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Application of Pramlintide in Combination with Insulin in Type 1 Diabetes Mellitus

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Abstract:

Diabetes is a common disease in current society, it can be easily found in middle-aged who have an unhealthy diet. However, only a small portion of them have the condition of T1DM, which is sometimes congenital, and related to genetic factors. One of the common symptoms of T1DM is weight loss. Pramlintide is an analog of the pancreatic β-cell hormone, Amylin. Current studies on Pramlintide focus on exploring Pramlintide's role in improving glycemic control in T1DM. This article is limited to short-term studies on Pramlintide. This article reviews the mechanisms of T1DM, Amylin and Pramlinte and analyzes two risk factors of T1DM. Additionally, this article analyzes the current study on the role of Pramlintide in the reduction of postprandial glucose, an expected reduction of total daily Insulin dose, and expected weight loss. This paper provides longer study period and multifactorial for Pramlintide studies as a reference for future research. There are side effects problems, such as nausea, that haven't be solved, so future research can focus on finding adjuvant drug for Pramlintide and Insulin.

Keywords: Type 1 Diabetes Mellitus; Pramlintide; Insulin.

1. Introduction

While metabolic disorders are spreading globally and being a great proportion of the pandemic, type 1 diabetes mellitus (T1DM) is one of the irreversible metabolic diseases which millions of different people are suffering. T1DM requires improving management to avoid serious long-term complications. T1DM is caused by the autoimmune loss of the pancreatic β cells responsible for generating Insulin [1]. Insulin is a game-changing medical treatment, it has gained attention since the discovery of Insulin in the 1900s. However, the treatment of T1DM has been limited to metabolic glucose dysregulation monitoring and treatment [1].

Immunotherapy, targeting T cells to postpone the autoimmune destruction of pancreatic β-cells, received FDA approval in 2022, contributed to the immune system playing an important role in disease pathogenesis and leading the way for future development of interventions other immune-targeted for T1DM [1]. It also highlights the demand for more understanding of the immunobiology of T1DM and technologies to monitor the remaining β-cell mass and function.

Pancreatic β cells secrete a hormone called Amylin,

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which works in tandem with Insulin to regulate blood glucose levels in the body. Amino acids make up 37 amino acids of Amylin, while 89 amino acids make up its precursor molecule. In both health and sickness, the hormone is essential for controlling how energy is metabolized. It interacts with other hormones involved in metabolic control and primarily acts on the periventricular tissues of the central nervous system [2]. Despite the widespread of Insulin therapy, maintaining glycemic control remains challenge because of the risk of hypoglycemia and mimicking physiological Insulin secretio patterns [3].

Pramlintide, an amylinomimetic compound, is a relatively stable, bioactive synthetic analog of amylin. It is a peptide based on Amylin and is used as a therapeutic in clinical settings to treat T1DM. In 2005, Pramlintide received FDA approval for the treatment of elevated postprandial glucose levels in T1DM. Pramlintide can effectively contribute to negatively affect glycemic control and cardiovascular health markers for reducing postprandial glucose excursions according to several clinical test. [4]. Long-term postprandial glucose excursions increase the risk of microvascular(i.e., diabetic retinopathy) and macrovascular (i.e., peripheral artery disease).

This article aims to contribute to the ongoing efforts to improve T1DM treatment and management and focus on the mechanisms of action of Pramlintide, reviews the current state of research regarding its clinical efficacy and side effects, and discusses the improvement of its delivery systems for enhanced therapeutic outcomes.

2. Mechanism of T1DM

The onset of T1DM is due to the attack of the islet beta cells by the own immune system, resulting in the destruction of their function. Beta cells in the pancreas are damaged by the immune system misidentifying them as targets for attack and are unable to secrete Insulin properly. This pathological process suggests that immunotargeted therapy may play a role in the prevention and control of T1DM. A clinical trial of teplizumab, which targets T cells, showed that patients at high risk of T1DM had a three-year delay in the progression of the disease after using the drug compared with a placebo group. In addition, studies indicate that the application of monoclonal antibodies against tumor necrosis factor (TNF)-α, such as golimumab, can enhance the activity of beta cells while reducing the need for Insulin in patients [5].

There is evidence that beta cell dysfunction directly contributes to the development of T1DM. The disorder is associated with mutations in genes associated with beta cells, including the INS gene. Endoplasmic reticulum stress, as an important factor in the dysfunction of beta cells, can trigger the unfolded protein response (UPR), which leads to the apoptosis of beta cells. UPR is regarded as an adaptive response in maintaining cell homeostasis, but under excessive stress it may trigger terminal UPR and lead to apoptosis. In addition, the granase pathway is also a mechanism that promotes the apoptosis of beta cells. Although necrosis has been investigated as a potential pathogenesis of T1DM, its results are unclear.

The particular causes of T1DM remain unclear, however one key area of current research is β cell senescence. The DNA damage response (DDR) is frequently observed in senescent β cells, as evidenced by phosphorylated histone H2A.X being more prevalent. Furthermore, in these senescent cells, increased concentrations of cyclin-dependent kinase inhibitors such p21, p19, and p16 cause growth arrest. The idea of β cell transdifferentiation is supported by defective proinsulin processing and the simultaneous production of glucagon and Insulin by β cells. Autophagy and mitochondrial failure are additional pathways linked to β cell malfunction, which adds to the complexity of the pathophysiology of T1DM.

3. Risk Factor

The risk factors of T1DM are multifactorial, involving genetic predisposition, environment, autoimmune, and age, etc. Autoantibodies work as markers of the immune response against beta cells, and their presence can occur a year before clinical diagnosis.

3.1 Gene Factor

T1DM is caused by the destruction of pancreatic β cells mediated by the immune system. Its etiology is related to the complex interaction of genetic risk genes and environmental factors. More than 50 susceptibility loci associated with T1DM have been found, among which the major histocompatibility complex (HLA) region located on chromosome 6p21 accounts for about 50% of the genetic risk. In addition, non-HLA genetic factors are also associated with an increased risk of T1DM, and 58 genomic regions have shown evidence of association, including genes such as IL27, BAD, and CLEC16A, which are considered to be possible pathogenic genes. Overall, the pathogenesis of T1DM is the result of the combined action of genetic variation and environmental triggers, which is complex and multifactorial [6].

3.2 Environmental Factor

Environmental determinants are critical to preventing or delaying T1DM. Environmental factors are closely linked to the development and function of the human micro-

biome, which plays a crucial role in health. Pramlintide works for blood glucose levels. Gastric emptying and food intake interact with gut microbiota, which could impact the composition and activity of gut microbiota. Gut microbiota significantly affects lipid and glucose metabolism and influence immunity and systemic inflammation outside the intestines. Some studies have reported that children with islet autoimmunity, a precursor to T1DM, often have lower microbial diversity compared to healthy children, suggesting a potential link between gut microbiota and diabetes risk.

Breastfeeding could offer a protective effect regarding how dietary factors influence the risk of T1DM according to some studies. Children who were still breastfed at the time of the beginning of cereals had a reduced risk of islet autoimmunity and T1DM. There are several studies on the relationship between Solid foods and cereals. The age of children‘s exposure to solid foods and whether the child‘s intake of key nutrients is insufficient before the introduction of solid foods leads to an increased risk of islet autoimmunity. It’s worth noticing that studies from different countries drew different conclusions in most cases on Heterogeneity of T1DM and Birthweight and infant growth. More potential factors need to be studied in comparison. [7].

4. Pramlintide

Pramlintide is a new treatment for T1DM that offers society an additional choice. It is an Amylin analog that can be used with mealtime Insulin in the treatment of T1DM. Despite Pramlintide have the limitation of cost and issues with human tests, it is still a potential alternative to Insulin.

4.1 Mechanism of Pramlintide

Amylin slows stomach emptying, which means food is absorbed more slowly, causing blood sugar levels to rise more steadily, rather than sharply. In addition, Pramlintide promotes satiety by acting on the brain, thereby reducing overall food intake and helping with weight control. Pramlintide binds to the Amylin receptors, it has equal strength in activating the Amylin receptors as human Amylin. Pramlintide controls blood sugar levels after meals by reducing glucagon levels, slowing gastric emptying, and increasing feelings of fullness and decreased food intake through a central mechanism. When postprandial glucose cannot reach the expected level, this drug is used in conjunction with Insulin. Pramlintide treatment of T1DM may benefit highly motivated patients who are not performing optimally on basal Insulin therapy or who gain weight while receiving Insulin pump therapy despite all recommended lifestyle changes [8, 9].

Studies have shown that after intravenous injection in rats, the half-life of Amylin and Pramlintide in circulating plasma is about 13 minutes, and they are rapidly metabolized to delysine metabolites. Although these metabolites are truncated at their N-termini, they still retain full activity as Amylin agonists, and their potency in vivo is similar to that of the full-length peptide [8]. Pramlintide has shown multiple advantages in the treatment of T1DM, especially in postprandial blood sugar control, lowering glycated hemoglobin levels, and weight loss. These research results further confirm the important role of Pramlintide in the treatment of T1DM [9].

4.2 Research Status of Pramlintide

An ideal adjunct agent would help maintain stable blood glucose levels, reduce weight change, decrease the need for Insulin and minimize the chance of complications (e.g. microvascular, coronary artery disease) without increasing hypoglycemia. Pramlintide is an injectable Amylin analogue drug, sold as an acetate salt solubilized at an acidic pH of 4, and it is consecreted with mealtime Insulin when postprandial goal levels of glucose cannot be reached. It operates by suppresses the post prandial secretion of glucagon, decrease gastric emptying and eventually contributes to satiety of the patients via a central mechanism. Pramlintide is principally eliminated via the kidneys.

Pramlintide is offered in both vial form for injections and as pen injector. SYMLIN, a trade name of Pramlintide (developed by Amylin Pharmaceuticals and approved in March 16, 2005), is suggested usual starting dose as 15 micrograms (mcg) injected under the skin just before a main meal for people who have T1DM [10]. However, Pramlintide is more commonly used as Pen injector, with a trade name of Symlinpen. The dosage of Pramlintide is determined by various factors including the patient‘s medical condition, concurrent use of other medications, and individual response to the treatment. To minimize the risk of side effects, it is often recommended that patients begin with a lower dose of Pramlintide. This initial dosage is then gradually increased under the guidance of the prescribing physician to tailor the treatment to the patient‘s specific needs.

4.2.1 clinical trials of pramlintide

The beneficial impact of Pramlintide includes reduction of A1C, postprandial glucose, an expected reduction of total daily Insulin dose, and expected weight loss due to its pharmacodynamics. Additionally, Pramlintide improves long-term blood sugar control without causing weight gain or a higher risk of hypoglycemia.

In a randomized study and open-label extension, the long-

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term effectiveness of Pramlintide as an adjunct to Insulin therapy in patients with T1DM was evaluated. The findings suggest that combining Pramlintide with Insulin for mealtime treatment can improve long-term blood sugar control in patients without weight gain and without increasing the overall risk of severe hypoglycemia. The study included 480 patients with T1DM, all of whom had a disease course of more than a year, were between the ages of 16 and 70, and did not have severe symptoms of low or high blood sugar in the two weeks prior to the trial. Patients received 30 mcg of Pramlintide or placebo combined with Insulin before each meal and before bed. At week 20 of the trial, if the patient's A1c changed less than 0.05%, the dose of Pramlintide was adjusted to 60 mcg. The results showed that the incidence of severe hypoglycemia (requiring help from others) was consistent across all study groups. [11].

Furthermore, Pramlintide reduce Hemoglobin A1C. Based on a conjoint analysis, Pramlintide lower A1C by 0.2% to 0.4% in patients with T1DM with an initial A1C of 8% to 9%. Pramlintide generally reduces 2-hour postprandial glucose between 4 and 6 mmol/L and has a minimal impact on fasting glucose. The transient weight loss of 0.5 to 1 kg observed with Pramlintide therapy may be advantageous compared to the increase in weight, which is typically associated with Insulin, sulfonylureas and thiazolidinediones [12].

4.2.2 Side effects of pramlintide

Although Pramlintide is approved by the FDA for the treatment of T1DM and T2DM, its use worldwide is limited. This is partly because the drug is associated with a variety of side effects, although these are generally mild to moderate and dose-related. Side effects of Pramlintide are generally more pronounced at the beginning of treatment and may gradually decrease over time. The most common side effect is nausea. According to a double-blind study, nausea usually occurred within the first two weeks of treatment and was the main reason for patients to withdraw from the study (7.4% of the Pramlintide group and 1.7% of the placebo group) [13]. The fact that nausea is most prevalent during the early stages of treatment and is a significant reason for patient withdrawal suggests that managing these side effects is crucial for improving patient adherence. The dose-related nature of these side effects also indicates that careful dosage adjustments might help mitigate adverse reactions, potentially increasing the drug's acceptance and usage worldwide. This highlights the importance of balancing efficacy with tolerability to ensure broader adoption of Pramlintide in diabetes treatment.

The side effects are resulting from Pramlintide's impact on gastric emptying and food intake. While it does not directly cause hypoglycemia in healthy individuals, these effects can contribute to a higher risk of hypoglycemia in clinical settings. Its mechanism can inadvertently increase the risk of hypoglycemia particularly if Insulin doses are not carefully adjusted. The combination of these factors necessitates careful monitoring of blood glucose levels and precise Insulin dose adjustments to prevent hypoglycemic episodes [14, 15].

5. Optimizing Drug Delivery and Future Developments

Although Pramlintide has the effects of weight loss and glucagon suppression, its application is limited due to its complicated use process and certain adverse reactions. In a study on the preference of patients with T1DM for Insulin-assisted therapy, the joint analysis results showed that only 9% of the participants chose Pramlintide, while 83% preferred low-dose SGLTi and 8% preferred high-dose SGLTi. When the drug name or dose was not displayed, when the respondents were asked about their preference for Insulin-assisted therapy, 6% chose Pramlintide, while 69% chose low-dose SGLTi, 17% chose high-dose SGLTi, and 9% chose to use Insulin alone. [14]. It can be concluded that Pramlintide, despite its benefits in weight loss and glucagon suppression, faces limitations in usage due to its administration complexity and adverse effects.

Weight loss is more significant in patients with severe obesity and is observed independently of nausea, supporting the idea that the reduction in weight is a direct effect of Pramlintide rather than a secondary result of nausea. However, it is important to consider that this beneficial effect is accompanied by some side effects. [13].

However, there is still a lack of high-quality, long-term evidence regarding the effects of Pramlintide. The current researches have considerable uncertainty about Pramlintide's effectiveness and safety. To address this, larger randomized controlled trials (RCTs) with follow-up periods longer than one year are needed to provide a thorough evaluation. This would help clarify the long-term benefits and risks associated with Pramlintide therapy.

6. Conclusion

Patients with T1DM, which is caused by the autoimmune destruction of the β-cells in the pancreatic islets, are influenced primarily by the risk factor of gene factor and enviornment factors. Pramlintide contributes to regulating postprandial glucose levels by reducing the need for food intake by indirectly affecting the brain. It also reduces the risks and side effects caused by Insulin, especially obesi-

ty. However, the side effects affected the widespread use of Pramlintide. This article suggests the requirement for exploring adjunctive therapy of Pramlintide and the lack of accurate, long-term research on different risk factors of Pramlintide. One limitation of this review is the lack of evidence for the potential risk factor of side effects of Pramlintide. This article only analyses the side effects of nausea and hypoglycemia. The extent of the potential effect of Pramlintide on hypoglycemia needs to be taken out. The relationship between Pramlintide and incidental side effects such as loss of appetite, vomiting, and dizziness needs further analysis. Additionally, the current studies are small sample sizes, which reduces the generality of the findings. There is a need to develop or finding new drugs that can complement Pramlintide. These requirements can expand our understanding of Pramlintide's sustained benefits and risks.

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