Claims

[Claim 1] A pharmaceutical composition for the prevention or treatment of diabetes comprising a long-acting insulin conjugate and a long-acting insulinotropic peptide conjugate, wherein each of the long-acting insulin conjugate and the long-acting insulinotropic peptide conjugate is prepared by liking insulin or insulinotropic peptide with an immunoglobulin Fc region via a non-peptidyl linker selected from the group consisting of polyethylene glycol, polypropylene glycol, ethylene glycol-propylene glycol copolymer, polyoxyethylated polyol, polyvinyl alcohol, polysaccharide, dextran, polyvinyl ethyl ether, a biodegradable polymer, a lipid polymer, chitin, hyaluronic acid, and a combination thereof.

[Claim 2] The composition according to claim 1, wherein the insulin is a native insulin, a basal insulin, an insulin variant prepared by any one of substitution, addition, deletion, modification or a combination thereof of the amino acid sequences of the native insulin, an insulin derivative, or a fragment thereof.

[Claim 3] The composition according to claim 1, wherein the insulin is modified with a non-peptidyl polymer.

[Claim 4] The composition according to claim 3, wherein the non-peptidyl polymer is selected from the group consisting of polyethylene glycol, polypropylene glycol, ethylene glycol-propylene glycol copolymer, polyoxyethylated polyol, polyvinyl alcohol, polysaccharide, dextran, polyvinyl ethyl ether, a biodegradable polymer, a lipid polymer, chitin, hyaluronic acid, and a combination thereof.

[Claim 5] The composition according to claim 1, wherein the insulinotropic peptide is selected from the group consisting of GLP-1, exendin-3, exendin-4, agonists thereof, derivatives thereof, fragments thereof, variants thereof, and combinations thereof.

[Claim 6] The composition according to claim 1, wherein the insulinotropic peptide is prepared by substituting the N-terminal histidine residue of insulinotropic peptide with a substance selected from the group consisting of des-amino-histidyl, dimethyl-histidyl, beta-hydroxy imidazopropionyl, 4-imidazoacetyl, and beta-carboxy imidazopropionyl.

[Claim 7] The composition according to claim 1, wherein the insulinotropic peptide is selected from the group consisting of a native exendin-4, an exendin-4 derivative prepared by deleting N-terminal amine group, an

exendin-4 derivative prepared by substituting N-terminal amine group with hydroxyl group, an exendin-4 derivative prepared by modifying N-terminal amine group with dimethyl group, an exendin-4 derivative prepared by deleting α-carbon of the first amino acid of exendin-4 (histidine), an exendin-4 variant prepared by substituting 12th amino acid (lysine) of exendin-4 with serine, and an exendin-4 variant prepared by substituting 12th amino acid (lysine) of exendin-4 with arginine.

[Claim 8] The composition according to claim 1, wherein the immunoglobulin Fc region is aglycosylated.

[Claim 9] The composition according to claim 1, wherein the immunoglobulin Fc region is composed of one to four domains selected from the group consisting of CH1, CH2, CH3 and CH4 domains.

[Claim 10] The composition according to claim 1, wherein the immunoglobulin Fc region further includes a hinge region.

[Claim 11] The composition according to claim 1, wherein the immunoglobulin Fc region is an Fc region derived from IgG, IgA, IgD, IgE, or IgM.

[Claim 12] The composition according to claim 1, wherein each domain of the immunoglobulin Fc region is a hybrid domain of a different origin selected from the group consisting of IgG, IgA, IgD, IgE, and IgM.

[Claim 13] The composition according to claim 1, wherein the immunoglobulin Fc region is a dimer or a multimer composed of single-chain immunoglobulins of the same origin.

[Claim 14] The composition according to claim 1, further comprising a pharmaceutically acceptable carrier.

[Claim 15] The composition according to any one of claims 1 to 14, wherein the long-acting insulin conjugate and the long-acting insulinotropic peptide conjugate are administered simultaneously, sequentially, or reversely.

[Claim 16] A method for preventing or treating diabetes, comprising the step of administering the composition of any one of claims 1 to 14 to a subject having diabetes or at risk of having diabetes.

[Claim 17] The method according to claim 16, wherein the administration step is performed by concurrent administration of the long-acting insulin conjugate and the long-acting insulinotropic peptide conjugate.

[Claim 18] The method according to claim 17, wherein the concurrent administration is performed by administrating the long-acting insulin conjugate and the long-acting insulinotropic peptide conjugate simultaneously, sequentially, or reversely.

[Claim 19] A pharmaceutical composition for the prevention or treatment of diabetes comprising a long-acting insulin conjugate and an insulinotropic peptide.

[Claim 20] A pharmaceutical composition for the prevention or treatment of diabetes comprising insulin and a long-acting insulinotropic peptide conjugate.

Claims

1. A pharmaceutical composition for the prevention or treatment of diabetes comprising a long-acting insulin conjugate and a long-acting insulinotropic peptide conjugate, wherein each of the long-acting insulin conjugate and the long-acting insulinotropic peptide conjugate is prepared by liking insulin or insulinotropic peptide with an immunoglobulin Fc region via a non-peptidyl linker selected from the group consisting of polyethylene glycol, polypropylene glycol, ethylene glycol-propylene glycol copolymer, polyoxyethylated polyol, polyvinyl alcohol, polysaccharide, dextran, polyvinyl ethyl ether, a biodegradable polymer, a lipid polymer, chitin, hyaluronic acid, and a combination thereof,

wherein the insulinotropic peptide is selected from the group consisting of a native exendin-4, an exendin-4 derivative prepared by deleting N-terminal amine group, an exendin-4 derivative prepared by substituting N-terminal amine group with hydroxyl group, an exendin-4 derivative prepared by modifying N-terminal amine group with dimethyl group, an exendin-4 derivative prepared by deleting α-carbon of the first amino acid of exendin-4 (histidine),

and wherein the composition shows a more rapid hypoglycemic effect than an individual long-acting insulin conjugate or a long-acting insulinotropic peptide conjugate.

2. The composition according to claim 1, wherein the insulin is a native insulin or a basal insulin.

3. The composition according to claim 1, wherein the insulin is further modified with a non-peptidyl polymer at different site of said non-peptidyl linker.

4. The composition according to claim 3, wherein the non-peptidyl polymer is selected from the group consisting of polyethylene glycol, polypropylene glycol, ethylene glycol-propylene glycol copolymer, polyoxyethylated polyol, polyvinyl alcohol, polysaccharide, dextran, polyvinyl ethyl ether, a biodegradable polymer, a lipid polymer, chitin, hyaluronic acid, and a combination thereof.

5. The composition according to claim 1, vomiting, nausea, or weight gain is not shown in a subject when the composition is administered to the subject.

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

7. The composition according to claim 1, wherein the immunoglobulin Fc region is composed of one to four domains selected from the group consisting of CH1, CH2, CH3 and CH4 domains.

8. The composition according to claim 1, wherein the immunoglobulin Fc region further includes a hinge region.

9. The composition according to claim 1, wherein the immunoglobulin Fc region is an Fc region derived from IgG, IgA, IgD, IgE, or IgM.

10. The composition according to claim 1, wherein each domain of the immunoglobulin Fc region is a hybrid domain of a different origin selected from the group consisting of IgG, IgA, IgD, IgE, and IgM.

11. The composition according to claim 1, wherein the immunoglobulin Fc region is a dimer or a multimer composed of single-chain immunoglobulins of the same origin.

12. The composition according to claim 1, further comprising a pharmaceutically acceptable carrier.

13. A kit for preventing or treating diabetes, comprising

(i) a first composition comprising a long-acting insulin conjugate; and

(ii) a second composition comprising a long-acting insulinotropic peptide conjugate, wherein each of the long-acting insulin conjugate and the long-acting insulinotropic peptide conjugate is prepared by liking insulin or insulinotropic peptide with an immunoglobulin Fc region via a non-peptidyl linker selected from the group consisting of polyethylene glycol, polypropylene glycol, ethylene glycol-propylene glycol copolymer, polyoxyethylated polyol, polyvinyl alcohol, polysaccharide, dextran, polyvinyl ethyl ether, a biodegradable polymer, a lipid polymer, chitin, hyaluronic acid, and a combination thereof,

wherein the insulinotropic peptide is selected from the group consisting of a native exendin-4, an exendin-4 derivative prepared by deleting N-terminal amine group, an exendin-4 derivative prepared by substituting N-terminal amine group with hydroxyl group, an exendin-4 derivative prepared by modifying N-terminal amine group with dimethyl group, an exendin-4 derivative prepared by deleting α-carbon of the first amino acid of exendin-4 (histidine),

and wherein the composition shows a more rapid hypoglycemic effect than an individual long-acting insulin conjugate or a long-acting insulinotropic peptide conjugate

14. Use of a composition of any one of claims 1 to 12; or the first composition comprising a long-acting insulin conjugate and the second composition comprising a long-acting insulinotropic peptide conjugate of kit of claim 13 in the manufacture of a medicament for treating or preventing diabetes

15. The use according to claim 14, wherein the administration the first and the second composition step is performed by concurrent administration of the first composition comprising the long-acting insulin conjugate and the second composition comprising the long-acting insulinotropic peptide conjugate.

16. The use according to claim 15, wherein the concurrent administration is performed by administrating the first composition comprising the long-acting insulin conjugate and the second composition comprising the long-acting insulinotropic peptide conjugate simultaneously, sequentially, or reversely.