPP 4 inhibitor degradation. Limited information from two published studies indicates that HBA1C was decreased by about 1.1 percent. There was a greater incidence of exenatide gastrointestinal side effects and hypersensitivity reactions observed (Dong et al., 2011, Ratner et al., 2010).

Liraglutide

Is an acylated GLP 1 analog that is self-associated to a heptametrical structure that delays subcutaneous injection site absorption? It was approved for use in 2009 by the EU and in 2010 by the USFDA. It shares the indigenous GLP 1's 97 percent homology. It has between 9 and 14 hours of plasma half-life and is metabolized with 10 to 18 hours of DPP 4 and neutral endopeptidasis. It has an initiate dose of 0.6 mg/day titrated to a maximum of 1.8 mg/day on a week. It mildly impacts renal and gastrointestinal excretion with mild and serious hepatic impairment[35-45]. The average decrease in HBA1C is as high as 1.6 percent and the weight loss is as high as 2.5 kg over 30 weeks. Nausea and vomiting are the most common side effects in roughly 8 percent of patients that trigger the withdrawal of treatment. There is a warning of rare pancreatitis complications (Madsbad et al., 2011, Croom and McCormack, 2009).

Lixisenatide

It is a novel human GLP 1R agonist undergoing phase 3 trials. It is a very powerful and selective agonist of GLP 1R (four times more powerful than human GLP 1). It causes important weight loss; however, up to 22 percent of patients may experience mild nausea. 20 µg once daily dose of lixisenatide demonstrates the best efficacy to tolerability ratio (Barrington et al., 2011).

Albiglutide

It is a long acting GLP 1, resistant to DPP 4 degradation. It is also currently in phase 3 trials. Compared with currently available GLP 1 analogus, it may provide a more patient friendly dosing profile (once weekly or less common dosing). Efficacy information shown in 40 Japanese patients

suggest a mean reduction in HBA1C of 0.58 percent (15 mg / week), 0.57 percent (30 mg/week), 0.63 percent (50 mg/week) and 0.51 percent (100 mg/month). Common adverse reactions included nausea, vomiting, headache, dizziness, nasopharyngitis, back pain, upper respiratory tract infections, and local skin reactions (Seewoodhary and Davies, 2011).

Dulaglutide

It is a long acting GLP 1 analogue it was planned to have a convenient dosage once a week. In a randomized double blinded placebo controlled research (262 obese patients of type 2), a decrease in HBA1C of roughly 1,28 to 1,52 percent was observed along with a weight loss of 1,40 and 2,51 kg. The most commonly reported negative occurrences were upper gastrointestinal symptoms of nausea, diarrhea, and abdominal distension (Gupta, 2013).

Common adverse effects

GLP 1 receptor agonist most prevalent adverse effects are gastrointestinal, including Diarrhea, nausea, and vomiting. Over time, for many patients, these are often self-limiting (Copley et al., 2006).In clinical studies, these agents were discontinued by less than 5 percent owing to gastrointestinal impacts (Prasad-Reddy and Isaacs, 2015). With greater doses, adverse effects are more prevalent and typically enhance over time. Slow dose titration contributes to these impacts. Taspoglutide developed to have a longer duration of action than Liraglutide and was studied in more than 6000 patients to compare the efficacy and safety of Taspoglutide once a week with exenatide twice a day (Retterstøl, 2009). HBA1C, fasting plasma glucose, and body weight without serious hypoglycaemia was considerably decreased by both exenatide and Taspoglutide (Prasad-Reddy and Isaacs, 2015). Taspoglutide's generally is given at 20 mg weekly, however, was worse than 10 µg daily exenatide, This included more gastrointestinal impacts (21.6 percent *vs*. 10.1 percent), hypersensitivity (4.1 percent vs. 0.8 percent), and site responses (10.9 percent vs. 0.8 percent). The 10 mg weekly Taspoglutide had fewer adverse effects than the 20 mg daily dose, but it was worse than exenatide. Nearly twice as many patients withdrew from the research in the Taspoglutide arm (Prasad-Reddy and Isaacs, 2015). It has been suggested that the increased nausea and vomiting with Taspoglutide may reflect some of the pharmacokinetic variations, and generally on the day of injection these impacts were worse[45-55]. Because of the study's elevated levels of adverse effects and elevated discontinuation rate, tests were stopped in September 2010, and it is not anticipated that this drug will be released (Prasad-Reddy and Isaacs, 2015).

GLP1RA Analogue as Mono-therapy

In their anti-hyperglycaemic impacts, all the presently accessible GLP1RA are more or less equally effective. They have been shown to be non-inferior to the highest doses of metformin, pioglitazone, SU and insulin (Madsbad et al., 2011). Liraglutide was seen to have an advantage over exenatide in relation to HBA1C Reduced by 0.33 percent for Liraglutide, with a greater proportion of patients attaining HBA1C of<7.0 percent relative to exenatide (54 percent vs. 43 percent) (Madsbad et al., 2011) . Comparing sustained release exenatide (LAR) and Liraglutide suggest that Liraglutide has glycaemic efficacy could see an advantage over long acting release exenatide (LAR), with a more secure side effect profile (Buse et al., 2013). Exenatide LAR may have a higher advantage relative to exenatide; however, a higher post prandial glucose lowering impact has been shown by daily exenatide. Weight loss for all the three GLP 1 analogues (exenatide, exenatide LAR, and Liraglutide) seems to be more or less similar. A meta-analysis of the effectiveness of GLP1RA (exenatide and Liraglutide) proposed a decrease of HBA1C between 0.81 and 1.13 percent; a 21 to 33 mg decrease in blood glucose and a 16 to 41 mg decrease in post prandial glucose. Average weight loss ranged from 0.78 to 3.95 kg, higher than Liraglutide for exenatide (Kayaniyil et al., 2016). Upper gastrointestinal symptoms (nausea, vomiting, abdominal fullness, and uncommon Diarrhea) are the most commonly observed adverse effects using GLP 1 analogues. This contributes to a withdrawal rate of about 4 percent, more for exenatide compared to Liraglutide, according to a meta-analysis. The exenatide LAR showed have the least side effects when compared to exenatide (26 percent vs. 35 percent) for nausea and 110 percent vs. 19 percent for vomiting) with greatest therapy. (Madsbad et al., 2011, Seewoodhary and Bain, 2010, Aroda and DeYoung, 2011)

GLP as Combination Therapy

GLP1RA are currently approved for the treatment of T2DM as monotherapy, dual therapy and triple therapy medications (Zinman et al., 2009). Studies have shown an improvement of HBA1C by 0.6 to 1.5 percent over a three year study period with a continuous advantage of > 1 percent (Best et al., 2012). It was evident from the LEAD meta-analysis that when Liraglutide is added to current oral treatment, the advantage in HBA1C is about 1.5 percent. Similarly, exenatide LAR and exenatide showed an advantage of an HBA1C decrease of up to 1.1 percent (Best et al., 2012). In combination with metformin HBA1C: 1.0 percent for Liraglutide versus 0.8 percent for exenatide, with target HBA1C of<7 percent for 66 percent and 46 percent for patients respectively. Fasting glucose: 18 –27 mg percent post prandial glucose: average 47 mg percent. It

was shown to be non-inferior the combination therapy of glimepiride and metformin combination (Best et al., 2012).

Combined with SU HBA1C was observed to be decrease by 1.1 percent for Liraglutide versus 0.86 percent for exenatide, with 66 percent and 41 percent of patients attaining target HBA1C of < 7 percent in combination with dual oral treatment respectively (Marre et al., 2009).

Exenatide in dual or triple oral therapy was shown to be non-inferior to insulin glargine in terms of HBA1C reduction, a much higher proportion of patients achieved their exenatide HBA1C target of<7 percent (53.4 per cent) compared to insulin glargine (19.8 per cent) (Davies et al., 2009).

A systematic review of the use of exenatide in clinical practice disclosed a significant reduction in HBA1C (0.4 to 0.9 percent), blood glucose (10 mg / dl), weight (2 to 11 kg) and blood pressure (2 to 11 mmHg). The use of exenatide led to a decrease in the concomitant dosage of anti-diabetes medicines in SU by up to 75 percent, 22 percent in metformin, and 66 percent in TZDs[56-65]. The study also indicated that exenatide use was associated with significantly reduced levels of hospitalization and mortality associated with all cause and cardiovascular (Best et al., 2012).

GLP Combined with Insulin

Insulin therapy is well known to be the ultimate connection between an exhausted beta cell and plasma glucose in most patients. Most trials using GLP1RA in patients with current insulin therapy have performed so on the basis that clinical improvement could be seen due to weight loss (enhanced resistance to insulin) and possibly because of an insulin sparing effect (improved health / insulin secretion of beta cells) (Eng et al., 2014). Several small studies have shown clear benefits in terms of improvements in HBA1C, weight (3–5 kg) and reduction of the total dose of insulin in patients with T2DM by as much as 30 to 50 percent (Marre et al., 2009). "The British Clinical Diabetologists Association" researched 4874 patients using exenatide as part of a domestic UK audit, of which 1921 patients (39.6 percent) used exenatide. Adding exenatide to current insulin therapy led in a 0.51±0.06 percent decrease in mean HBA1C; 5.8 ± 0.2kg decreases in weight; and a complete decrease in insulin dose of 44±4 units per day. 17.1 percent cessation of insulin treatment, 23.1 percent discontinuation of SU treatment, and 54.3 percent discontinuation of TZD treatment. 34.2 percent Insulin continuing patients accomplished a decrease of HBA1C>=1 percent. The same population, however, had a greater level of discontinuation of exenatide (31.0 *vs.* 13.9 percent) hypoglycaemia (8.9 vs. 6.1 percent), gastrointestinal side effects (28.4 *vs.* 25.0 percent), and treatment dissatisfaction (20.8 *vs.* 5.7 percent) (Thong et al., 2011).

Most trials using GLP1RA have chosen patients with elevated Body Mass Index (BMI) and important weight loss has also been proved. Therefore, the issue remains whether the advantages of reducing HBA1C are due to weight loss (improvement in insulin resistance) or enhancement in the mass / health of beta cells or both. A study using Liraglutide in patients with type 1 diabetes mellitus (T1DM) cannot answer this question better. Although the number of individuals studied was only 14, a decrease in mean fasting glucose (130 +/ 10 to 110 +/ 8mg/dl) and mean daily glucose (137.5 +/ 20 to 115 +/ 12mg/dl) was shown for the first time in just 1 week. Basal demands for insulin reduced from 24.5+/ 6 to 16.5 +/ 6 units and 22.5+/ 4 to 15.5 +/ 4 units for bolus insulin. Both HBA1C and body weight decreased significantly respectively from 6.5 percent to 6.1 percent and 4.5 +/ 1.5kg. Treatment with Liraglutide provided an additional strategy to improve glycaemic control in T1DM LEAD meta-analysis (improvements in HOMA beta results and pro-insulin/insulin ratios) obviously showed improvements in beta cell health (Thong et al., 2011).

Non glycaemic benefits

The brain and cardiac tissue express the same GLP 1R as the pancreatic tissue. However, in the liver, GLP 1R stimulation creates anabolic impact rather than neoglucogenesis and glycogenolysis as it would be anticipated to be stimulated by glucagon, implying that GLP 1R on hepatocyte will be different from an unknown locus gene encoding, a second GLP 1R or an alternative spliced receptor associated to the glucagon related peptide receptor superfamily (Cuthbertson et al., 2012).

GLP1RA showed beneficial effects on myocardial contractility, hypertension(natriuretic/diuretic), endotheliu m (anti atherosclerotic), and lipid profile. An absolute gain in the parameters of lipids (enhancement of HDL, cholesterol, rapid triglycerides). GLP1RA play a role in protecting neurons, leading to improved cognition, memory, and spatial learning[66-75]. It modifies eating conduct by satiety, decreasing power consumption by around 12 percent via key peripheral nervous system communication (vagus), GLP 1 augmentation causes gastric slowing, inducing a post prandial satiety (Gupta, 2012).

Dose dependent and progressive weight loss caused by GLP1RA. Liraglutide has shown to cause a mean weight loss of estimated 6.0kg with >35 percent of topics attaining more or equal 10 percent weight decrease. Similarly, long acting exenatide (exenatide LAR) has shown an improvement in body weight with an average weight decrease of 5.8 lbs (Taylor et al., 2011).

By restoring insulin signaling and reducing hepatic gluconeogenesis, GLP 1 has shown a decrease in insulin sensitivity. Increased insulin secretion creates enhanced muscle and adipocyte glucose uptake and decreased liver glucose outpouring[70-80]. By encouraging loss of weight the peripheral insulin mediated glucose uptake has also been shown to be enhanced. Locally at the stage of beta cell and fat cell (decreased release of free fatty acids) and systemically (down gradation of inflammation markers) it has shown to decrease insulin resistance (Lee et al., 2007).

Drug-Drug Interactions with GLP1RA

Exenatide

The potential for interaction between exenatide and acetaminophen was evaluated in a randomized, single blind, placebo controlled, exenatide resulted in decreased acetaminophen (Blase et al., 2005).The effect of exenatide on steady state digoxin pharmacokinetics was determined in an open label fixed sequence study, Exenatide did not affect the steady state area under the curve (AUC) of digoxin but decreased the maximum concentration in blood (C max), increased the median time to reach C max (t max) of digoxin from 1.5 to 4 hours[81-90]. The results suggest that exenatide does not affect the overall absorption of digoxin, which has a narrow therapeutic index (Kothare et al., 2005). The potential for an interaction between exenatide and lovastatin was studied in an open label, fixed sequence, crossover study; Twenty two healthy subjects received lovastatin. The AUC and C max ratios of lovastatin were decreased with concurrent exenatide, Exenatide prolonged the median t max of lovastatin from 2 to 6 hours (Kothare et al., 2007).

Liraglutide

The potential for interaction between steady state Liraglutide and single dose of Oral Contraceptive Pills (OCP) (ethinyl estradiol / levonorgestrel) was assessed, Liraglutide decreased the C max of ethinyl estradiol by 12 percent and levonorgestrel by 13 percent Relative to placebo, liraglutide increased the t max of both ethinyl estradiol and levonorgestrel by 1.5 hours (Jacobsen et al., 2011).

One relevant publication was found evaluating the pharmacokinetics of single dose acetaminophen 1000 mg when administered with or without steady state liraglutide. Increased the t max by 15 minutes, and decreased the C max. The overall exposure of acetaminophen was comparable for subjects taking liraglutide or placebo, and the clinical impact of the lower C max and delay in absorption of acetaminophen is likely without clinical relevance (Kapitza et al., 2011).

One study evaluated the pharmacokinetics of 4 drugs when administered with or without steady state liraglutide 1.8 mg. 21 Healthy subjects were randomized to 1 of 2 treatment sequences in this double blind, placebo controlled, crossover study. Single doses of atorvastatin 40 mg, placebo and lisinopril 20 mg, received single doses of digoxin 1 mg and griseofulvin 500 mg (Malm-Erjefält et al., 2015).

Liraglutide decreased the AUC of lisinopril by 15 percent and digoxin by 16 Relative to placebo, liraglutide increased the t max of atorvastatin, lisinopril, and digoxin by 1.25, 2, and 1.12 hours. The C max of atorvastatin, lisinopril, and digoxin was decreased subsequent to liraglutide administration, it was increased for griseofulvin (Malm-Erjefält et al., 2015).

Albiglutide

The effect of albiglutide on warfarin and digoxin was evaluated in an open label study. Albiglutide increased the t max of R and S warfarin and digoxin from 1 to 1.5 hours. The C max ratio of R and S warfarin was not altered Subsequent to albiglutide administration; however, it was increased for digoxin, These data suggest that potential gastric emptying effects of albiglutide did not significantly affect the absorption profile of warfarin or digoxin (Hurren and Pinelli, 2012).

Aim of the Study

Evaluating the risk of thyroid and pancreatic cancer associated with GLP 1 R agonists (GLP 1RAs), by carrying out a meta-analysis based on collecting information about cancers associated with GLP 1RAs in patients with type 2 diabetes mellitus (T2DM).

Significance of the study

- Using GLP1 drugs was reported to induce a number of risks as thyroid cancer and pancreatitis.
- These reports lack any safety data about the drug.
- In the recent years, there is an increase in the use of GLP1 RA in Saudi Arabia

Questions

Would GLP1 RA treatment for long term use increase the risks of different types of cancer?

Literature review

Experimental Evidence Review

The FDA reported the rise in the incidence of carcinomas in rodents translated into low human risk, as statistically significant increase occurred only at levels of drug exposure several times those predicted in humans, and the rise in cancers did not affect overall survival rates. Nonetheless, extrapolating results from animal studies to humans is still difficult (Bjerre Knudsen et al., 2010).

Evidence from rodent studies showed that liraglutide was associated with increased risk of thyroid C cell focal

hyperplasia and C cell tumors. C cell hyperplasia is thought to be a preneoplastic lesion contributing to medullary thyroid cancer (MTC) in rodents (McConnell et al., 1986), also Rodent studies have documented early increases in calcitonin (CT) plasma in relation to both liraglutide and exenatide dosage. Several studies using rat thyroid C cell lines and thyroid tissues have shown that activation of the GLP 1 receptor results in CT secretion, which is reduced by the antagonist of the GLP 1 receptor (Crespel et al., 1996, Lamari et al., 1996). The harmful effect of GLP 1 receptor agonists in rodents, but not primates, suggests that the proliferative effects of C cells may be specific to rodents (Rosol, 2013).

The occurrence of thyroid C cell tumors in animals was higher due to GLP 1 analogues in mice and rats studies. Liraglutide, exenatide, taspoglutide, and lixisenatide stimulate potent GLP 1 receptors in thyroid C cells, increasing the expression of the CT gene and inducing the dose dependent release of CT (Bjerre Knudsen et al., 2010).

After lifelong exposure in supra therapy doses, liraglutide and exenatide are correlated with the growth of thyroid C cell tumors in rodents. Significant increases in C cell hyperplasia plasma CT and incidence are associated with prolonged exposure to liraglutide or exenatide. The GLP 1Ra s they were not seen in GLP 1R knockout mice mediated these effects. Such issues are based primarily on studies of rodents (Bjerre Knudsen et al., 2010, Madsen et al., 2012).

Long term liraglutide therapy in mice resulted in a gradual, dose dependent rise in CT plasma, often accompanied by excessive proliferation of C cells, C cell hyperplasia and MTC in rats, particularly during the first months of administration, a CT releasing effect of liraglutide was also identified. A statistically significant increase in the incidence of MTC was observed in rats at all doses once a week with exenatide. The effects of GLP 1R agonists were not found to be mediated by phosphorylation of the MAP Kinase pathway and by activating RET proto oncogene mutations, at least on rodent C cells (Madsen et al., 2012).

Another study reported the occurrence of MTC caused by liraglutide did not affect the overall rate of survival among rats or mice. GLP 1 therapy was shown to contribute to C cell hyperplasia in rats, 0.075 mg / kg / day and 1.0 mg / kg / day were shown to cause a significant increase in C cell tumor development in rats and mice. The dosage in rats (0.075 mg / kg / day) which was equal to the recommended dose in humans for the treatment of type 2 diabetes. On the other hand, C cell tumors developed in mice with a daily dose of liraglutide 10 times higher than the equivalent human dose. Dose dependent C cell hyperplasia and neoplasia developed only at doses that also caused increased CT levels (Bjerre Knudsen et al., 2010).

The rates of C cell and CT increase significantly with age in rodents, and spontaneous proliferative lesions of C cells are frequently observed. Specific receptor mediated mechanism that is particularly sensitive to rodents, whereas non-human primates and human beings are not sensitive (O'toole et al., 1985, Kurosawa et al., 1988, Bjerre Knudsen et al., 2010).

The GLP 1 receptor dependent effects of C cell hyperplasia and CT release associated with GLP 1 agonists in wild type mice were not observed in GLP 1 receptor knockout mice was reported (Madsen et al., 2012).

C cell hyperplasia was caused by liraglutide binding to the GLP 1 receptor on murine thyroid C cells (Madsen et al., 2012). However, prolonged administration of liraglutide at very high doses did not produce C cell proliferation in monkeys (Bjerre Knudsen et al., 2010). In these species, Ct functions in relation to feeding as an acute regulator of plasma calcium levels (Wang et al., 2002). After long term liraglutide administration, neoplasms were not observed in monkeys, indicating that GLP 1 induced C cell proliferation in rodents but not in primates and suggesting that potential species specific differences in GLP 1R expression and activation may occur in the thyroid (Bjerre Knudsen et al., 2010).

Finally, another study in monkeys also showed that dulaglutide was not associated with increases in serum CT or changes in thyroid weight, histology, C cell proliferation or absolute / relative volume of C cells at 500 fold maximum human plasma exposure for 52 weeks (Vahle et al., 2015).

Human Clinical Trials review

Contrary to previous findings, their relevance to human effects of GLP 1 therapy is uncertain, levels of GLP 1R in the thyroid gland have been reported to be significantly lower in humans than in rats. The GLP 1R TT cells are not active, while the C cell rat thyroid line expresses a biologically functional GLP 1R that could be activated by various GLP 1R agonists (Bjerre Knudsen et al., 2010).

Heged et al. reported no significant risk of activation or development of C cell cancer in response to liraglutide over a 2 year period in a series of clinical trials with either diabetes or non-diabetic obesity. Nonetheless, in thyroid glands of 20, 91, and 100 percent of patients with papillary carcinoma, MTC, and C Cell hyperplasia, GLP 1R activation could also be observed, respectively. Analysis of liraglutide studies did not reveal any significant change in treatment groups with respect to CT levels or the proportion of participants with CT levels above 20 pg / ml (Hegedüs et al., 2011, Gier et al., 2012, Bjerre Knudsen et al., 2010).

No difference was reported in the approximate mean geometric CT levels between liraglutide 1.8 mg once daily and exenatide 10 µg twice daily in the diabetes study (Buse et al., 2009). Additionally, there has been no substantial

change in the concentration of CT over time, no significant difference in the concentration of CT between liraglutide and placebo, and no randomization of C cell malignancies in the liraglutide side (Crespel et al., 1996).

During treatment with GLP 1 receptor agonists in patients with type 2 diabetes, some prospective clinical studies found no rise in levels of CT (Bjerre Knudsen et al., 2010, Hegedüs et al., 2011).

A meta-analysis showed that liraglutide was not significantly associated with an increased risk of thyroid cancer, and no thyroid malignancies were reported with exenatide. None of the studies evaluating exenatide reported cases of thyroid cancer, whereas five of the studies evaluating liraglutide did. In total, thyroid cancer has been diagnosed in nine patients treated with liraglutide. These findings do not indicate that GLP 1 receptor agonists cause MTC. Thanks to the extremely low incidence of MTC (Alves et al., 2012).

GLP 1 receptors are present in 100 percent of cases in rats with C cell hyperplasia and MTC, compared to 27 percent of human MTC (Waser et al., 2011). In randomized clinical trials, there was a rise in CT levels in a slightly higher percentage of liraglutide treated patients than in control patients. Furthermore, results from a long term analysis did not reveal any significant difference in mean CT levels between Liraglutide and control groups over 2 years of follow up (Parks and Rosebraugh, 2010).

A FDA Adverse Event Reporting System (FAERS) study showed a significant rise in cases of thyroid cancer with exenatide. Concerns about a possible link between GLP 1 receptor agonists and MTC were also expressed. The occurrence of thyroid cancer in exenatide treated patients was higher (30 events) than the control panel (3 events). Nevertheless, this research did not distinguish between forms of thyroid cancer, and its analysis is complicated by the inherent limitations of retrospective databases. The occurrence of MTC has increased significantly, but this does not seem to be true (Elashoff et al., 2011).

Several other human tumors have been shown to express GLP 1 receptors in addition to MTC (Korner et al., 2007).

Monitoring review

The occurrence of MTC in the United States is around 600 cases per year, making it impossible to perform a clinical trial to identify an increased risk of Liraglutide related cancer of this type. Continued Ct secretion caused by GLP 1R agonists was accompanied by a compensatory increase in Ct biosynthesis, as demonstrated by a rise in Ct mRNA before CCH started (Bjerre Knudsen et al., 2010).

CT, a hormone secreted by thyroid C cells, is considered to be an important clinical biomarker for C cell diseases such as MTC and hereditary C cell hyperplasia due to its high sensitivity and specificity; CT levels have been tested regularly in clinical trials and could be a useful indicator. Serum CT levels below 10 pg per millilitre are considered evidence of MTC absence, while levels above 100 pg per milliliter are highly predictive of MTC. Standard CT screening was recommended as a standard and cost effective treatment for the identification of medically occult MTC in patients undergoing evaluation for thyroid nodules (Elisei, 2008, Elisei et al., 2004) (Costante et al., 2006, Machens et al., 2009).

Only C cells, which comprise a small fraction of the thyroid mass (0.1 percent), contain Ct, a 32 amino acid peptide hormone whose production in fish and rodents is closely associated with calcium homeostasis, in which it tends to suppress osteoclast mediated bone resorption (Hoff et al., 2002).

Para thyroid hormone (PTH), the main hormone mobilizing calcium, and CT are physiologically antagonists, the latter acting as an emergency hormone secreted to protect against hypercalcemia caused by feeding. Some gastrointestinal peptides, such as cholecystokinin (CCK), stimulate CT secretion, suggesting a connection between the gastrointestinal tract and the thyroid C cells. (Persson et al., 1988) In addition, while CT plays an important role in some species, there has been no significant physiological involvement in humans (Hirsch and Baruch, 2003).

Whereas in virtually all MTC patients, either basal or stimulated plasma CT levels are elevated. It is useful for screening people at risk, such as patients genetically predisposed to MTC (Wu et al., 2011). The serum CT increase reported in non thyroid patients and patients with benign thyroid disorders l imits the clinical usefulness of CT dosing (d'Herbomez et al., 2007).

Preoperative CT rates are strongly associated with tumor vol ume, and the plasma CT concentration will typically reach 1 000 pg / ml in the presence of a detectable MTC (Raue and Frank-Raue, 2010).

Methodology

Design of study

Systematic review which is a type of literature reviews that collects and critically analyses multiple research studies using methods that are selected. Before one or more research questions are formulated and then finding and analyzing studies that relate to and answer those questions in a structured methodology.

The Five Steps to Conduct a Systematic Review (Khan et al., 2003).

Step 1

Framing questions for a review

The problem to be addressed by the review will be specified in the form of clear structured questions before beginning the review work. In this study our question was about the relationship between GLP 1RAs and thyroid cancer.

Step 2

Identifying relevant works

Studies from multiple resources will be searched with selection criteria that flow directly from the review questions. Reasons for inclusion and exclusion will be recorded. I use key words GLP 1 receptor agonists, thyroid Cancer, Meta-analysis, T2DM. The studies were in English only.

Step 3

Assessing the quality of studies

Selected studies will be subjected to a more refined quality assessment by using general critical appraisal guidelines and design based quality checklists.

Step 4

Summarizing the evidence

The study characteristics, quality and effects as well as the methods will be tabulated to explore the differences between studies and combine their effects (meta-analysis).

Step 5

Interpreting the findings

Any recommendations will be graded by reference to the strengths and weaknesses of the evidence

Registration

The research was registered with the REU with registration number (FPGRP/2019/446)

Data collection

The inclusion and exclusion of the articles and research followed the prisma techniques and flow chart.

In this research we used open Meta analytic program. The program is recommended by all academics for their students as well and I found a recommendation from my supervisor, the program helps the researcher (systemic review) to collect all data related to the study. (Authors, year of publication, gender of patients, number of patients).

During the study, all studies were added until they were analyzed accurately as seen in figure 1.The information recorded during the research period was as follows:

- Authors name.
- Type of study.
- Year of Publication.
- Number of patients in the study.
- The number of patients with high level of CT.

Results and Discussion

Evaluating the risk of Thyroid cancer associated with GLP 1 R agonists (GLP 1RAs)

A total of 58 studies were found using the keywords GLP 1 receptor agonists, thyroid Cancer, Meta-analysis, T2DM, on the PubMed database. After removal of duplicates, a total of 54 records were found to match the keyword search. 30 studies were excluded as it was clear from the abstract that they did not meet the Patient Intervention comparator and outcome criteria of the study. Of The 24 articles whose full text were assessed, 11 studies were included in the final qualitative synthesis. All these articles were found to be statistically capable of inclusion in the meta‐analysis, figure 2.

Summary of Studies Reviewed (Table 1)

In a cohort study created by Giuseppe Costante et al (2006) in Italy, 5817 patients taken GLP1RA medication included in this study, 66 patients (1.13 percent) showed increase in CT level (Costante et al., 2006). In FDA database review created by Mary Parks et al (2010) in USA, 1079 patients taken GLP1RA medication included in this study, no patients showed increase in CT level (Parks and Rosebraugh, 2010).

A cohort study created by Laszlo Hegedu¨ s et al (2011) in Denmark, were 5000 patients taken GLP1RA medication were included in this study, no patients showed increase in CT level (Hegedüs et al., 2011). In FDA database review created by MICHAEL ELASHOFF et al (2011) in USA , 1433 patients taken GLP1RA medication included in this study, 30 patients (2.1 percent) showed increase in CT level (Elashoff et al., 2011).

In a review of clinical trials and observational human studies created in Taiwan, 5000 patients taken GLP1RA medication included in this study and no patients showed increase in CT level (Chiu et al., 2012). In another cohort study created by David D. Dore et al (2012) in UK, 32,800 patients who have taken GLP1RA medication included in this study and no patients showed increase in CT level (Dore et al., 2012). Furthermore, in a cohort study by Maria Elena Lunati et al (2016) in italy, 20 patients who took GLP1RA medication included in this study and again no patients showed increase in CT level (Lunati et al., 2016).

In a randomized, double blind controlled trial in Germany, 4,668 patients who took GLP1RA medication were included in this study and 470 patients (10.06 percent) patients showed increase in CT level (Nauck et al., 2018). In another randomized trial in Denmark, 9,340 patients who have taken GLP1RA medication were included in the study and again no patients showed increase in CT level (Hegedüs et al., 2018). Finally, in a randomized trial in UK, 12,831 patients who took GLP1RA medication were included in this study, 30 patients (0.023 percent) patients showed increase in CT level (Bethel et al., 2019). All the included studies and the information extracted are listed in Table 1.

Complications reported to be associated with increased level of CT

In addition to increasing level of CT hormone these studies also reported a number of specific complications which when grouped showed that the incidence of thyroid cancer was 22 Patients (Giuseppe Costante et al, 2007), 30 patients (MICHAEL ELASHOFF et al, 2011), 37 patients (David D. Dore et al, 2012), 470 patients (Michael A. Nauck et al, 2017) and 2 patients (Laszlo Hegedus et al, 2018) with a total of 561 patients' incidence of thyroid cancer.

Table 2 and 3 is the calculation of the mean probability of increase of CT level as risk of thyroid cancer using a binary random effect model was 0.004 (0.4 percent) with CI between 0.003– 0.005. However, there is no heterogeneity ($p<0.001$). This confirms the significant variation in the studies as shown the forest plot **(Figure 3).**

The boxes show the effect estimates from the single studies, size of boxes show the strong of study, while the diamond shows the pooled result. The horizontal lines through the boxes illustrate the length of the confidence interval. The longer lines and wider confidence interval is the less reliable study results. The vertical line is the line of no effect (i.e. the position at which there is no clear difference between the intervention group and the control group). The outcome of interest level of CT, the results to the left of the vertical line favor the increase level of CT [91-100].

The diamond at the bottom of the forest plot shows the result when all the individual studies are combined together and averaged. The horizontal points of the diamond are the limits of the 95 percent confidence intervals and are subject to the same interpretation as any of the other individual studies on the plot.

To combine it all, our systemic review of the studies chosen shows the following,

- There is a low probability to increase level of CT during the use of the treatment.
- Studies included showed small confidence interval, this indicates that the studies have a reliable result.
- 4 studies showing correlation between treatment and level of CT and therefore risk of thyroid cancer one of these studies showing strong correlation.
- 5 studies showing no correlation between treatment and level of CT.
- 2 studies showed no association between treatment and level of CT.
- From the diamond there is heterogeneity, all the effect estimates of studies near to the line of no effect and that mean there is no association between treatment and CT level ($p<0.001$).

Evaluating the risk of pancreatitis associated with GLP 1 R agonists (GLP 1RAs)

A total of 349 studies were found. After removal of duplicates, a total of 316 records were found to match the keyword search. 288 studies were excluded as it was clear from the abstract that they did not meet the Patient Intervention Comparator and Outcome criteria of the study. Of The 28 articles whose full text was assessed, 11 studies were included in the final qualitative synthesis. All these articles were found to be statistically capable of inclusion in the meta-analysis, as seen in the prisma flow chart in figure 4.

Summary of Studies Reviewed (Table, 4)

In a case report by paul set al (2006) in USA, 1 patient who have taken GLP1RA medication showed pancreatitis (Denker and Dimarco, 2006). In another case report by NR tripathy et al (2008) in India, 1 patient who also took GLP1RA medication, also showed pancreatitis (Tripathy et al., 2008).

In FDA data review by Michael Elashoff et al (2011) in USA, 1433 patients who took GLP1RA medication,971 patients (67.75 percent) showed pancreatitis (Elashoff et al., 2011). In meta-analysis by Carlos alves et al (2012) in Portugal, 63488 patients taking GLP1RA medication, 85 patients (0.13 percent) showed pancreatitis (Alves et al., 2012).

In a retrospective cohort study in USA, 268561 patients taking GLP1RA medication were included in this study, 6982 patients (2.6 percent) showed pancreatitis (Romley et al., 2012). In a follow up study by m.wenten et al (2012) in USA, 24237 patients taking GLP1RA medication were included in this study, 46 patients (0.18 percent) showed pancreatitis (Wenten et al., 2012).

A prospective cohort study by D funch et al (2014) in USA, 38080 treatment patients were included in this study, 71 patients (0.18 percent) showed pancreatitis (Funch et al., 2014). Another cohort study done in at multi centers, 2024441 patients taking GLP1RA medication were included in this study, 1221 patients (0.06 percent) showed pancreatitis (Azoulay et al., 2016).

In a meta-analysis done by han chen (2016) in china, 24462 treatment patients were included in this study, 318 patients (1.29 percent) showed pancreatitis (Chen et al., 2016). In another meta-analysis in Italy, 14866 treatment patients were included in this study, 71 patients (0.47 percent) showed pancreatitis (Monami et al., 2017).

A retrospective cohort study by Mathieu boniol et al (2018) in france, 33292 patients taking GLP1RA medication were included in the study, 85 patients (0.25 percent) showed pancreatitis (Boniol et al., 2018). All the included studies and the information extracted are listed in Table 4.

Table 5 and 6 show the calculated mean probability of increase of CT level as risk of pancreatitis using a binary random effect model was 0.027 (2.7 percent) with CI between 0.022– 0.032. However, there is a no heterogeneity ($p<0.001$). This confirm the significant variation in the studies as shown the forest plot (Figure 5).

To explain it all, our systemic review of the studies chosen proves the following,

- There is a low probability to increase level of pancreatitis during use treatment.
- Studies included showed small confidence interval, this indicates that the studies have a reliable result.
- 2 studies showing strong correlation between treatment and pancreatitis.
- 7 studies showing no correlation between treatment and pancreatitis.
- 2 studies showed no association between treatment and pancreatitis.
- From the diamond there is no heterogeneity, all the effect estimates of studies near to the line of no effect and that mean there is no association between treatment and pancreatitis ($p<0.001$).

Strengths and Limitations of this study

Strength

1. This meta-analysis for testing all forms of therapies based on GLP1 RAs.

2. Specific types of FDA and EMA approved GLP 1 receptors have been included.

Limitations

1. Among all qualifying research, there are different diagnostic criteria for thyroid cancer, only one was used and analyzed.

Conclusion

This meta-analysis provides convincing evidence against the presumption that the therapeutic class of GLP1 RAs increases the risk of thyroid cancer and pancreatitis. Subgroup analysis also suggests potential beneficial effects requiring direct testing in the future.

Given the carcinogenic potential as seen in one strong study that explains the risk of thyroid cancer and another two strong studies explain the risk of pancreatitis, there is an urgent need for more large scale RCTs with long term thyroid safety monitoring while administering this group of medications.

References

1. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. Diabet Med. 1998;15(7):539-53. Doi: 10.1002/(SICI)1096-9136(199807)15:7<539::AID-DIA668>3.0.CO;2-S.
2. Alves C, Batel-Marques F, Macedo AF. A meta-analysis of serious adverse events reported with exenatide and liraglutide: acute pancreatitis and cancer. Diabetes Res Clin Pract. 2012;98(2):271-84. Doi: 10.1016/j.diabres.2012.09.008.
3. Aroda VR, DeYoung MB. Clinical implications of exenatide as a twice-daily or once-weekly therapy for type 2 diabetes. Postgrad Med. 2011;123(5):228-38. Doi: 10.3810/pgm.2011.09.2479.
4. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2010;33(1):S62-9. Doi: 10.2337/diacare.28.suppl_1.s37.
5. Care D. Classification and diagnosis of diabetes. Diabetes Care. 2016;39(1):S13-22. Doi: 10.2337/dc16-er09.
6. Azoulay L, Filion KB, Platt RW, et al. Incretin based drugs and the risk of pancreatic cancer: international multicentre cohort study. Br Med J. 2016;352. Doi: 10.1136/bmj.i581
7. Barnett A. Exenatide. Expert Opin Pharmacother. 2007;8(15):2593-608. Doi: 10.1517/14656566.8.15.2593
8. Barrington P, Chien JY, Showalter HD, et al. A 5-week study of the pharmacokinetics and pharmacodynamics of LY2189265, a novel, long-acting glucagon-like peptide-1 analogue, in patients with type 2 diabetes. Diabetes, Obesity and Metabolism. 2011;13(5):426-33. Doi: 10.1111/j.1463-1326.2011.01364.x.
9. Best JH, Lavillotti K, DeYoung MB, et al. The effects of exenatide bid on metabolic control, medication use and hospitalization in patients with type 2 diabetes mellitus in clinical practice: a systematic review. Diabetes, Obesity and Metabolism. 2012;14(5):387-98. Doi: 10.1111/j.1463-1326.2011.01533.x
10. Bethel MA, Patel RA, Thompson VP, et al. Changes in serum calcitonin concentrations, incidence of medullary thyroid carcinoma, and impact of routine calcitonin concentration monitoring in the EXenatide Study of Cardiovascular Event Lowering (EXSCEL). Diabetes Care. 2019;42(6):1075-80. Doi: 10.2337/dc18-2028
11. Bjerre Knudsen L, Madsen LW, Andersen S, et al. Glucagon-like peptide-1 receptor agonists activate rodent thyroid C-cells causing calcitonin release and C-cell proliferation. Endocrinology. 2010;151(4):1473-86. Doi: 10.1210/en.2009-1272
12. Black C, Donnelly P, McIntyre L, et al. Meglitinide analogues for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2007(2). Doi: 10.1002/14651858.CD004654.pub2
13. Blase E, Taylor K, Gao HY, et al. Pharmacokinetics of an oral drug (acetaminophen) administered at

various times in relation to subcutaneous injection of exenatide (exendin-4) in healthy subjects. J Clin Pharmacol. 2005;45(5):570-7. Doi: 10.1177/0091270004274432
14. Boniol M, Franchi M, Bota M, et al. Incretin-based therapies and the short-term risk of pancreatic cancer: results from two retrospective cohort studies. Diabetes Care. 2018;41(2):286-92. DOI: 10.2337/dc17-0280
15. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature. 2001;414(6865):813-20. Doi: 10.1038/414813a
16. Buse JB, Drucker DJ, Taylor KL, et al. DURATION-1: Exenatide once weekly produces sustained glycemic control and weight loss over 52 weeks. Diabetes care. 2010;33(6):1255-61. Doi: 10.2337/dc09-1914
17. Buse JB, Nauck M, Forst T, et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): A randomised, open-label study. Lancet. 2013;381(9861):117-24. Doi: 10.1016/S0140-6736(12)61267-7
18. Buse JB, Rosenstock J, Sesti G, et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). Lancet. 2009;374(9683):39-47. Doi: 10.1016/S0140-6736(09)60659-0
19. Chen H, Zhou X, Chen T, et al. Incretin-based therapy and risk of pancreatic cancer in patients with type 2 diabetes mellitus: A meta-analysis of randomized controlled trials. Diabetes Therapy. 2016;7:725-42. Doi: 10.1007/s13300-016-0198-3
20. Chiu WY, Shih SR, Tseng CH. A review on the association between glucagon-like peptide-1 receptor agonists and thyroid cancer. J Diabetes Res. 2012. Doi: 10.1155/2012/924168
21. Committee TI. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes care. 2009;32(7):1327. Doi: 10.2337/dc09-9033
22. Copley K, McCowen K, Hiles R, et al. *Investigation of exenatide elimination and its in vivo and in vitro* degradation. Curr Drug Metab. 2006;7(4):367-74. Doi: 10.2174/138920006776873490
23. Costante G, Meringolo D, Durante C, et al. Predictive value of serum calcitonin levels for preoperative diagnosis of medullary thyroid carcinoma in a cohort of 5817 consecutive patients with thyroid nodules. J Clin Endocrinol Metab. 2007;92(2):450-5. Doi: 10.1210/jc.2006-1590
24. Crespel A, De Boisvilliers F, Gros L, et al. Effects of glucagon and glucagon-like peptide-1-(7-36) amide on C cells from rat thyroid and medullary thyroid carcinoma CA-77 cell line. Endocrinology. 1996;137(9):3674-80. Doi: 10.1210/endo.137.9.8756532
25. Croom KF, McCormack PL. Liraglutide: a review of its use in type 2 diabetes mellitus. Drugs. 2009;69:1985-2004. Doi: 10.2165/11201060-000000000-00000
26. Cuthbertson DJ, Irwin A, Gardner CJ, et al. Improved glycaemia correlates with liver fat reduction in obese, type 2 diabetes, patients given glucagon-like peptide-1 (GLP-1) receptor agonists. Plos. 2012;7(12):e50117. Doi: 10.1371/journal.pone.0050117
27. d'Herbomez M, Caron P, Bauters C, et al. Reference range of serum calcitonin levels in humans: Influence of calcitonin assays, sex, age, and cigarette smoking. Eur J Endocrinol. 2007;157(6):749-55. Doi: 10.1530/EJE-07-0566
28. Davies MJ, Donnelly R, Barnett AH, et al. Exenatide compared with long-acting insulin to achieve glycaemic control with minimal weight gain in patients with type 2 diabetes: Results of the Helping Evaluate Exenatide in patients with diabetes compared with Long-Acting insulin (HEELA) study. Diabetes Obes Metab. 2009 Dec;11(12):1153-62. Doi: 10.1111/j.1463-1326.2009.01154.x
29. Denker PS, Dimarco PE. Exenatide (exendin-4)-induced pancreatitis: a case report. Diabetes care. 2006;29(2):471-2. Doi: 10.2337/diacare.29.02.06.dc05-2043.
30. Diamant M, Heine RJ. Thiazolidinediones in type 2 diabetes mellitus: Current clinical evidence. Drugs. 2003;63:1373-406. Doi: 10.2165/00003495-200363130-00004
31. Dong JZ, Shen Y, Zhang J, et al. Discovery and characterization of taspoglutide, a novel analogue of human glucagon-like peptide-1, engineered for sustained therapeutic activity in type 2 diabetes. Diabetes Obes Metab. 2011;13(1):19-25.
    a. Doi: https://doi.org/10.1111/j.1463-1326.2010.01313.x
32. Dore DD, Bloomgren GL, Wenten M, et al. A cohort study of acute pancreatitis in relation to exenatide use. Diabetes Obes Metab. 2011;13(6):559-66. Doi: https://doi.org/10.1111/j.1463-1326.2011.01376.x
33. Dore DD, Seeger JD, Chan KA. Incidence of health insurance claims for thyroid neoplasm and pancreatic malignancy in association with exenatide: signal refinement using active safety surveillance. Ther Adv Drug Saf. 2012;3(4):157-64. Doi: https://doi.org/10.1177/2042098612446473
34. Elashoff M, Matveyenko AV, Gier B, et al. Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1–based therapies. Gastroenterology. 2011;141(1):150-6.Doi: https://doi.org/10.1053/j.gastro.2011.02.018
35. Elisei R. Routine serum calcitonin measurement in the evaluation of thyroid nodules. Best Pract. Res Clin Endocrinol Metab. 2008;22(6):941-53. Doi:

https://doi.org/10.1016/j.beem.2008.09.008
36. Elisei R, Bottici V, Luchetti F, et al. Impact of routine measurement of serum calcitonin on the diagnosis and outcome of medullary thyroid cancer: experience in 10,864 patients with nodular thyroid disorders. J Clin Endocr. 2004;89(1):163-8. Doi: https://doi.org/10.1210/jc.2003-030550
37. Elrishi MA, Khunti K, Jarvis J, et al. The dipeptidyl-peptidase-4 (DPP-4) inhibitors: a new class of oral therapy for patients with type 2 diabetes mellitus. Pract Diabetes Int. 2007;24(9):474-82. Doi: https://doi.org/10.1002/pdi.1181
38. Eng C, Kramer CK, Zinman B, et al. Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis. The Lancet. 2014;384(9961):2228-34. Doi: https://doi.org/10.1016/S0140-6736(14)61335-0
39. Ferrannini E, Gastaldelli A, Iozzo P. Pathophysiology of prediabetes. Medical Clinics. 2011;95(2):327-39.
40. Funch D, Gydesen H, Tornøe K, et al. A prospective, claims-based assessment of the risk of pancreatitis and pancreatic cancer with liraglutide compared to other antidiabetic drugs. Diabetes Obes Metab. 2014;16(3):273-5.
    a. Doi: https://doi.org/10.1111/dom.12230
41. Gier B, Butler PC, Lai CK, et al. Glucagon like peptide-1 receptor expression in the human thyroid gland. J Clin Endocrinol Metab. 2012;97(1): 121-31.
    a. Doi: https://doi.org/10.1210/jc.2011-2407
42. Grundy SM. Pre-diabetes, metabolic syndrome, and cardiovascular risk. J Am Coll Cardiol. 2012;59(7):635-43.
43. Gupta V. Pleiotropic effects of incretins. Indian J Endocrinol Metab. 2012;16(Suppl1):S47. Doi: https://doi.org/10.4103%2F2230-8210.94259
44. Gupta V. Glucagon-like peptide-1 analogues: an overview. Indian J Endocrinol Metab. 2013;17(3):413.
    a. Doi: https://doi.org/10.4103%2F2230-8210.111625
45. Hargrove DM, Kendall ES, Reynolds JM, et al. Biological activity of AC3174, a peptide analog of exendin-4. Regul Pept. 2007;141(1-3):113-9. Doi: https://doi.org/10.1016/j.regpep.2006.12.021
46. Hegedüs L, Moses AC, Zdravkovic M, et al. GLP-1 and calcitonin concentration in humans: lack of evidence of calcitonin release from sequential screening in over 5000 subjects with type 2 diabetes or nondiabetic obese subjects treated with the human GLP-1 analog, liraglutide. J Clin Endocr Metab. 2011;96(3):853-60.
47. Hegedüs L, Sherman SI, Tuttle RM, et al. No evidence of increase in calcitonin concentrations or development of C-cell malignancy in response to liraglutide for up to 5 years in the LEADER trial. Diabetes Care. 2018;41(3):620-2.
    a. Doi: https://doi.org/10.2337/dc17-1956
48. Hirsch PF, Baruch H. Is calcitonin an important physiological substance?. Endocr. 2003;21:201-8. Doi: https://doi.org/10.1385/ENDO:21:3:201
49. Hoff AO, Catala-Lehnen P, Thomas PM, Priemel M, Rueger JM, Nasonkin I, Bradley A, Hughes MR, Ordonez N, Cote GJ, Amling M. Increased bone mass is an unexpected phenotype associated with deletion of the calcitonin gene. J Clin Investig. 2002;110(12):1849-57.
50. Hu FB, Manson JE, Stampfer MJ, et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. N Engl J Med. 2001;345(11):790-7.
    a. Doi: 10.1056/NEJMoa010492
51. Hurren KM, Pinelli NR. Drug-drug interactions with glucagon-like peptide-1 receptor agonists. Ann Pharmacother. 2012;46(5):710-7. Doi: https://doi.org/10.1345/aph.1Q583
52. Jabbour SA, Goldstein BJ. Sodium glucose co-transporter 2 inhibitors: blocking renal tubular reabsorption of glucose to improve glycaemic control in patients with diabetes. Int J Clin Pract. 2008;62(8):1279-84. Doi: https://doi.org/10.1111/j.1742-1241.2008.01829.x
53. Jacobsen LV, Vouis J, Hindsberger C, et al. Treatment with liraglutide—a once-daily GLP-1 analog—does not reduce the bioavailability of ethinyl estradiol/levonorgestrel taken as an oral combination contraceptive drug. J Clin Pharmacol. 2011;51(12):1696-703. Doi: https://doi.org/10.1177/0091270010389471
54. Kapitza C, Zdravkovic M, Hindsberger C, et al. The effect of the once-daily human glucagon-like peptide 1 analog liraglutide on the pharmacokinetics of acetaminophen. Adv Ther. 2011;28:650-60. Doi: https://doi.org/10.1007/s12325-011-0044-y
55. Kayaniyil S, Lozano-Ortega G, Bennett HA, et al. A network meta-analysis comparing exenatide once weekly with other GLP-1 receptor agonists for the treatment of type 2 diabetes mellitus. Diab Ther. 2016;7:27-43. Doi: https://doi.org/10.1007/s13300-016-0155-1

56. Khan KS, Kunz R, Kleijnen J, et al. Five steps to conducting a systematic review. J R Soc Med. 2003;96(3):118-21. Doi: https://doi.org/10.1177/014107680309600304
57. Körner M, Stöckli M, Waser B, et al. GLP-1 receptor expression in human tumors and human normal tissues: potential for *in vivo* targeting. J Nuclear Med. 2007;48(5):736-43.
58. Kothare PA, Linnebjerg H, Skrivanek Z, et al. Exenatide effects on statin pharmacokinetics and lipid response. Int J Clin Pharmacol Ther. 2007;45(2):114-20. Doi: https://doi.org/10.5414/cpp45114
59. Kothare PA, Soon DK, Linnebjerg Het al. Effect of exenatide on the steady-state pharmacokinetics of digoxin. J Clin Pharmacol. 2005;45(9):1032-7. Doi: https://doi.org/10.1177/0091270005278806
60. Kurosawa M, Sato A, Shiraki M, et al. Secretion of calcitonin from the thyroid gland increases in aged rats. Arch Gerontol Geriatr. 1988;7(3):229-38. Doi: https://doi.org/10.1016/0167-4943(88)90006-4
61. Lamari Y, Boissard C, Moukhtar MS, et al. Expression of glucagon-like peptide 1 receptor in a murine C cell line Regulation of calcitonin gene by glucagon-like peptide 1. FEBS letters. 1996 393(2-3):248-52. Doi: https://doi.org/10.1016/0014-5793(96)00895-2
62. Lebovitz HE. Alpha-glucosidase inhibitors. Endocrinol Metab Clin North Am. 1997;26(3):539-51. Doi: https://doi.org/10.1016/S0889-8529(05)70266-8
63. Lee YS, Shin S, Shigihara T, et al. Glucagon-like peptide-1 gene therapy in obese diabetic mice results in long-term cure of diabetes by improving insulin sensitivity and reducing hepatic gluconeogenesis. Diabetes. 2007;56(6):1671-9. Doi: https://doi.org/10.2337/db06-1182
64. Lunati ME, Grancini V, Colombo C, et al. Basal and stimulated calcitonin levels in patients with type 2 diabetes did not change during 1 year of Liraglutide treatment. Metabolism. 2016;65(1):1-6. Doi: https://doi.org/10.1016/j.metabol.2015.09.010
65. Machens A, Hoffmann F, Sekulla C, et al. Importance of gender-specific calcitonin thresholds in screening for occult sporadic medullary thyroid cancer. Endocr Relat Cancer. 2009;16(4):1291-8.
66. Madsbad S, Kielgast U, Asmar M, et al. An overview of once-weekly glucagon-like peptide-1 receptor agonists—available efficacy and safety data and perspectives for the future. Diab Obes Meta. 2011;13(5):394-407. Doi: https://doi.org/10.1111/j.1463-1326.2011.01357.x
67. Madsen LW, Knauf JA, Gotfredsen C, et al. GLP-1 receptor agonists and the thyroid: C-cell effects in mice are mediated via the GLP-1 receptor and not associated with RET activation. Endocrinol. 2012;153(3):1538-47. Doi: https://doi.org/10.1210/en.2011-1864
68. Malm-Erjefalt M, Ekblom M, Vouis J, et al. Effect on the gastrointestinal absorption of drugs from different classes in the biopharmaceutics classification system, when treating with liraglutide. Mol Pharmaceutics. 2015;12(11):4166-73. Doi: https://doi.org/10.1021/acs.molpharmaceut.5b00278
69. Marre M, Shaw J, Brändle M, et al. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with type 2 diabetes (LEAD-1 SU). Diab Med. 26(3):268-278.Doi: https://doi.org/10.1111/j.1464-5491.2009.02666.x
70. McConnell EE, Solleveld HA, Swenberg JA, et al. Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. J Natl Cancer Inst. 1986;76(2):283-9. Doi: https://doi.org/10.1093/jnci/76.2.283
71. Monami M, Nreu B, Scatena A, et al. Safety issues with glucagon-like peptide-1 receptor agonists (pancreatitis, pancreatic cancer and cholelithiasis): D ata from randomized controlled trials. Diabetes Obes Metab. 2017;19(9):1233-41.
    a. Doi: https://doi.org/10.1111/dom.12926
72. Nathan DM. Long-term complications of diabetes mellitus. N Engl J Med. 1993;328(23):1676-85. Doi: 10.1056/NEJM199306103282306
73. Nauck MA, Jensen TJ, Rosenkilde C, et al. Neoplasms reported with liraglutide or placebo in people with type 2 diabetes: results from the LEADER randomized trial. Diabetes Care. 2018;41(8):1663-71. Doi: https://doi.org/10.2337/dc17-1825
74. Norris SL, Lee N, Thakurta S, et al. Exenatide efficacy and safety: a systematic review. Diabetic Med. 2009;26(9):837-46. Doi: https://doi.org/10.1111/j.1464-5491.2009.02790.x
75. O'toole K, Fenoglio-Preiser C, Pushparaj N. Endocrine changes associated with the human aging process: III. Effect of age on the number of calcitonin immunoreactive cells in the thyroid

gland. Hum. Pathol. 1985;16(10):991-1000. Doi: https://doi.org/10.1016/S0046-8177(85)80276-8

76. Parks M, Rosebraugh C. Weighing risks and benefits of liraglutide—the FDA's review of a new antidiabetic therapy. New Eng J Med. 2010;362(9):774-7.
    a. Doi: 10.1056/NEJMp1001578
77. Persson P, Grunditz T, Axelson J, et al. Cholecystokinins but not gastrin-17 release calcitonin from thyroid C-cells in the rat. Regul Pept. 1988;21(1-2):45-56. Doi: https://doi.org/10.1016/0167-0115(88)90090-0
78. Plum L, Belgardt BF, Brüning JC. Central insulin action in energy and glucose homeostasis. J Clin Inves. 2006;116(7):1761-6.
79. Prasad-Reddy L, Isaacs D. A clinical review of GLP-1 receptor agonists: efficacy and safety in diabetes and beyond. Drugs in context. 2015;4. Doi: https://doi.org/10.7573%2Fdic.212283
80. Ratner R, Nauck M, Kapitza C, et al. Safety and tolerability of high doses of taspoglutide, a once-weekly human GLP-1 analogue, in diabetic patients treated with metformin: a randomized double-blind placebo-controlled study 1, 2. Diabetic Med. 2010;27(5):556-62.Doi: https://doi.org/10.1111/j.1464-5491.2010.02990.x
81. Raue F, Frank-Raue K. Update multiple endocrine neoplasia type 2. Familial cancer. 2010 ;9(3):449-57.
    a. Doi: https://doi.org/10.1007/s10689-010-9320-2
82. Retterstol K. Taspoglutide: a long acting human glucagon-like polypeptide-1 analogue. Expert Opin Investig Drugs. 2009;18(9):1405-11. Doi: https://doi.org/10.1517/13543780903164205
83. Romley JA, Goldman DP, Solomon M, et al. Exenatide therapy and the risk of pancreatitis and pancreatic cancer in a privately insured population. Diabetes Technol. Ther. 2012;14(10):904-11. Doi: https://doi.org/10.1089/dia.2012.0075
84. Rosol TJ. On-target effects of GLP-1 receptor agonists on thyroid C-cells in rats and mice. Toxicol Pathol. 2013;41(2):303-9.
85. Schäfer G. Biguanides. A review of history, pharmacodynamics and therapy. Diabetes Metab. 1983;9(2):148-63.
86. Schjoldager BT, Mortensen PE, Christiansen J, et al. GLP-1 (glucagon-like peptide 1) and truncated GLP-1, fragments of human proglucagon, inhibit gastric acid secretion in humans. Dig Dis Sci. 1989;34:703-8. Doi: https://doi.org/10.1007/BF01540341
87. Seewoodhary J, Bain S. New once-weekly formulation of exenatide for type 2 diabetes. Future Prescriber. 2010;11(3):18-21. Doi: https://doi.org/10.1002/fps.71
88. Seewoodhary J, Davies J. Novel GLP-1 mimetics in diabetes: lixisenatide and albiglutide. Future Prescriber. 2011;12(2):20-2. Doi: https://onlinelibrary.wiley.com/doi/abs/10.1002/fps.79
89. Sennik D, Ahmed F, Russell-Jones D. Exenatide, a GLP-1 agonist in the treatment of Type 2 diabetes. Expert Rev Endocrinol Metab. 2012;7(1):15-26. Doi: https://doi.org/10.1586/eem.11.79
90. Shah Z, Shafi S. Diabetes the Global Economic Burden of Adults and the Role of Herbalism as a safe & altenative cost-effective therapy. An Updared Overview. J Drug Deliv Ther. 2019;9(3-s):954-61. Doi: https://doi.org/10.22270/jddt.v9i3-s.3085
91. Taylor K, Gurney K, Han J, et al. Exenatide once weekly treatment maintained improvements in glycemic control and weight loss over 2 years. Endocrine Disorders. 2011;11:1-9. Doi: https://doi.org/10.1186/1472-6823-11-9
92. Thong KY, Jose B, Sukumar N, et al. Safety, efficacy and tolerability of exenatide in combination with insulin in the Association of British Clinical Diabetologists nationwide exenatide audit. Diabetes Obes Metab. 2011;13(8):703-10. Doi: https://doi.org/10.1111/j.1463-1326.2011.01393.x
93. Tripathi BK, Srivastava AK. Diabetes mellitus: complications and therapeutics. Med Sci Monit. 2006;12(7):130-47.
94. Tripathy NR, Basha S, Jain R, et al. Exenatide and acute pancreatitis. J Assoc Physicians India. 2008;56(6):987-8.
95. Vahle JL, Byrd RA, Blackbourne JL, et al. Effects of dulaglutide on thyroid C cells and serum calcitonin in male monkeys. Endocrinol. 2015;156(7):2409-16. Doi: https://doi.org/10.1210/en.2014-1717
96. Wang W, Lewin E, Olgaard K. Role of calcitonin in the rapid minute-to-minute regulation of plasma Ca2+ homeostasis in the rat. Eur J Clin. Invest. 2002;32(9):674-81. Doi: https://doi.org/10.1046/j.1365-2362.2002.01054.x
97. Waser B, Beetschen K, Pellegata NS, et al. Incretin receptors in non-neoplastic and neoplastic thyroid C cells in rodents and humans: relevance for incretin-based diabetes therapy. Neuroendocrinology. 2011;94(4):291-301. Doi: https://doi.org/10.1159/000330447

98. Wenten M, Gaebler JA, Hussein M, et al. Relative risk of acute pancreatitis in initiators of exenatide twice daily compared with other anti-diabetic medication: a follow-up study. Diabetic medicine. 2012;29(11):1412-8. Doi: https://doi.org/10.1111/j.1464-5491.2012.03652.x
99. Wu LS, Roman SA, Sosa JA. Medullary thyroid cancer: an update of new guidelines and recent developments. Curr Opin Oncol. 2011;23(1):22-7. Doi: 10.1097/CCO.0b013e328340b527
100. Zinman B, Gerich J, Buse JB, et al. Efficacy and safety of the human GLP-1 analog liraglutide in combination with metformin and TZD in patients with type 2 diabetes mellitus (LEAD-4 Met+ TZD). Diabetes care. 2009;32(7):1224-30.

PEER REVIEW

Not commissioned. Externally peer reviewed.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

FUNDING

None

Figures and Tables

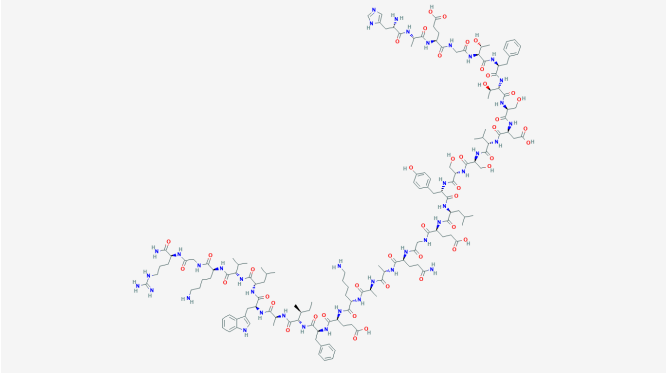

Figure 2: Chemical structure of Incretin

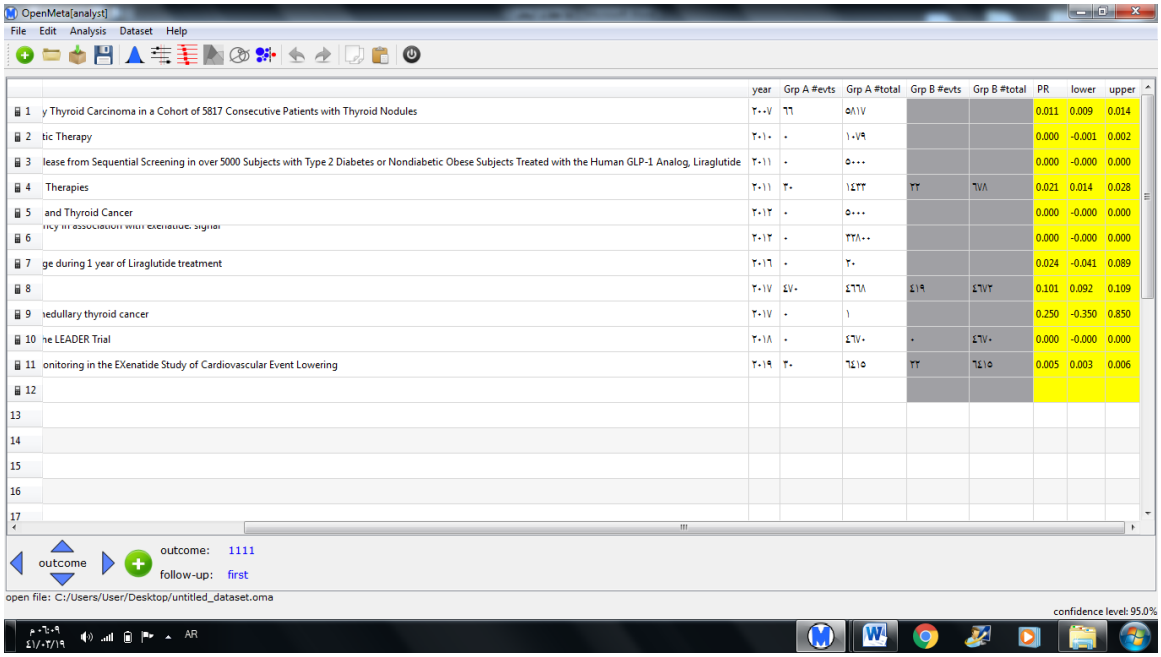

Figure 2: Shows steps to use and fill the program during the search (Open Meta analytic)

Column 1: name of studies used in systematic review.

Column 2: The year of publication for each study.

Column 3: total Number of samples.

Column 4: Number of patients with high level of CT.

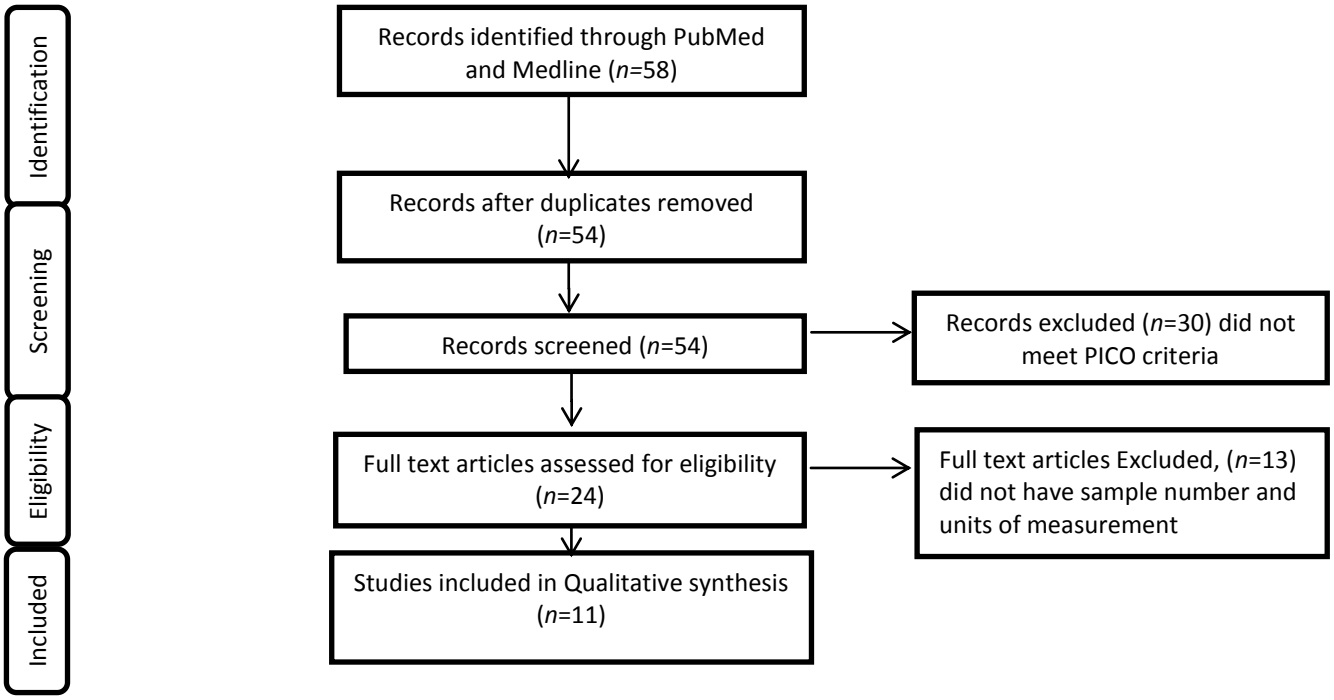

Figure 2: PRISMA flowchart of the article selection process for analysing, inclusion and meta-analysis of the Thyroid Cancer specifically

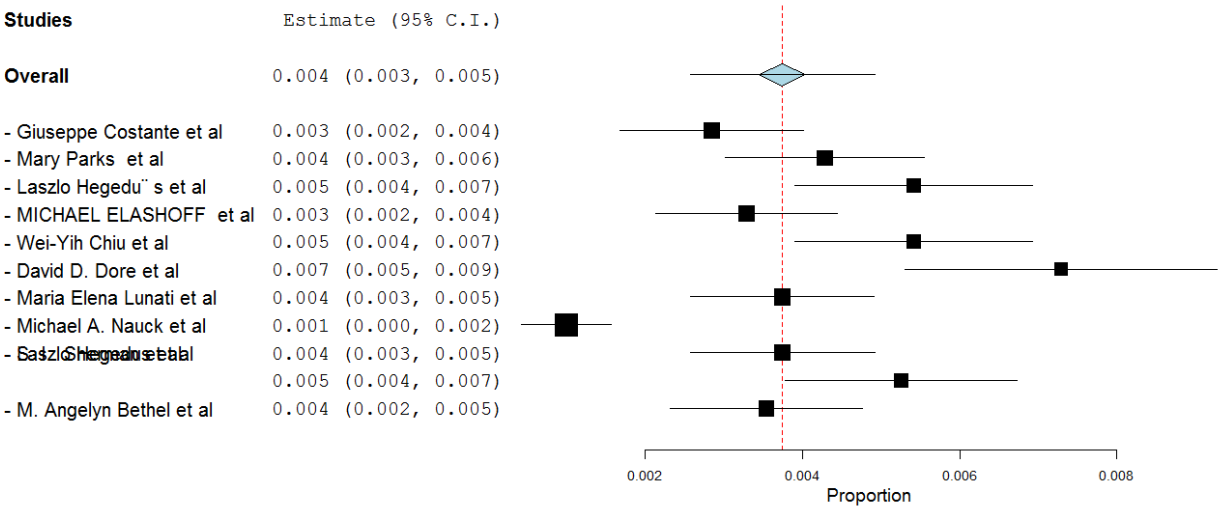

Figure 3: Overall meta-analysis of studies showing binary probability of increase CT level.

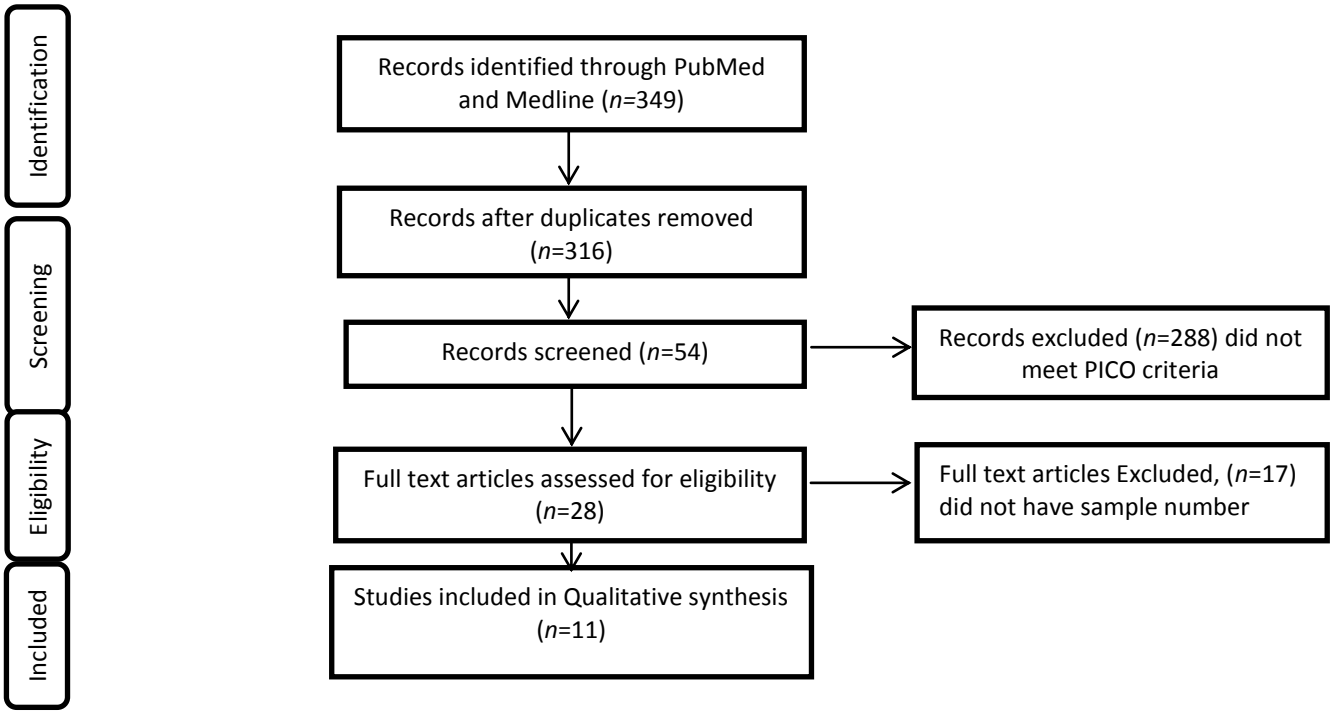

Figure 4: PRISMA flowchart of the article selection process for analysing, inclusion and meta-analysis of pancreatitis.

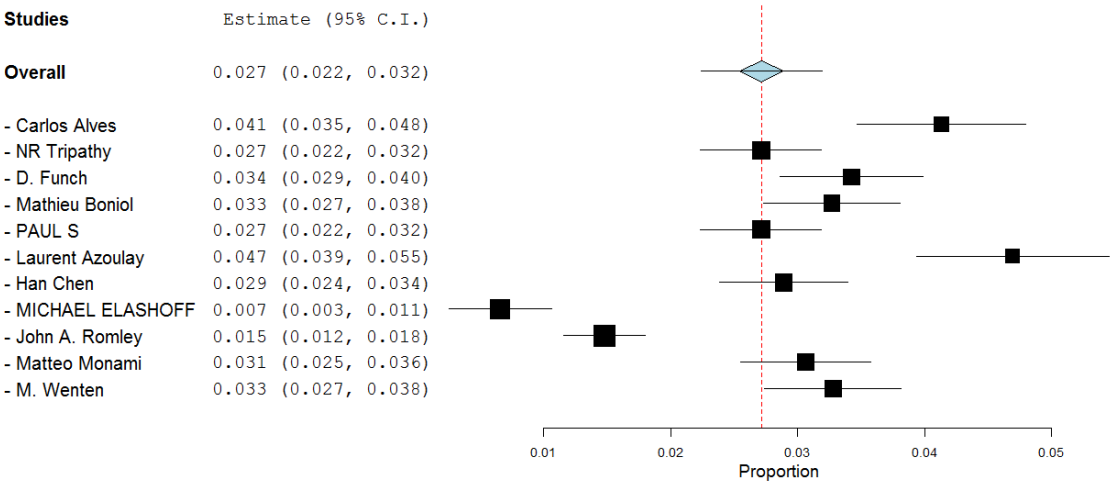

Figure 5: Overall meta‑analysis of studies showing binary probability of pancreatitis.

Table 1: the list of studies involved in the meta-analysis of the association between GLIP1 receptors and thyroid cancer

Study author	country	time	type of study	Total number of patient	The number of CT level >20 pg
Giuseppe Costante et al	italy	2007	Cohort methodology	5817	66
Mary Parks et al	USA	2010	FDA database Review	1079	0
Laszlo Hegedu¨s et al	Denmark	2011	Cohort methodology	5000	0
MICHAEL ELASHOFF et al	USA	2011	FDA database review	1433	30
Wei-Yih Chiu et al	taiwan	2012	Review clinical trials and observational human studies	5000	0
David D. Dore et al	UK	2012	cohort methodology	32,800	0
Maria Elena Lunati et al	italy	2016	Cohort methodology	20	0
Michael A. Nauck et al	germany	2017	LEADER review randomized, double-blind-controlled trial	4,668	470
S. I. Sherman et al	USA	2017	case study	1	0
Laszlo Hegedus et al	denmark	2018	LEADER review randomized trials	9,340	0
M. Angelyn Bethel et al	UK	2019	Randomized trials	12,831	30

Table 1 Binary Random Effect Model for thyroid cancer (Dersimonian laird).

Estimate	Lower Bound	Upper Bound	SD Error	P Value
0.004	0.003	0.005	0.001	<0.001

Table 2: Heterogeneity of the thyroid cancer samples

tau^2	Q(df=13)	Heterogeneity p Value	I^2
0.000	651.855	<0.001	98 percent

Table 4: the list of studies involved in the meta-analysis of the association between GLIP1 receptors and pancreatitis

Study author	country	time	Type of study	Total number of patient	The number of outcome
PAUL S	USA	2006	Case study	1	1
NR Tripathy	india	2008	Case study	1	1
MICHAEL ELASHOFF	USA	2011	FDA data review	1433	971
Carlos Alves	Portugal	2012	Meta analyses	63488	85
John A. Romley	USA	2012	retrospective cohort analysis	268,561	6982
M. Wenten	USA	2012	follow-up study	24 237	46
D. Funch	USA	2014	Prospective cohort analysis	38080	71
Laurent Azoulay	multicenter	2016	cohort study	2 024 441	1221
Han Chen	china	2016	Meta-analysis	24,462	318
Matteo Monami	italy	2017	Meta-analysis	14,866	71
Mathieu Boniol	france	2018	Retrospective Cohort Studies	33,292	85

Table 3 : Binary Random Effect Model for pancreatitis (Dersimonian laird)

Estimate	Lower Bound	Upper Bound	SD Error	P Value
0.027	0.022	0.032	0.002	<0.001

Table 4 : Heterogeneity of the pancreatitis sample

tau^2	Q(df=13)	Heterogeneity p Value	I^2
0.000	10486.468	<0.001	100 percent

Received: *28-May-2023, Manuscript No. AMJ-23-3757;* ***Editor assigned:*** *02-Jun-2023, PreQC No. AMJ-23-3757(PQ);* ***Reviewed:*** *15-Jun-2023, QC No. AMJ-23-3757;* ***Revised:*** *20-Jun-2023, Manuscript No. AMJ-23-3757(R);* ***Published:*** *27-Jun-2023*