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Improved β-cell Function and Prolonged Remission of Diabetes Type 1 by GLP-1 Agonist Treatment in Newly Diagnosed Adolescences

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ABSTRACT

Aims: To investigate the effect of GLP-1 agonists on the β-cell function and on the remission phase of the diabetes type 1.

Background: GLP-1 agents are known to have positive effects in patients with diabetes type 2, but their benefits in diabetes type 1 have only been investigated the last few years. In the current research proposal, it is suggested that GLP-1 in addition to insulin therapy, can preserve β-cell function and remission phase.

Methods: Fifty-eight newly diagnosed adolescences (10-17 years old) are enrolled in this randomized, open label, controlled trial for two years duration. Subjects are randomly assigned to receive either exenatide twice daily or no exenatide in addition to intensified insulin therapy.

Outcomes: The primary outcome is change in stimulates C-peptide levels and the secondary outcome is preservation of remission phase.

Expected Impact: Reduced stimulated C-peptide levels, insulin requirements, improved glycemic control and longer remission phase in exenatide group

Lay Summary

Diabetes type 1 is an autoimmune disease which is characterized by the destruction of β-cells, which are responsible for insulin production. GLP-1 agents are drugs that promote β-cell function and neogenesis in animal studies. In human studies, these agents seem to promote glycemic control by decreasing insulin requirements in patients with long standing diabetes type 1, but not improve their β-cells function. Therefore, GLP-1 agents would have the greatest effect in the onset of the disease where β-cell mass and function are the highest in both preserving β-cell function and remaining these patients in partial remission.

INTRODUCTION (citing key references, searches used, etc.)

Type 1 Diabetes Mellitus is a chronic, autoimmune disorder that it is caused by a progressive destruction of the pancreatic, insulin secreting β-cells, which end up to an absolute insulin deficiency [1]. According to the natural course of the disease, newly diagnosed type 1 diabetes is often characterized by a temporal, partial remission phase of the β-cell function, usually within months of DT1 diagnosis and the introduction of insulin treatment. During this phase, which is also called as "honeymoon period", exogenous insulin requirements decrease, while the survived β-cell are still producing insulin and an improved glycemic control can be achieved. However, patients still require insulin in order to maintain their blood sugar at normal levels [2,3]. In the majority of the studies, the remission is temporal, but there are few cases in the literature that describe a complete remission, where patients remain healthy (0-3.2%) [4]. In the literature, many studies suggest that approximately half of the newly diagnosed children with type 1 diabetes (43-56%) will enter the remission, whose duration can vary largely from 1 month until 13 years, with a median of about 9 months [4-6].

There are many clinical factors that can affect the duration and the rate of the remission. In recent years, there has been a considerable interest in identification of these factors such as the age, the existence of diabetic ketoacidosis at the time of the diagnosis, the value of HbA1c both at the time of diagnosis and during the disease, the appearance of autoantibodies, the time that insulin treatment is introduced and other [2,4,10]. Concerning the age, it has been suggested that longer remission can occur to adolescences after 15 years old or after puberty

than in younger children [7]. Remission duration falls, as the age of diagnosis decreases [2]. Regarding the HbA1c levels, it is considered to be a criterion to evaluate the possibility of entering into a remission. In addition to that, several studies suggest that lower HbA1c levels during the remission, can extend its duration [4,6,8]. It seems that the existence of diabetic ketoacidosis at the diagnosis is related with decreased duration and lower incidence of remission (49% of patients without ketoacidosis had remission while only 18% with ketoacidosis had remission) [2,9,10]. The presence of autoantibodies identified at the diagnoses may not affect the chance of entering the remission, but it may influence the prolongation [2]. Specifically, it is cited that patients with 2 positive autoantibodies, anti-GAD65 and anti-IA2 autoantibodies, had shorter remission phase (85 days), in comparison with those who had only 1 positive autoantibody (198 days) [6]. The time that insulin therapy is introduced and consequently better and early glycemic control can prolong the remission [11]. It has been noticed that patients using sensor-augmented insulin pumps had less downgrading on β-cell function [12]. These results could possibly be contributed to the fact that achieving glycemic goals and steady, normal blood glucose at an early stage of the disease can extend remission's duration by preserving β-cell function [2]. In any circumstances, patients could be benefited by the extended remission period as the glycemic control is stable, normal blood glucose levels can be achieved easier and the incidence of long-term complications is reduced. Interestingly, a growing body of recent studies show that, taking into account the above influence factors, an appropriate treatment and follow-up could probably make possible the prolongation of "honeymoon" for years or even permanently by inhibiting the destruction of the remaining β-cells [2,4].

Several studies have been conducted on the possible effects of GLP-1 agonist in glucose metabolism. GLP-1 increase insulin secretion, decrease glucagon secretion and inhibits gastric emptying [13,14]. In the literature, there is also suggested that GLP-1 agonists have positive effects on β-cell physiology such as inhibiting the apoptosis of the live β-cells [15] and promoting β-cells regeneration, neogenesis and proliferation [16-18].

In the literature, there is a growing body of studies that have investigated the relationship between GLP-1 agents and the prevention of the diabetes in diabetic mouse. In Zhang et al. randomized control trial [2007], there are data presented that show GLP-1 treatment can increase β-cell mass and not only promote the proliferation, but also inhibit the apoptosis and consequently delay the onset of diabetes type 1 in prediabetic mice. Mice that were taking GLP-1 had not only higher β-cell mass, but also the number of the newly formed β-cells was increased in contrast to the control mice. This study suggests that GLP-1 can also act during the immune activation [19]. In another study performed in autoimmune NOD (non-obese diabetic) mice, researchers established a system of continuous secretion of GLP-1 levels by creating a recombinant adenoviral vector (rAd-βGLP-1) and investigated whether there is an effect in remission phase and in β-cell function. Mice taking rAd-βGLP-1 had significantly increased insulin-positive cells in the pancreatic islets and C-peptide levels and the remission phase was 1 year longer compared to the control group [20]. Similarly, the effects of an agent of exenatide (GLP-1 agonist) in NOD mouse showed significant higher β-cell mass and delayed the onset of the disease compared to the controlled group [20].

Concerning safety issues, Phase 1 and 2 clinical trials have been conducted in pediatric Diabetes or Pre-diabetics in order to investigate the safety, tolerability and the efficacy of GLP-1 agents. Klein et al., [2014] investigated the safety and tolerability of different Liraglutide doses (0.3, 0.6, 0.9, 1.2 and 1.8 mg) in children with Diabetes type 2 in a randomized control trial. They found that Liraglutide did not cause adverse events, including hypoglycemia, and there was no difference in pancreatic enzymes between the placebo and drug group. In conclusion, they stated that the drug not only improved glycemic control but also was safe and well tolerated. However, the major limitations of this study were the number of participants, only 21, and the duration of the study which was 5 weeks [21]. In another randomized, blind, dose-escalation, crossover study in 13 diabetics type 2 adolescents, the safety of single doses of exenatide (2.5 μg and 5 μg) was investigated. Similarly, both doses of exenatide improved postprandial glucose control and were well tolerated with no hypoglycemic effects [22]. In a more recent randomized controlled trial [2017], Zhou et al., evaluated the clinical efficacy of GLP-1 agents in children with pre-diabetes and investigated whether these agents can delay or reverse the disease. The study was performed in 42 newly diagnosed pre-diabetic children randomizing them into control or Liraglutide group in 3-month period. Among others, they found that Liraglutide group had significantly higher values of islet function index of β-cells, significantly lower insulin resistance, lower HbA1c and lower values of fasting plasma glucose and 2-h postprandial glucose compared to the control group [23]. Although there are not available data concerning the long-term safety in Diabetes Type 1, GLP-1 agents have been tasted largely in diabetics type 2, so regarding children, it seems that they would be a more secure option than other immunosuppressants [18].

Several clinical trials have been conducted in type 1 diabetic patients looking at the positive outcomes of GLP-1 agonists. In their cutting-edge paper of 2012, Kass et al. described for the first time a significant relation both between GLP-1 and proinsulin levels, and between remission phase and GLP-1 levels in type 1 diabetic patients [24]. Kielgast et al. [2011] investigated the effect of Liraglutide (GLP-1 agonist) on β-cell protection in C-peptide positive and C-peptide negative type 1 diabetics for 4 weeks. Interestingly, although insulin dose had a greater decrease in C-peptide positive group, it was reduced in both groups, so they suggested that GLP-1 agonist may go beyond β-cell protection [25]. In another study, Liraglutide was administered in 14 C-peptide negative patients for 1-week period with half of the patients continuing for 6 months. After the 6-month period, reductions of insulin dose as well a decrease in HbA1c, have been demonstrated [26]. In their cutting-edge paper, Rother et al. [2009] investigated for the first time, in an RCT where the C-peptide was the main end point, whether GLP-1 agonist (Exenatide) combined with intensive insulin therapy can improve β-cell function in patients with long-standing Diabetes type 1. Interestingly, they found that insulin requirements decreased in the intervention group, but the C-peptide levels were not changed. The main reason for this negative finding may be the advanced patients' age and the long duration of the disease. Other limitations of the study were the number of the participants (only 14) and the short duration of the study (6-9 months) [27]. The first randomized, control trial which investigated the effect of GLP-1 agonist (exenatide) in newly diagnosed adult type 1 diabetics (1 month from diagnosis) was by Kumar et al. [2013]. The patients were randomized into the insulin only group (control) and the exenatide group (Intervention) for 1-year period. They found that the addition of exenatide decreased significantly insulin requirements but not due to the increased insulin production. In addition, C-peptide was increased only in the intervention group compared to the baseline, but not significantly. However, the sample size was very small (18 adults) and the study period was short [28].

Therefore, previous work has mainly focused on GLP-1 treatment benefits in adult patients or whose disease duration was long. The major limitation of studies investigating GLP-1 effects in patients with long-standing disease is that usually only 1-2% of their β-cells are still alive, while in newly diagnosed patients about 10% is still viable [29]. A recent review on the GLP-1 agonists in diabetes type 1 [2013] cite that these agonists may not only prevent the damage in β-cells and improve cells health, but also help these patients remain C-peptide positive by giving them immediately at the time of the diagnosis. It is also stated that trials should take place in which GLP-1 would be introduced in the early stage of the disease, in combination with insulin, in order to evaluate the medication's preventative or preservative capacity [18]. Many other studies suggest similarly that treatment with GLP-1 agents would result in better outcomes in newly diagnosed children [24, 29-31].

Hypothesis

Glucagon-like peptide 1 (GLP-1) agonists can promote the β-cell function and preserve the remission phase of the disease in newly

diagnosed adolescences with Diabetes Type 1.

Objectives

Investigate the effect of GLP-1 agonists on the β-cell function and on the remission phase preservation of the disease in newly diagnosed adolescences with Diabetes Type 1.

Research Plan, Methods, Statistical Power

Study participants: Fifty-eight (58) newly diagnosed with Diabetes Type 1 adolescents (age 10-17) are recruited from 5 clinical centers in different cities in Scotland. Inclusion criteria at the time of the diagnosis are BMI between 5th and 85th percentile for age and gender and have at least one positive antibody (Anti-GAD65, anti-ICA512 and anti-IA2) and weeks from diagnosis ≤ 2. Exclusion criteria include any major illnesses (i.e., Cardiovascular disease, renal disease, hepatic disease, hypertension and high blood lipid profile), stimulated C-peptide < 0.1 nmol/L, diabetic ketoacidosis at the diagnosis, other medication.

Research Plan: The adolescents are randomly divided into the intervention group and the control group. Both groups start intensified insulin therapy and they have started already insulin therapy. The intervention group inject 5 μg exenatide (GLP-1 agonist) s.c twice daily for the first month and 10 μg twice daily from the second month until the end of the study, while the control group start intensified insulin therapy only. All participants inject insulin at least three times per day (both short- and long- acting insulin) and/or receive continuous subcutaneous insulin therapy and continue insulin therapy through the whole study period. All participants get same advises about diet (i.e. Carbohydrates counting, healthy eating) and exercise modification. Participants are matched for the sex, age, presence of autoantibodies identified at the diagnosis (anti-GAD65 and anti-IA2), C-peptide, which are clinical factors that can affect remission.

Methods

β-cell function assessment

Stimulated C-peptide is assessed 2 h after consumption of a standardized mixed meal and the test takes place at the second week after randomization in order to be achieved metabolic balance and every 6 months until the end of the study.

Partial remission assessment

Total duration of partial remission period in months is evaluated and it is measured as an insulin-dose adjusted A1C (IDAA1C) as A1C (percent) + [4 × insulin dose (units/kg/24 h)]. A calculated IDAA1C ≤ 9 is used to define partial remission. HbA1c and insulin dose are measured at onset and every 3 months until the end of the study.

Statistical Power-Study Sample

Comparison of stimulated C-peptide levels and total duration of remission phase between the two groups is based on two-sample t-test and two-sided p values ≤ 0.05 are considered significant. Sample size calculation is based on 1) a population-based study with 94 newly diagnosed adolescences (<4 weeks) aged 10-17 years, who had a meal-stimulated C-peptide at the diagnosis of 0.6 ± 0.3 ng/ml [32] and 2) data from a prospective study investigating the effect of exenatide in diabetes type 1 [33]. A difference in C-peptide is considered important when there is 50% increase of C-peptide levels in intervention group. Therefore, at a 5% significance level and 90% statistical power, 23 patients would be on each group and 46 would be totally. On the assumption that 20% of the participants would not complete the study, the final number of participants would be 29 on each group and 58 totally.

Milestones

- 1st-6th month: Submit approval from NHS ethics committee, Submit budget approval
- 7th-12th month: Develop Clinical Trial Agreement and Clinical study protocol, obtain intervention related products (exenatide), develop template for informed consent
- First week of 13th month: 70% of the patients' recruitment
- Second week of 13th month: 100% of the patients' recruitment
- Last 15 days of 13th month: Randomization of the participants into control and intervention group
- 14th-38th month: Collecting measurements of stimulated C-peptide levels every 6 months, Hba1c and insulin requirements every 3 months
- 25th month: First report about changes in stimulated C-peptide levels and presentation of the first results in conference
- 39th-41st month: Statistical analysis of the data
- 42nd-44th month: Publication writing and deliver publication document

Ethical Considerations

Written informed consent is obtained both from all the participants and their parents. If parents do not consent, the research cannot go ahead. One of the 11 NHS ethics committee in Scotland approves the protocol. All participants are informed for the possible risks and the potential benefits of the treatment. The risks include a very small risk of gastrointestinal adverse effects like nausea and diarrhea and a small risk of hypoglycemia. The possible beneficial effects include increase or even preserve C-peptide levels, preserve remission period, decrease insulin requirements, improve glycemic control, delay gastric emptying and promote weight loss. The findings will provide evidence for the effects of GLP-1 agonists on β-cell function in the onset of diabetes type 1, suggest an alternative possible treatment in addition to insulin therapy in the diagnosis of the disease, suggest a different way to inhibit β-cell destruction than the usual immunosuppressants, contribute to the prolongation of the remission phase of the disease and potentially improve disease adverse impact of the participants. Consequently, the importance of these benefits is in proportion greater to the possible risk.

Dissemination Plan

Once the data are collected and analyzed, it is expected that these findings will be disseminated through oral presentations at community meetings and scientific conferences for diabetes research and treatment strategies. Secondly, it is expected that this project will be published in a scientific journal enabling scientific community and colleagues to access it. The final step includes dissemination of the information to board audiences and simplification of the findings by creating a short video, uploading it to social media.

BIBLIOGRAPHY

1. Atkinson MA. The pathogenesis and natural history of type 1 diabetes. Cold Spring Harb Perspect Med. 2012;1;2(11).
2. Abdul-Rasoul M, Habib H, Al-Khouly M. 'The honeymoon phase' in children with type 1 diabetes mellitus: frequency, duration, and influential factors. Pediatr Diabetes. 2006;7(2):101-107.
3. Mortensen HB, Hougaard P, Swift P, Hansen L, Holl RW, Hoey H, et al. New definition for the partial remission period in children and adolescents with type 1 diabetes. Diabetes Care. 2009;32(8):1384-1390.
4. Sokołowska M, Chobot A, Jarosz-Chobot P. The honeymoon phase - what we know today about the factors that can modulate the remission period in type 1 diabetes. Pediatr Endocrinol Diabetes Metabol. 2016;22(2):66-70.
5. Robles, DT. Millennium award recipient contribution. Identification of children with early onset and high incidence of anti-islet autoantibodies. Clin. Immunol. 2002;102:217-224.
6. Aurore Pecheur, Thierry Barrea, Valérie Vandooren, Véronique Beauloye, Annie Robert, Philippe A. Lysy. Characteristics and Determinants of Partial Remission in Children with Type 1 Diabetes Using the Insulin-Dose-Adjusted A1C Definition. J Diabet Res. 2014;851378.
7. Dost A, Herbst A, Kintzel K, et al. Shorter Remission Period in Young Versus Older Children with Diabetes Mellitus Type 1. Xp

Clin Endrocrinol Diabetes. 2007.

8. Schloot NC, Hanifi-Moghaddam P, Aabenhus-Andersen N, et al. Association of immune mediators at diagnosis of Type 1 diabetes with later clinical remission. Diabetic Medecine. 2007.
9. Bowden SA, Duck MM, Hoffman RP. Young children (< 5 yr) and adolescents (>12 yr) with type 1 diabetes mellitus have low rate of partial remission: diabetic ketoacidosis is an important risk factor. Pediatric Diabetes. 2008;9:197-201.
10. Neylon OM, White M, O Connell MA, Cameron FJ. Insulin-dose adjusted HbA1c-defined partial remission phase in a paediatric population – when is the honeymoon over? Diabet Med. 2013;30:627-628.
11. Komulainen J, Lounamaa R, Knip M, et al. Ketoacidosis at the diagnosis of type 1 (insulin dependent) diabetes mellitus is related to poor residual beta cell function. Childhood Diabetes in Finland Study Group. Arch Dis Child. 1996;75:410-415.
12. Kordonouri O, Hartmann R, Pankowska E, et al. Sensor augmented pump therapy from onset of type 1 diabetes: late follow-up results of the Pediatric Onset Study. Pediatr Diabet. 2012;13:515-518.
13. Kjems LL, Holst JJ, Vølund A, Madsbad S. The influence of GLP-1 on glucose stimulated insulin secretion: effects on b-cell sensitivity in type 2 and nondiabetic subjects. Diabetes. 2003;52:380-386.
14. Komatsu R, Matsuyama T, Namba M, et al. Glucagonostatic and insulinotropic action of glucagons like peptide 1 (7-36)- amide. Diabetes. 1989;38:902-905.
15. Farilla L, Bulotta A, Hirshbirg B, et al. GLP-1 inhibits cell apoptosis and improves glucose responsiveness of freshly isolated human islets. Endocrinol. 2003;144:5149-5158.
16. Zhou J, Wang X, Pineyro MA, Egan JM. Glucagon-like peptide 1 and exendin-4 convert pancreatic AR42J cells into glucagon- and insulin-producing cells. Diabetes. 1999;48:2358-2366.
17. Drucker DJ. Glucagon-like peptide-1 and the islet beta-cell: augmentation of cell proliferation and inhibition of apoptosis. Endocrinol.12003;44:5145-5148.
18. Pettus J, Hirsch I, Edelman S. GLP-1 agonists in type 1 diabetes. Clin Immunol. 2013;149(3):317-323.
19. Zhang J, Tokui Y, Yamagata K, Kozawa J, Sayama K, Iwahashi H. Continuous stimulation of human glucagon-like peptide-1 (7-36) amide in a mouse model (NOD) delays onset of autoimmune type 1 diabetes. Diabetologia. 2007;50(9):1900-1909.
20. Hadjiyanni I, Baggio LL, Poussier P, Drucker DJ. Exendin-4 modulates diabetes onset in nonobese diabetic mice. Endocrinol. 2008;149:1338-1349.
21. Klein DJ, Battelino T, Chatterjee DJ, Jacobsen LV, Hale PM, Arslanian S. Liraglutide's safety, tolerability, pharmacokinetics, and pharmacodynamics in pediatric type 2 diabetes: a randomized, double-blind, placebo-controlled trial. Diabetes Technol Ther. 2014;16(10):679-687.
22. Malloy J, Capparelli E, Gottschalk M, Guan X, Kothare P, Fineman M. Pharmacology and tolerability of a single dose of exenatide in adolescent patients with type 2 diabetes mellitus being treated with metformin: a randomized, placebo-controlled, single-blind, dose escalation, crossover study. Clin Ther. 2009;31(4):806-815.
23. Zhou QX, Wang ZY, Zhao HF, Wang S. The effects of GLP-1 analogues on pre-diabetes of the children. Experimental and Therapeutic Medicine. 2017;13(4):1426-1430.
24. Kaas A, Andersen ML, Fredheim S, Hougaard P, Buschard K, Petersen JS, et al, Hvidoere Study Group on childhood diabetes. Proinsulin, GLP-1, and glucagon are associated with partial remission in children and adolescents with newly diagnosed type 1 diabetes. Pediatr Diabet. 2012;13(1):51-58.
25. Kielgast U. Four weeks of treatment with liraglutide reduces insulin dose without loss of glycemic control in type 1 diabetic patients with and without residual beta-cell function, Diabetes Care. 2011;34:(7)1463-1468.
26. Varanasi A, Liraglutide as additional treatment for type 1 diabetes. Eur J Endocrinol. 2011;165(1):l77-184.
27. Rother KI, Spain LM, Wesley RA, et al. Effects of Exenatide Alone and in Combination With Daclizumab on β-Cell Function in Long-Standing Type 1 Diabetes. Diabetes Care. 2009;32(12):2251-2257.
28. Hari Kumar KV, Shaikh A, Prusty P. Addition of exenatide or sitagliptin to insulin in new onset type 1 diabetes: a randomized, open label study. Diabet Res Clin Pract. 2013;100(2).
29. Bosi E. Time for testing incretin therapies in early type 1 diabetes?. J Clin Endocrinol Metabol. 2010;95:2607-2609.
30. Zhou QX, Wang ZY, Zhao HF, Wang S. The effects of GLP-1 analogues on pre-diabetes of the children. Experimental and Therapeutic Medicine. 2017;13(4):1426-1430.
31. Kielgast U, Holst JJ, Madsbad S. Treatment of type 1 diabetic patients with glucagon-like peptide-1 (GLP-1) and GLP-1R agonists. Curr Diabetes Rev. 2009;5:266-275.
32. Pozzilli P, Visalli N, Buzzetti R. Metabolic and immune parameters at clinical onset of insulin-dependent diabetes: a population based study. Metabol. 1998;47:1205-1210.
33. Rother KI, Spain LM, Wesley RA, et al. Effects of Exenatide Alone and in Combination with Daclizumab on β-Cell Function in Long-Standing Type 1 Diabetes. Diabetes Care. 2009;32(12):2251-2257.