What Is The Role of Incretin Mimetics In The Treatment of Type 2 Diabetes?

Isaac Silberstein

Abstract

Type 2 diabetes mellitus (DM) is an intricate disorder defined by insulin resistance, impaired insulin secretion, hyperglycemia, and both microvascular and macrovascular complications. Standard antidiabetic agents like metformin, insulin, sulfonylureas and thiazolidinediones are often insufficient at glucoregulation and do not address the decline in beta cell function that characterizes type 2 diabetes. Moreover, the adverse effects of some of these pharmaceuticals, such as hypoglycemia and weight gain, are disappointing and further limit their clinical utility. Research demonstrates that the actions of two potent incretins, Glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide (GIP), address these concerns as they stimulate beta cell activity, increase insulin secretion and decrease glucagon secretion both in a glucose dependent fashion, and increase satiety which results in weight loss. These effects have attracted increasing interest and excitement in the scientific literature as incretin mimetics have been introduced for patients in which first line therapy is unsatisfactory. Three drugs that mimic the actions of endogenous GLP-1 have been introduced---Exenatide, Exenatide LAR, and liraglutide---and this paper will focus on the role and efficacy that these novel treatment options play in the management of type 2 diabetes as clinicians are shifting away from traditional therapy.

Introduction

Type 2 Diabetes Mellitus (DM) is characterized as a chronic metabolic disorder disrupting the delicate balance of glucose homeostasis. Hyperglycemia, which is the most common hallmark of the disease, is closely linked with alterations in protein and lipid metabolism. Long term complications such as myocardial infarction, stroke, neuropathy, nephropathy, and retinopathy occur due to derangements in glucose metabolism. Most cases of diabetes are divided into two categories: Insulin-dependent or type 1 and Non-insulin dependent or type 2 diabetes mellitus. Type 1 diabetes comprises approximately 10% of the diagnosed population, and is usually caused by an autoimmune response of the body against the pancreas. Clinically, the pancreas is unable to secrete insulin and patients require insulin replacement in the form of subcutaneous injections in order to survive. Individuals with type 1 diabetes are usually less than 30 years of age, have no functional reserve in the pancreas, and display symptoms of polyuria, polyphagia, and polydipsia. In contrast, persons with type 2 DM make up approximately 90-95% of the diabetic population. Type 2 patients exhibit insulin resistance, manifested by a positive family history and obesity and display hypertension and dyslipidemia. The onset is often gradual and often goes undiagnosed for years. Treatment includes diet and exercise, in combination with medications. The prevalence of type 2 DM increases dramatically with age and obesity. Due to modern science, both men and women have increased longevity, which predisposes them to diabetes because of an aging pancreas. The risk of diabetes has increased fourfold among the elderly, who have increased amounts of abdominal fat (American Diabetes Association, 2009). There are also differences among ethnic groups, with the highest incidence found among American Indians and Alaskan Natives, followed by African Americans, Hispanics, and non-Hispanic whites. The health care costs of managing diabetes are staggering, with a total cost of about 170 billion dollars. Approximately, 55% of all medical expenditures spent on diabetes comprise the elderly. Physician visits, hospital and nursing home admissions, and medication, all place an excessive toll on overloading our already fragile health care system (Centers for Disease Control and Prevention, 2011). With both early prevention and diagnosis, type 2 diabetics can reduce long term complications and the burden on our nation's health care. This paper will, therefore, analyze the increased role of novel pharmaceutical agents called the incretin mimetics as a treatment approach to type 2 diabetes.

Methods

The author located the relevant information for this paper using the PubMed search engine in order to select and extract the most appropriate journal articles pertaining to the role of incretin mimetics in the treatment of type 2 diabetes.

Discussion

The pathogenesis of type 2 Diabetes Mellitus is extremely intricate, and research has uncovered several important factors contributing to the disorder. One of the main features of type 2 diabetes is insulin resistance during which the body cells are no longer sensitive to the actions of insulin. This unresponsiveness leads to reduced glucose uptake, rising blood glucose levels, and the utilization of both proteins and fat for energy (Peterson, Shulman, 2006). In addition, insulin deficiency is another factor leading to hyperglycemia, caused by defective secretion or a reduction in beta cell mass. Research has shown that insulin secretion is directly related to the amount of beta cells present in the pancreas. In fact, most patients with type 2 diabetes mellitus have lost about 50% of their beta cell function at the time of diagnosis, and this decline continues over time. With a steady loss of beta cells, the natural progression of the condition results in rising HbA1c levels, indicating poor glycemic control (Wajchenberg, 2007).

Additionally, impaired insulin secretion results in proteins being broken down into amino acids, which are then converted to glucose by a process known as gluconeogenesis. This new glucose released into circulation further aggravates hyperglycemia. Ultimately, this protein catabolism may even lead to organ dysfunction and muscle weakness (Guillet, et. al. 2012). Another factor contributing to hyperglycemia is hepatic

Isaac Silberstein graduated in 2013 with a B.S. degree in Biology.

glucose output resulting from non-inhibition of glucagon. This results in the degradation of glycogen to glucose by the liver and leads to elevated blood glucose levels (Dunning, Gerich, 2007). There is also growing evidence that adipose tissue plays a significant role in the pathology of type 2 diabetes. Under normal circumstances, insulin inhibits lipolysis, preventing an increase in free fatty acids in circulation. With impaired insulin secretion, however, hormone sensitive lipase breaks down triglycerides in adipose tissue, allowing high levels of Free Fatty Acids (FFA's) to accumulate in the blood. In the liver, the FFA's are converted into triglycerides. The excess triglycerides stored in the hepatic organ results in a fatty liver, which can eventually lead to cirrhosis. Moreover, the increased levels of FFA's stimulate hepatic glucose output from the liver, further aggravating the current hyperglycemic state (Bayes, et. al. 2004).

Type 2 Diabetes is usually diagnosed during a routine blood test. A fasting plasma glucose level greater than 126mg/dl on 2 consecutive occasions is highly suggestive of the disorder. The HbA1c level is a significant determinant in allowing the clinician insight into the patient's blood glucose regulation for the previous 60 to 90 days. The result of this test will determine whether one will develop long term complications such as neuropathy, nephropathy and retinopathy. The American Diabetes Association recommends that an HbA1c value below or equal to 7% is preferred for most type 2 diabetics (ADA, 2007). Another essential diagnostic tool is the C-peptide level test during which an amino acid is released from the beta cells in combination with insulin. This test is an indirect measure of insulin secretion and is important in determining the need for insulin in type 2 diabetes patients. The normal C-peptide level is between 0.17 to 0.83 umol/liter. Sinking below this level will alert the physician that some deterioration of beta cell function has occurred and that exogenous insulin may be required as a treatment option. Finally, another test known as the fructosamine assay measures glycation of albumin and affords the clinician critical insight into glycemic control over the previous 2 to 3 weeks (Van Cauter, et. al. 1992). The fructosamine assay demonstrates the most diagnostic utility when patients are afflicted with medical conditions, such as hemolytic and iron deficiency anemia, or blood loss transfusions, rendering the previously mentioned HbA1c test inaccurate. Therefore, the fructosamine assay would reveal glycemic control over the previous three weeks (Goldstein, et. al. 2004).

Treatment Strategy

The American Diabetes Association, the American College of Endocrinology, and the National Institutes of Health, have all published guidelines for the selection of medications that should be incorporated into the type 2 diabetes treatment plan. All three organizations agree that newly diagnosed patients should begin lifestyle changes such as diet and exercise, along with the drug metformin (Inzucchi, et. al. 2012). There is a disagreement, however, among the organizations concerning drug selection as an add-on to metformin when the patient doesn't reach their HbA1c target goal within a 3 month period. If the HbA1c value is still elevated after this period of time, then a second drug that has a different mechanism of action is added to metformin monotherapy. If after another 3 months, the HbA1c goal is still not reached, then a third drug or insulin injection may be incorporated in the antidiabetic treatment regimen. For example, insulin will usually be required when the HbA1c levels are above 10%, or when fasting blood glucose levels are greater than 250mg/dl, or in individuals who display symptoms such as polyuria or ketosis in the blood Therefore, the choice of which drug to select, coupled with metformin, is dependent on several factors: 1) Weight loss 2) Aversion to injection 3) Fasting and/or postprandial hyperglycemia 4) Cost of medications 5) Hepatorenal function 6) Pre-existing edema or heart failure 7) Erratic eating patterns 8) Osteoporosis (Inzucchi, et. al. 2012). All these factors will be further elucidated as each drug class is discussed at length.

Overview of Traditional Oral Therapies

To begin, metformin is an anti-hyperglycemic agent which has been shown to suppress hepatic gluconeogenesis. It also improves the sensitivity of both skeletal muscles and the liver to insulin, lowering insulin resistance (Kirpichnikov, et. al. 2002). Since metformin's mechanism of action does not involve insulin secretion, the drug does not pose significant issues with hypoglycemia and weight gain. Metformin can be used safely together with all other anti-diabetic agents, both oral and injectable, and has been recommended to treat pre-diabetes from developing into overt diabetes. The main adverse effects are gastrointestinal in nature, such as abdominal discomfort, cramping, nausea, and diarrhea. These side effects can be minimized by taking the medication with food and slowly titrating upward toward a maximal dose of 2000mg/day (Campbell, et. al. 1996). Chronic use of the drug may lead to malabsorption of folate and vitamin B12, so periodic blood tests are required to measure these levels (De Jager, et. al. 2010). Importantly, the use of metformin provides benefits, such as a significant reduction in of HbA1c levels and decreasing fasting blood glucose levels about 50-70 mg/dL (Kirpichnikov, et. al. 2002). It has an excellent safety profile, does not cause weight gain or hypoglycemia, and can be combined with other antidiabetic medications. All these advantages make metformin the physician's first choice in the treatment of type 2 diabetes (Inzucchi, et. al. 2012).

Another treatment option is the collection of Thiazolidinediones (TZD's), which are drugs that counteract insulin resistance by making skeletal muscle, adipose tissue, and liver cells more responsive to insulin. TZD's stimulate a peroxisome proliferator activated receptor-y (PPAR-Y), which in a diabetic is downregulated due to insulin resistance. Once triggered by the drug, this unique receptor activates genes which affect glucose and lipid metabolism. For instance, the enzyme Glut-4, which is the chief glucose transporter activated by PPAR-Y, enables the blood glucose to enter the cells and reduce hyperglycemia. TZD's have a slow onset of action with a maximum effect only visible after about 2 months. Fasting blood glucose is reduced by about 60-70 mg/dl, with an HbA1c decline between 0.5% and 1.4%. They are usually given in

combination with other agents, rather than monotherapy (Yki-Järvinen, 2004). The side effect profile and the high association with bladder cancer and bone fractures, has relegated these drugs almost extinct. For example, a study involving the TZD known as pioglitazone, and its prevention in macrovascular events, showed that patients receiving the drug had a higher incidence of bladder cancer compared to placebo (Dormandy, et. al. 2005). Additionally, French health officials found that patients who used pioglitazone had a 22% increased risk of bladder cancer, and that high doses and prolonged usage greater than 2 years placed patients at a high risk for the disease (Nuemann, et. al. 2012). A recent study confirmed that women who took TZD's had a higher fracture rate of about 25% due to a reduction in osteoblastic activity and an increased excretion of calcium in the urine (Bazelier, et. al. 2012). TZD's cause both significant edema and weight gain and, therefore, must be cautiously prescribed to patients with cardiovascular disease (Yki-Järvinen, 2004). For example, heart failure can be induced when TZD's are given to patients with pre-existing edema (Giles, et. al. 2008). Although TZD's target insulin resistance, their side effects and safety profile limit their use.

Yet, another drug option is the insulin secretagogues known as the sulfonylureas (SU). Originally, these drugs were considered first line agents in the treatment of type 2 diabetes until they were replaced by metformin. Their mechanism of action is blocking the outflow of ATP sensitive potassium channels and allowing the inflow of calcium intracellularly, which leads to increased insulin secretion (Panten, et. al. 1996). Therefore, these medications are only effective in patients with adequate beta cell reserve. The SU's reduce HbA1c levels of about 1.5%, with a reduction of fasting blood glucose similar to metformin. There are several major concerns when prescribing these medications. First, most type 2 diabetics are obese, with insulin resistance already present at the time of diagnosis. Since sulfonylureas cause insulin secretion, patients must eat to avoid hypoglycemic episodes, causing excess pounds to accrue, further aggravating insulin resistance (Porta, Trento, 2007). Second, these agents exhibit a primary failure rate ranging between 15% to 25%, and a secondary failure rate of 5% to 7% per year. Whether this failure is due to this drug class, or to the declining progression of the disease, remains unclear (Donath. et. al. 2005). Third, besides weight gain, hypoglycemia is an adverse effect, particularly in the elderly. In this population of individuals, large doses of a long acting SU preparation, in conjunction with renal dysfunction and reduced carbohydrate intake, are prime factors in causing hypoglycemia (Halter, Morrow, 1990). In addition to the SU's, but similar in action, are the non-sulfonylureas known as meglitinides. Like SU's, these drugs cause an increase in insulin secretion and require the patient to possess an adequate beta cell reserve. Their main function is in lowering postprandial glucose levels. They must be given approximately 30 minutes before meals, and if a meal is skipped, the dose should not be taken as the risk for hypoglycemia is increased. Due to their mechanism of action of insulin secretion, hypoglycemia and weight gain are to be expected (Koda-Kimble, et. al. 2013). The utilization of sulfonylureas has declined, mainly due to the increased number of hypoglycemic events, along with weight gain, which further exacerbates the resistance to insulin. Newer drugs, such as incretins, are replacing SU's because they either cause weight loss or are weight neutral, and do not induce hypoglycemia.

A New Paradigm of Treatment

In the 1960's, scientists wanted to test whether the route of glucose infusion in the body would produce a marked effect on insulin secretion. Indeed, when both oral and intravenous glucose infusions were offered to the participants of the study, the researchers found that even though equal amounts of glucose were infused through both routes, the oral glucose load produced a greater insulin response (Perley, Kipnis, 1967). A similar effect has been proven in other studies as well in regards to the amount of postprandial C-peptide released, as opposed to insulin, during an intravenous and oral glucose challenge (Nauck, et. al. 1986b). This remarkable effect has come to be known as the incretin effect, in which gut hormones, known as incretins, stimulate the secretion of insulin in response to food ingestion. The incretin effect has been well established to be present in both diabetics and nondiabetics. In type 2 diabetic patients, however, the incretin effect has been shown to be substantially diminished (Nauck, et. al. 1986a).

So what exactly are the incretins? There are mainly two incretins that have been identified: Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). GIP is synthesized and secreted from the enteroendocrine cells, known as the K cells, the majority of which are located in the duodenum and proximal jejunum. GIP is released in response to ingestion of carbohydrates and fats and binds to specific pancreatic beta cells. Once bound, it carries out a number of interesting effects on glucose regulation. In the pancreas, GIP has been shown to increase glucose-dependent insulin secretion. It has also been shown to increase beta cell proliferation and mass even in an environment rich with chemicals toxic to beta cells, such as streptozotocin. And GIP has antiapoptotic and neogenetic effects on the beta cells. Although GIP has a multitude of effects of on the beta cells, it does not affect the alpha cells in any way. In addition, it does not influence gastric emptying or satiety. Even though GIP has numerous beneficial effects on carbohydrate metabolism, GLP-1 is secreted in much higher concentrations and lowers glucagon release (Baggio, Drucker, 2007). Most importantly, for reasons not well understood, studies have shown that GIP has lost a significant portion of its insulinotropic activity, which renders the hormone not very useful as a pharmacological agent (Meier, et. al. 2001). Therefore, the remainder of this paper will explore the other significant incretin: GLP-1.

GLP-1 is a peptide hormone synthesized and secreted from the L cells of the lower small intestine, specifically the distal ileum and colon (Baggio, Drucker, 2007). Once released, it exerts a number of glucoregulatory effects. For example, in a 1993 study, researchers examined the effect of GLP-1 in type 2 diabetic patients exhibiting hyperglycemia while in a fasting state. On the first day, the placebo subjects received an

administration of intravenous saline and their blood glucose levels decreased at a slow rate. On the following day, however, the participants received a GLP-1 infusion and their blood concentrations fell at a significantly faster rate. Based on this experiment, the investigators concluded that GLP-1 is effective at dramatically lowering glucose levels by stimulating insulin secretion. More interestingly, the researchers noted that GLP-1 stimulates the beta cells to release insulin in a glucose-dependant manner. That is, as the glucose concentrations fell to homeostatic levels, the ability of GLP-1 to stimulate insulin was slowly becoming diminished. This is an extremely vital characteristic of GLP-1: it will stimulate insulin secretion only under hyperglycemic circumstances, not when glucose levels are below normal; this action prevents the occurrence of hypoglycemia. Similarly, this study indicated that GLP-1 exerts a glucose-dependent effect on the alpha cells as well. GLP-1 will decrease glucagon secretion but only to an essential minimum. Thus, if glucose levels start to fall to the normal range, glucagon will stop decreasing and start to rise in concentrations, demonstrating its glucose-dependent action (Nauck, et. al. 1993).

In addition to acting as an insulin secretagogue and suppressing glucagon in a glucose dependent fashion, GLP-1 has been found to slow gastric emptying in type 2 diabetics (Wettergren, et. al. 1993).This finding is important because the gastric emptying rate has been observed to be accelerated in type 2 diabetics, which explains why their postprandial glucose levels are elevated (Smith, 1996). By delaying this process, GLP-1 ensures a more gradual release of glucose into the bloodstream, which can now be properly balanced by the delayed or reduced insulin response found in type 2 diabetics. This results in a slower rise in blood glucose after a meal (Wettergren, et. al. 1993). The mechanism of this action is as follows: high density receptors for GLP- 1 are located in the central nervous system, specifically the medullary structure called the area postrema (Yamamoto, et. al. 2003). After GLP-1 binds to its receptor in this area, it activates the efferent projections of the vagus nerve which ultimately decreases the smooth muscle contractions of the stomach (Nauck, et. al. 2002). As a consequence of lowering gastric activity, GLP-1 reduces appetite and, in turn, decreases food intake, which ultimately leads to weight loss (Parker, et. al. 2013).

GLP-1 also works by expanding beta cell mass, particularly beta cell proliferation and growth by activating the phosphatidylinositide 3-kinases. Although the precise mechanism has yet to be elucidated, it has been proposed that perhaps it is carried out by transactivating the epidermal growth factor receptor (Buteau, et. al. 2003). GLP-1 has been shown to decrease beta cell apoptosis in isolated human islets (Farilla, et. al. 2003) and increase neogenesis. The combination of beta cell proliferation and antiapoptosis results in beta cell mass expansion (Baggio, Drucker, 2007).

With all of the advantageous effects of native GLP-1 in type 2 diabetes, exogenous GLP-1 would nevertheless act as an ineffective pharmaceutical agent due to its very short plasma half-life of less than 2 minutes. This is because GLP-1's last two amino acids of its N-terminal, arginine and glycine, are immediately cleaved by the enzyme dipeptidyl peptidase-IV (DPP-IV). Following proteolysis, inactivation of the molecule occurs, rendering it therapeutically useless (Vilsbøll, et. al. 2003). Through what means then have researchers circumvented the challenge posed by the DPP-IV system? The answer has unexpectedly taken a turn to the southwest, where venomous lizards called Gila monsters reside. Analyzing their saliva, investigators have discovered a peptide molecule called exendin-4. Even though researchers are unaware of what function this molecule serves for the reptile, they are aware that Exendin 4 is resistant to degradation by DPP-IV because of its unique amino acid sequence (Holst, 2006). However, it nonetheless shares 52% amino acid homology with native GLP-1 (Chen, Drucker, 1997), and because of this similarity in structure, it binds to the GLP-1 receptor and mimics its glucoregulatory effects. From this knowledge, researchers have developed an antidiabetic drug, using synthetic exendin-4, called exenatide which is administered to patients in the form of a twice daily subcutaneous injection. Since this incretin mimetic is a peptide, it cannot be orally infused as it would be degraded by gastric secretions (Holst, 2006).

Exenatide has been found to mimic many key actions of GLP-1. First, it increases glucose dependent insulin production (Egan, et. al., 2002) and decreases glucagon secretion after meals in type 2 diabetic patients suffering from postprandial hyperglycemia (Kolterman, et. al. 2003). Exenatide has also been shown to reduce gastric emptying (Nielsen, et. al. 2004) and decrease food intake which results in weight loss (Szayna, et. al. 2000). Furthermore, exenatide has been shown to both enhance the first and second phase insulin response when the beta cells are exposed to infused glucose (Fehse, et. al. 2005) and increase islet cell growth (Tourrel, et. al. 2001). Another incretin mimetic is the GLP-1 agonist exenatide long acting release (LAR). In this unique form, exenatide is encased in microspheres to lengthen its interval of action. Unlike twice daily exenatide, the long acting formulation is more convenient as it is administered as a once weekly subcutaneous injection. The GLP-1 agonist escapes from the microspheres over a period of 6 to 10 weeks but exerts its complete effect after 9 weeks. Because of this, the clinical effectiveness of exenatide LAR cannot be determined immediately (Krause, Kirwin, 2010). Clinical trials comparing the effectiveness of exenatide with its long acting counterpart demonstrated that exenatide once weekly produced a significantly greater decline in A1C and fasting blood glucose levels. In fact, the HbA1c value for the exenatide LAR group dropped 0.7% greater than the twice daily exenatide group from baseline, and the fasting blood glucose value declined by a difference of 23mg/dL between the two groups (Blevins, et. al. 2011).

In addition to exenatide, once daily liraglutide was introduced as yet another incretin mimetic. This analogue has a 97% structural identity with endogenous GLP-1 by the substitution of the amino acid arginine for lysine near the tail of the molecule and the linkage of a C16 fatty acid to lysine at position 26. This acylation allows liraglutide to bind with serum

albumin and protect it from the proteolytic effects of DPP-IV (Agersø, Vicini), greatly increasing the biological half- life of the drug to approximately 12.6 hours (Agersø, et. al. 2002). As with exenatide, liraglutide has been shown to exhibit similar effects like glucose dependant insulin production, glucagon suppression, beta cell growth, decreased gastric emptying time, and satiety, all of which lead to weight loss (Wajcberg, Amarah, 2010). In a 2009 study, researchers formed two groups of participants who were on metformin, a sulfonylurea, or both. One group received liraglutide and the other was treated with twice daily exenatide. This trial demonstrated that liraglutide lead to a modest decline in HbA1c (-1.12%), as opposed to exenatide (-0.79%) but was nevertheless a superior glycemic controller (Buse, et. al. 2009). Furthermore, patients who replaced their exenatide treatment with liraglutide showed an even further decline in HbA1c (-0.32%) (Buse, et. al. 2010).

There are a number of safety considerations and adverse effects that clinicians should keep in mind before prescribing an incretin mimetic. For example, nausea was by far the most common complaint experienced by those receiving treatment exclusively with liraglutide or exenatide. Clinical trials have demonstrated that such gastrointestinal disturbances, however, subsided the longer the treatment progressed. In addition, increasing the dose of exenatide from 5-µg to 10-µg increased the risk of gastrointestinal related side effects. Moreover, although the risk of a hypoglycemic episode is minimal while on incretin mimetic therapy due to its glucose dependant action, it can nevertheless occur if a GLP-1 agonist is combined with a non-glucose dependent drug like a sulfonylurea. In order to prevent hypoglycemia, therefore, antidiabetic treatment should begin with a small dose of sulfonylurea while on an incretin mimetic. Another factor for clinicians to take into account is that there have been some reports of acute pancreatitis while only on liraglutide or exenatide therapy. Patients with type 2 diabetes, however, have a higher risk of developing this severe condition (Noel, et. al. 2009) so the evidence focusing on the relationship between incretins and pancreatitis is inconclusive. But it is advised that doctors take a cautionary approach when prescribing incretins to type 2 diabetes patients.

Let us now focus on three recent clinical trials that have proven to be pivotal in providing evidence that incretin mimetics are superior to other treatments in a number of crucial parameters. First, in 2012, an open label, European Exenatide (EUREXA) study was conducted by Gallwitz and colleagues who wished to determine whether a GLP-1 agonist or a traditional treatment agent is more effective at reaching target HbA1c levels, when monotherapy with metformin failed. The researchers compared twice daily exenatide versus once daily glimeperide, an oral sulfonylurea, in addition to metformin therapy. A total of 1,029 participants were arbitrarily assigned to either exenatide or glimeperide as an add-on to metformin, with baseline HbA1c values between 7% and 9%. After a four year evaluation, the results in table 1 demonstrate that fewer subjects in the glimeperide group reached the HbA1c level of less than 7% as compared to the exenatide group. Furthermore, while taking exenatide, fewer patients succumbed to treatment failure and considerably more met their target HbA1c goal. Moreover, those receiving the incretin mimetic lost weight, whereas those in the glimeperide group gained weight, and hypoglycemic events were more commonly reported in those taking glimeperide. As can be seen, however, although a limited number of patients in the glimeperide group both reached their target HbA1c and blood glucose levels, nevertheless, its side effect profile decreases its usefulness. Therefore, these results indicate that the GLP-1 agonist exenatide is more efficacious than glimeperide in a number of crucial factors of successful diabetes treatment (Gallwitz, et. al. 2012).

	Exenatide	**Glimepiride**
Dosage	5-10mcg 2xday	1-8 mg/day
Population	515	514
Treatment Failure: HbA1c > 7%	54%	54%
Target HbA1c < 7%	44%	31%
Mean Weight	Lost 10 lb	Gained 5 lb
Hypoglycemia	186 Patients	338 Patients

Table 1: Results of the EUREXA trial (Gallwitz, et. al. 2012).

In 2010, another study that was 1.5 years in duration was conducted to determine whether exenatide LAR was more likely than insulin glargine to reach target HbA1c goals. Enlisted in this randomized trial were 456 participants who suffered from chronic type 2 diabetes. These patients were already taking oral first line treatment like metformin or sulfonylurea therapy. However, based on the average HbA1c value of 8.3%, their current treatment was deemed ineffective. The results of the trial showed that the average HbA1c value for the incretin mimetic group was 7.1% and 7.3% for the insulin glargine group. Even though there was not any profound clinical difference, this is nevertheless a statistically significant result. And this illustrates the notion that statistical significance does not always translate to clinical significance. In terms of weight, exenatide patients lost about 5lbs and insulin glargine subjects gained about 10lbs. Moreover, hypoglycemic episodes occurred with much greater frequency in those taking insulin glargine. Therefore, these findings demonstrate that once weekly exenatide is recommended for patients who favor convenience, weight loss, and have a high risk of hypoglycemic episodes (Diamant, et. al. 2012).

Finally, in 2012, a randomized, placebo controlled DURATION-4 trial was conducted by Russell-Jones and colleagues to compare the safety and efficacy of exenatide LAR with monotherapy treatment options for type 2 diabetes such as metformin, pioglitazone, and sitagliptin in drug naïve patients. This 26 week study enlisted 800 type 2 diabetes

patients who lacked glycemic control evidenced with a mean HbA1c level of 8.5%. The results of the study showed that metformin, exenatide, and pioglitazone shared a similar reduction in HbA1c of 1.5% and exhibited superior glycemic control than sitagliptin with a decline of 1.2%. Furthermore, those taking metformin and exenatide showed the greatest weight loss of 4.4lbs. In addition, major hypoglycemic episodes were not reported with the use of any of the aforementioned monotherapies (Russell-Jones, et. al. 2012). Taken together, these trials demonstrate that incretin mimetics are effective at positively addressing multiple diabetic factors like weight, hypoglycemia, and dysglycemia.

Conclusion

Type 2 diabetes is a progressive disease that clinicians have had profound difficulty in properly managing. Traditional pharmaceutical agents such as sulfonylureas, for example, have resulted in weight gain and risk of hypoglycemia which has unfortunately defined a typical diabetic's glucose lowering regimen. Now, however, with the introduction of incretin mimetics such as exenatide and liraglutide, patients can take advantage of this novel treatment approach. Counteracting the many pathophysiological mechanisms involved in the disease, coupled with the expansion of beta cell mass, is a significant advancement in the treatment of type 2 diabetes. In the past, clinicians were fighting an uphill battle against this condition, but with incretin based therapies, and recent high profile studies clearly demonstrating their efficacy and safety, we are moving one step closer to properly managing this multifaceted disease.

References

Agersø H, Jensen LB, Elbrønd B, Rolan P, Zdravkovic M. 2002. The pharmacokinetics, pharmacodynamics, safety and tolerability of NN2211, a new long-acting GLP-1 derivative, in healthy men. Diabetologia. 45(2):195-202.

Agersø H, Vicini P. 2003. Pharmacodynamics of NN2211, a novel long acting GLP-1 derivative. The European Journal of Pharmaceutical Sciences. 19(2-3):141-50.

American Diabetes Association (ADA). 2007. Standards of medical care in diabetes. Diabetes Care. 30(Suppl.1):4-41

American Diabetes Association. 2009. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 32(Suppl 1): S62–S67.

Baggio LL, Drucker DJ. 2007. Biology of incretins: GLP-1 and GIP. Gastroenterology. 132(6):2131-57.

Bays H, Mandarino L, DeFronzo RA. 2004. Role of the adipocyte, free fatty acids, and ectopic fat in pathogenesis of type 2 diabetes mellitus: peroxisomal proliferator-activated receptor agonists provide a rational therapeutic approach. The Journal of Clinical Endocrinology and Metabolism. 89(2):463-78.

Bazelier MT, Gallagher AM, van Staa TP, Cooper C, Leufkens HG, Vestergaard P, de Vries F. 2012. Use of thiazolidinediones and risk of osteoporotic fracture: disease or drugs? Pharmacoepidemiology and Drug Safety. 21(5):507-14.

Blevins T, Pullman J, Malloy J, Yan P, Taylor K, Schulteis C, Trautmann M, Porter L. 2011. DURATION-5: exenatide once weekly resulted in greater improvements in glycemic control compared with exenatide twice daily in patients with type 2 diabetes. The Journal of Clinical Endocrinology and Metabolism. 96(5):1301-10.

Buse JB, Rosenstock J, Sesti G, Schmidt WE, Montanya E, Brett JH, Zychma M, Blonde L; LEAD-6 Study Group. 2009. 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. 374(9683):39-47.

Buse JB, Sesti G, Schmidt WE, Montanya E, Chang CT, Xu Y, Blonde L, Rosenstock J. 2010.Liraglutide effect action in diabetes-6 study group. Switching to once-daily liraglutide from twice-daily exenatide further improves glycemic control in patients with type 2 diabetes using oral agents. Diabetes Care.33:1300–3.

Buteau J, Foisy S, Joly E, Prentki M. 2003. Glucagon-like peptide 1 induces pancreatic beta-cell proliferation via transactivation of the epidermal growth factor receptor. Diabetes. 52(1):124-32.

Campbell RK, White JR Jr, Saulie BA. 1996. Metformin: a new oral biguanide. Clinical Therapeutics. 18(3):360-71

Centers for Disease Control and Prevention. 2011. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011.

Chen YE, Drucker DJ. 1997. Tissue-specific expression of unique mRNAs that encode proglucagon-derived peptides or exendin 4 in the lizard. The Journal of Biological Chemistry. 272(7):4108-15.

De Jager J, Kooy A, Lehert P, Wulffelé MG, van der Kolk J, Bets D, Verburg J, Donker AJ, Stehouwer CD. 2010. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial.BMJ. 340:c2181

Diamant M, Van Gaal L, Stranks S, Guerci B, MacConell L, Haber H, Scism-Bacon J, Trautmann M. 2012. Safety and efficacy of once-weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes over 84 weeks. Diabetes Care. 35(4):683-9

Donath MY, Ehses JA, Maedler K, Schumann DM, Ellingsgaard H, Eppler E, Reinecke M. 2005. Mechanisms of beta-cell death in type 2 diabetes. Diabetes. 54 Suppl 2:S108-13.

Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, Skene AM, Tan MH, Lefèbvre PJ, Murray GD, Standl E, Wilcox RG, Wilhelmsen L, Betteridge J, Birkeland K, Golay A, Heine RJ, Korányi L, Laakso M, Mokán M, Norkus A, Pirags V, Podar T, Scheen A, Scherbaum W, Schernthaner G, Schmitz O, Skrha J, Smith U, Taton J; PROactive investigators. 2005. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet. 366(9493):1279-89.

Dunning BE, Gerich JE. 2007. The role of alpha-cell dysregulation in fasting and postprandial hyperglycemia in type 2 diabetes and therapeutic implications. Endocrine Reviews. 28(3):253-83.

Egan JM, Clocquet AR, Elahi D. 2002. The insulinotropic effect of acute exendin-4 administered to humans: comparison of nondiabetic state to type 2 diabetes. The Journal of Clinical Endocrinology Metabolism. 87(3):1282-90.

Farilla L, Bulotta A, Hirshberg B, Li Calzi S, Khoury N, Noushmehr H, Bertolotto C, Di Mario U, Harlan DM, Perfetti R. 2003. Glucagon-like peptide 1 inhibits cell apoptosis and improves glucose responsiveness of freshly isolated human islets. Endocrinology. 144(12):5149-58.

Fehse F, Trautmann M, Holst JJ, Halseth AE, Nanayakkara N, Nielsen LL, Fineman MS, Kim DD, Nauck MA. 2005. Exenatide augments first- and second-phase insulin secretion in response to intravenous glucose in subjects with type 2 diabetes. The Journal of Clinical Endocrinology and Metabolism. 90(11):5991-7.

Gallwitz B, Guzman J, Dotta F, Guerci B, Simó R, Basson BR, Festa A, Kiljański J, Sapin H, Trautmann M, Schernthaner G. 2012. Exenatide twice daily versus glimepiride for prevention of glycaemic deterioration

in patients with type 2 diabetes with metformin failure (EUREXA): an open-label, randomised controlled trial. Lancet. 379(9833):2270-8.

Giles TD, Miller AB, Elkayam U, Bhattacharya M, Perez A. 2008. Pioglitazone and heart failure: results from a controlled study in patients with type 2 diabetes mellitus and systolic dysfunction. Journal of Cardiac Failure.14 (6):445-52.

Goldstein DE, Little RR, Lorenz RA, Malone JI, Nathan D, Peterson CM, Sacks DB. 2004. Tests of glycemia in diabetes. Diabetes Care. 27(7):1761-73.

Guillet C, Masgrau A, Walrand S, Boirie Y. 2012. Impaired protein metabolism: interlinks between obesity, insulin resistance and inflammation. Obesity Reviews. 13 (Suppl) 2:51-7.

Halter J, Morrow L. 1990. Use of Sulfonylurea Drugs in Elderly Patients. Diabetes Care. 13(Suppl.2): 86-92

Holst JJ. 2006. Glucagon-like peptide-1: from extract to agent. The Claude Bernard Lecture, 2005. Diabetologia. 49(2):253-60.

Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR. 2012. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 35(6):1364-79.

Kirpichnikov D, McFarlane SI, Sowers JR. 2002. Metformin: an update. Annals of Internal Medicine. 137(1):25-33.

Koda-Kimble, Mary Anne, and Brian K. Alldredge. Applied Therapeutics: The Clinical Use of Drugs. Baltimore: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2013. Print.

Kolterman OG, Buse JB, Fineman MS, Gaines E, Heintz S, Bicsak TA, Taylor K, Kim D, Aisporna M, Wang Y, Baron AD. 2003. Synthetic exendin-4 (exenatide) significantly reduces postprandial and fasting plasma glucose in subjects with type 2 diabetes. The Journal of Clinical Endocrinology and Metabolism. 88(7):3082-9.

Krause A, Kirwin J. 2010. Exenatide LAR: A sustained-release formulation of exenatide for the treatment of type 2 diabetes. Formulary. 45:43-51.

Meier JJ, Hücking K, Holst JJ, Deacon CF, Schmiegel WH, Nauck MA. 2001. Reduced insulinotropic effect of gastric inhibitory polypeptide in first-degree relatives of patients with type 2 diabetes. Diabetes. 50(11):2497-504.

Nauck M, Stöckmann F, Ebert R, Creutzfeldt W. 1986a. Reduced incretin effect in type 2 (non-insulin-dependent) diabetes. Diabetologia. 29(1):46-52.

Nauck MA, Heimesaat MM, Behle K, Holst JJ, Nauck MS, Ritzel R, Hufner M, Schmiegel WH. 2002.Effects of glucagon-like peptide 1 on counterregulatory hormone responses, cognitive functions, and insulin secretion during hyperinsulinemic, stepped hypoglycemic clamp experiments in healthy volunteers. The Journal of Clinical Endocrinology Metabolism. 87:1239 -1246.

Nauck MA, Homberger E, Siegel EG, Allen RC, Eaton RP, Ebert R, Creutzfeldt W. 1986b. Incretin effects of increasing glucose loads in man calculated from venous insulin and C-peptide responses. The Journal of Clinical Endocrinology and Metabolism. 63(2):492-8.

Nauck MA, Kleine N, Orskov C, Holst JJ, Willms B, Creutzfeldt W. 1993. Normalization of fasting hyperglycaemia by exogenous glucagon-like peptide 1 (7-36 amide) in type 2 (non-insulin-dependent) diabetic patients. Diabetologia. 36(8):741-4.

Neumann A, Weill A, Ricordeau P, Fagot JP, Alla F, Allemand H. 2012. Pioglitazone and risk of bladder cancer among diabetic patients in France: a population-based cohort study. Diabetologia. 55(7):1953-62

Nielsen LL, Young AA, Parkes DG. 2004. Pharmacology of exenatide (synthetic exendin-4): a potential therapeutic for improved glycemic control of type 2 diabetes. Regulatory Peptides. 117(2):77-88.

Noel RA, Braun DK, Patterson RE, Bloomgren GL. 2009. Increased risk of acute pancreatitis and biliary disease observed in patients with type 2 diabetes: a retrospective cohort study. Diabetes Care. 32(5):834-8.

Panten U, Schwanstecher M, Schwanstecher C. 1996. Sulfonylurea receptors and mechanism of sulfonylurea action. Experimental and Clinical Endocrinology & Diabetes. 104(1):1-9.

Parker JA, McCullough KA, Field BC, Minnion JS, Martin NM, Ghatei MA, Bloom SR. 2013. Glucagon and GLP-1 inhibit food intake and increase c-fos expression in similar appetite regulating centres in the brainstem and amygdala. International Journal of Obesity. 37(10):1391-8

Perley MJ, Kipnis DM. 1967. Plasma insulin responses to oral and intravenous glucose: studies in normal and diabetic subjects. The Journal of Clinical Investigation. 46(12):1954-62.

Petersen KF, Shulman GI. 2006. Etiology of insulin resistance. International Journal of Clinical Practice. 119 (5 Suppl 1):S10-6.

Porta M, Trento M. 2007. Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 30(1):193.

Russell-Jones D, Cuddihy RM, Hanefeld M, Kumar A, González JG, Chan M, Wolka AM, Boardman MK; DURATION-4 Study Group. 2012. Efficacy and safety of exenatide once weekly versus metformin, pioglitazone, and sitagliptin used as monotherapy in drug-naive patients with type 2 diabetes (DURATION-4): a 26-week double-blind study. Diabetes Care. 35(2):252-8.

Smith U. 1996. Gastric emptying in type 2 diabetes: quick or slow? Diabetic Medicine: A Journal of the British Diabetic Association. 13(9 Suppl 5):S31-3.

Szayna M, Doyle ME, Betkey JA, Holloway HW, Spencer RG, Greig NH, Egan JM. 2000. Exendin-4 decelerates food intake, weight gain, and fat deposition in Zucker rats. Endocrinology. 141(6):1936-41.

Tourrel C, Bailbé D, Meile MJ, Kergoat M, Portha B. 2001. Glucagon-like peptide-1 and exendin-4 stimulate beta-cell neogenesis in streptozotocin-treated newborn rats resulting in persistently improved glucose homeostasis at adult age. Diabetes. 50(7):1562-70.

Van Cauter E, Mestrez F, Sturis J, Polonsky KS. 1992. Estimation of insulin secretion rates from C-peptide levels. Comparison of individual and standard kinetic parameters for C-peptide clearance. Diabetes. 41(3):368-77.

Vilsbøll T, Agersø H, Krarup T, Holst JJ. 2003. Similar elimination rates of glucagon-like peptide-1 in obese type 2 diabetic patients and healthy subjects. The Journal of Clinical Endocrinology and Metabolism. 88(1):220-4.

Wajcberg E, Amarah A. 2010. Liraglutide in the management of type 2 diabetes. The Journal of Drug Design, Development and Therapy. 4: 279–290

Wajchenberg BL. 2007. beta-cell failure in diabetes and preservation by clinical treatment. Endocrine Reviews. 28(2):187-218.

Wettergren A, Schjoldager B, Mortensen PE, Myhre J, Christiansen J, Holst JJ. 1993. Truncated GLP-1 (proglucagon 78-107-amide) inhibits gastric and pancreatic functions in man. Digestive Diseases and Sciences. 38(4):665-73.

Yamamoto H, Kishi T, Lee CE, Choi BJ, Fang H, Hollenberg AN, Drucker DJ, Elmquist JK. 2003. Glucagon-like peptide-1-responsive catecholamine neurons in the area postrema link peripheral glucagon-like peptide-1 with central autonomic control sites. The Journal of Neuroscience. 23(7):2939-46.

Yki-Järvinen H. 2004. Thiazolidinediones. The New England Journal of Medicine. 351(11):1106-18.