The present inventors have found that insulin and the dual agonist are inconvenient in that administration must be made daily to the patient due to a short half-life, and have suggested, as a technique of maintaining the activity of protein drug and achieving improved stability at the same time in order to solve the abovementioned problems, a long-acting protein conjugate in which a conventional physiologically active polypeptide and an immunoglobulin Fc region are covalently combined with each other by a non-peptidyl polymer linker (Korean Patent No. 10-0725315). In particular, the inventors have confirmed that the sustainability of the *in vivo* effects of both the long-acting insulin conjugate and long-acting dual agonist conjugate is dramatically increased (Korean Patent No. 10-1058290, Korean Patent Application No. 10-2014-0022909 and Korean Patent Application Publication No. 10-2012-0139579).

However, there are problems in that side-effects such as weight gain occur upon administration of GLP-1/glucagon dual agonist. Therefore, there still remains a need for the development of a therapeutic agent for diabetes having reduced side-effects, frequency and dosage

Disclosure of Invention

Technical Problem

The present inventors have made many efforts to develop a therapeutic agent for diabetes which can reduce high blood glucose levels, suppress weight gain, and reduce the risk of hypoglycemia, which are required to treat diabetes. As a result, the present inventors have attempted a combined administration which simultaneously administers an insulin receptor and GLP-1/glucagon dual agonist, and specifically discovered that when a combined administration of a long-acting insulin and long-acting GLP-1/glucagon can maximize compliance of the patient, reduce the dosage of the insulin drug, reduce the risk of hypoglycemia, and help to reduce blood glucose level and body weight, thereby completing the present invention.

Solution to Problem

An objective of the present invention is to provide a composition for treating diabetes mellitus including insulin and a GLP-1/glucagon dual agonist.

Another objective of the present invention is to provide a method for preventing or treating diabetes, including administering the composition to a subject at high risk of or having diabetes mellitus.

Summary

In one aspect, the present disclosure refers to the use of a composition in the manufacture of a medicament for treating diabetes mellitus, the composition comprising a long-acting insulin conjugate and a long-acting glucagon-like peptide-1 (GLP-1)/glucagon dual agonist conjugate, wherein the long-acting insulin conjugate is a conjugate in which insulin is linked to an immunoglobulin Fc region via a non-peptidyl polymer; and wherein the long-acting GLP-1/glucagon dual agonist conjugate is a conjugate in which GLP-1/glucagon dual agonist is linked to an immunoglobulin Fc region via a non-peptidyl polymer, wherein the insulin is native insulin, rapid-acting insulin, basal insulin, an insulin analog which is an insulin variant comprising substitution, addition, deletion, modification, or a combination thereof of the amino acid sequence of the native insulin, or a fragment thereof and has a blood glucose control functionality in vivo which is the same as that of insulin; and GLP-1/glucagon dual agonist comprises an amino acid sequence selected from the group consisting of amino acid sequences represented by SEQ ID NOs: 39 to 72.

In another aspect, the present disclosure refers to the use of a long-acting insulin conjugate and a long-acting GLP-1/glucagon dual agonist conjugate in the manufacture of a medicament for combination therapy of diabetes mellitus, wherein the insulin is native insulin, rapid-acting insulin, basal insulin, an insulin analog which is an insulin variant comprising substitution, addition, deletion, modification, or a combination thereof of the amino acid sequence of the native insulin, or a fragment thereof and has a blood glucose control functionality in vivo which is the same as that of insulin; and GLP-1/glucagon dual agonist comprises an amino acid sequence selected from the group consisting of amino acid sequences represented by SEQ ID NOs: 39 to 72.

In yet another aspect, the present disclosure refers to the use of a long-acting insulin conjugate and a long-acting GLP-1/glucagon dual agonist conjugate in the manufacture of a medicament for treating diabetes mellitus, wherein the long-acting insulin conjugate is to be administered simultaneously, sequentially or reversely with the long-acting GLP-1/glucagon dual agonist conjugate, wherein the insulin is native insulin, rapid-acting insulin, basal insulin, an insulin analog which is an insulin variant comprising substitution, addition, deletion, modification, or a combination thereof of the amino acid sequence of the native insulin, or a fragment thereof and has a blood glucose control functionality in vivo which is the same as that of insulin; and GLP-1/glucagon dual agonist comprises an amino acid sequence selected from the group consisting of amino acid sequences represented by SEQ ID NOs: 39 to 72.

Advantageous Effects of Invention

The long-acting insulin or its analog conjugate and a long-acting GLP-1/glucagon

[CLAIMS]

[Claim 1]

Use of a composition in the manufacture of a medicament for treating diabetes mellitus, the composition comprising a long-acting insulin conjugate and a long-acting glucagon-like peptide-1 (GLP-1)/glucagon dual agonist conjugate, wherein the long-acting insulin conjugate is a conjugate in which insulin is linked to an immunoglobulin Fc region via a non-peptidyl polymer; and wherein the long-acting GLP-1/glucagon dual agonist conjugate is a conjugate in which GLP-1/glucagon dual agonist is linked to an immunoglobulin Fc region via a non-peptidyl polymer,wherein the insulin is native insulin, rapid-acting insulin, basal insulin, an insulin analog which is an insulin variant comprising substitution, addition, deletion, modification, or a combination thereof of the amino acid sequence of the native insulin, or a fragment thereof and has a blood glucose control functionality in vivo which is the same as that of insulin;

and GLP-1/glucagon dual agonist comprises an amino acid sequence selected from the group consisting of amino acid sequences represented by SEQ ID NOs: 39 to 72.

[Claim 2]

The use according to claim 1, wherein the GLP-1/glucagon dual agonist simultaneously activates GLP-1 receptor and glucagon receptors.

[Claim 3]

The use according to claim 1, wherein the long-acting glucagon-like peptide-1 (GLP-1)/glucagon dual agonist has the amino acid sequence of SEQ ID NO: 40 and the amino acid at position 16 and 20 form a ring.

[Claim 4]

The use according to claim 1, wherein the non-peptidyl polymer is selected from the group

consisting of polyethylene glycol, polypropylene glycol, an ethylene glycol-propylene glycol copolymer, polyoxyethylated polyol, polyvinyl alcohol, a polysaccharide, dextran, polyvinyl ethyl ether, a biodegradable polymer, a lipid polymer, chitin, hyaluronic acid, and a combination thereof.

[Claim 5]

The use according to claim 1, wherein the immunoglobulin Fc region is aglycosylated.

[Claim 6]

The use according to claim 5, wherein the immunoglobulin Fc region comprises one to four region(s) selected from the group consisting of CH1, CH2, CH3 and CH4 domains.

[Claim 7]

The use according to claim 6, wherein the immunoglobulin Fc region further comprises a hinge region.

[Claim 8]

The use according to claim 7, wherein the immunoglobulin Fc region is an Fc region derived from IgG, IgA, IgD, IgE, or IgM.

[Claim 9]

The use according to claim 8, wherein each domain of the immunoglobulin Fc region is a hybrid of domains having a different origin selected from the group consisting of IgG, IgA, IgD, IgE, and IgM.

[Claim 10]

The use according to claim 1, wherein the immunoglobulin Fc region is a dimer or a multimer consisting of single-chain immunoglobulins consisting of domains having the same origin.

[Claim 11]

The use according to claim 1, wherein the composition further comprises a pharmaceutically acceptable carrier.

[Claim 12]

The use according to claim 3, wherein the long-acting insulin is a conjugate in which an insulin analog comprising substitution of the 14^{th} amino acid in the insulin A-chain with a glutamic acid and an immunoglobulin Fc region are linked by a non-peptidyl polymer linker, and the long-acting GLP-1/glucagon dual agonist is a conjugate in which a GLP-1/glucagon dual agonist represented by SEQ ID NO: 40 and an immunoglobulin Fc region are linked by a non-peptidyl polymer linker.

[Claim 13]

The use according to claim 12, wherein the 16^{th} and 20^{th} amino acid of the long-acting glucagon-like peptide-1 (GLP-1)/glucagon dual agonist represented by SEQ ID NO: 40 form a ring.

[Claim 14]

The use according to claim 12, wherein the non-peptidyl polymer linker is PEG.

[Claim 15]

The use of any one of claims 1 to 14, wherein the composition is to be administered to a subject at high risk of or having the diabetes mellitus.

[Claim 16]

Use of a long-acting insulin conjugate and a long-acting GLP-1/glucagon dual agonist conjugate in the manufacture of a medicament for combination therapy of diabetes mellitus,

wherein the insulin is native insulin, rapid-acting insulin, basal insulin, an insulin analog which is an insulin variant comprising substitution, addition, deletion, modification, or a combination thereof of the amino acid sequence of the native insulin, or a fragment thereof and has a blood glucose control functionality in vivo which is the same as that of insulin;

and GLP-1/glucagon dual agonist comprises an amino acid sequence selected from the group consisting of amino acid sequences represented by SEQ ID NOs: 39 to 72.

[Claim 17]

Use of a long-acting insulin conjugate and a long-acting GLP-1/glucagon dual agonist conjugate in the manufacture of a medicament for treating diabetes mellitus, wherein the long-acting insulin conjugate is to be administered simultaneously, sequentially or reversely with the long-acting GLP-1/glucagon dual agonist conjugate,

wherein the insulin is native insulin, rapid-acting insulin, basal insulin, an insulin analog which is an insulin variant comprising substitution, addition, deletion, modification, or a combination thereof of the amino acid sequence of the native insulin, or a fragment thereof and has a blood glucose control functionality in vivo which is the same as that of insulin;

and GLP-1/glucagon dual agonist comprises an amino acid sequence selected from the group consisting of amino acid sequences represented by SEQ ID NOs: 39 to 72.