[CLAIMS]

[Claim 1]

An insulin analog having a reduced insulin titer compared to the native form, wherein an amino acid in A chain of insulin is modified by substituting 14^{th} amino acid of A chain with glutamic acid or asparagine.

[Claim 2]

The insulin analog according to claim 1, wherein the reduced insulin titer is attributed to a reduced insulin receptor binding affinity.

[Claim 3]

The insulin analog according to claim 1, wherein the insulin analog is selected from the group consisting of SEQ ID NOs. 34 and 36.

[Claim 4]

An insulin analog conjugate, in which (i) the insulin analog according to any one of claims 1 to 3 is linked to (ii) one biocompatible material selected from the group consisting of polyethylene glycol, fatty acid, cholesterol, albumin and fragments thereof, albumin-binding materials, polymers of repeating units of particular amino acid sequence, antibody, antibody fragments, FcRn-binding materials, in vivo connective tissue or derivatives thereof, nucleotide, fibronectin, transferrin, saccharide, and polymers as a carrier capable of prolonging in vivo half-life of the insulin analog.

[Claim 5]

The insulin analog conjugate according to claim 4, wherein the insulin analog and the biocompatible material are linked to each other via a peptide or a non-peptidyl polymer as a linker.

[Claim 6]

The insulin analog conjugate according to claim 4, wherein the FcRn-binding material is an immunoglobulin Fc region.

[Claim 7]

The insulin analog conjugate according to claim 5, wherein (i) the insulin analog according to any one of claims 1 to 3 is linked to (ii) an immunoglobulin Fc region via (iii) a peptide linker or a non-peptidyl linker selected from the group consisting of polyethylene glycol, polypropylene glycol, copolymers of ethylene glycol-propylene glycol, polyoxyethylated polyols, polyvinyl alcohol, polysaccharides, dextran, polyvinyl ethyl ether, biodegradable polymers, lipid polymers, chitins, hyaluronic acid and combination thereof.

[Claim 8]

The insulin analog conjugate according to claim 7, wherein the non-peptidyl linker is linked to the N-terminus of B chain of the insulin analog.

[Claim 9]

The insulin analog conjugate according to claim 7, wherein both ends of the non-peptidyl polymer are linked to

the N-terminus of the immunoglobulin Fc region and the N-terminal amine group of the insulin analog or the ε-amino group or the thiol group of the internal lysine residue of B chain, respectively.

[Claim 10]

The insulin analog conjugate according to claim 7, wherein the immunoglobulin Fc region is aglycosylated.

[Claim 11]

The insulin analog conjugate according to claim 7, wherein the immunoglobulin Fc region is composed of 1 domain to 4 domains selected from the group consisting of CH1, CH2, CH3 and CH4 domains.

[Claim 12]

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

[Claim 13]

The insulin analog conjugate according to claim 12, wherein each domain of the immunoglobulin Fc region is a hybrid of domains having different origins and being derived from an immunoglobulin selected from the group consisting of IgG, IgA, IgD, IgE and IgM.

[Claim 14]

The insulin analog conjugate according to claim 7, wherein the immunoglobulin Fc region further includes a hinge region.

[Claim 15]

The insulin analog conjugate according to claim 12, wherein the immunoglobulin Fc region is a dimer or a multimer consisting of single-chain immunoglobulins composed of domains of the same origin.

[Claim 16]

The insulin analog conjugate according to claim 12, wherein the immunoglobulin Fc region is an IgG4 Fc region.

[Claim 17]

The insulin analog conjugate according to claim 16, wherein the immunoglobulin Fc region is a human IgG4-derived aglycosylated Fc region.

[Claim 18]

The insulin analog conjugate according to claim 7, wherein the reactive group of the non-peptidyl linker is selected from the group consisting of an aldehyde group, a propionaldehyde group, a butyraldehyde group, a maleimide group and a succinimide derivative.

[Claim 19]

The insulin analog conjugate according to claim 18, wherein the succinimide derivative is succinimidyl propionate, succinimidyl carboxymethyl, hydroxy succinimidyl, or succinimidyl carbonate.

[Claim 20]

The insulin analog conjugate according to claim 7, wherein the non-peptidyl linker has reactive aldehyde groups

at both ends thereof.

[Claim 21]

A long-acting insulin formulation having improved in vivo duration and stability, comprising the insulin analog conjugate of claim 4.

[Claim 22]

The long-acting insulin formulation according to claim 21, wherein the formulation is a therapeutic agent for diabetes.

[Claim 23]

A method for preparing the insulin analog conjugate of claim 4, comprising:

(i) preparing an insulin analog of any one of claims 1 to 3;

(ii) preparing a biocompatible material selected from the group consisting of polyethylene glycol, fatty acid, cholesterol, albumin and fragments thereof, albumin-binding materials, polymers of repeating units of particular amino acid sequence, antibody, antibody fragments, FcRn-binding materials, in vivo connective tissue or derivatives thereof, nucleotide, fibronectin, transferrin, saccharide, and polymers ; and

(iii) linking the insulin analog to the biocompatible material.