[CLAIMS]

[Claim 1]

An insulin analog having a reduced insulin titer compared to the native form, wherein an amino acid in B chain or A chain of insulin is modified by substituting one amino acid selected from the group consisting of 8^{th} amino acid, 23^{th} amino acid, 24^{th} amino acid, and 25^{th} amino acid of B chain and 2^{th} amino acid, and 19^{th} amino acid of A chain with alanine or 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 amino acid is modified by substituting one amino acid selected from the group consisting of 8^{th} amino acid, 23^{th} amino acid, 24^{th} amino acid, and 25^{th} amino acid of B chain and 1^{th} amino acid, 2^{th} amino acid, and 19^{th} amino acid of A chain with alanine or is modified by substituting 14^{th} amino acid of A chain with glutamic acid or asparagine.~~

[Claim ~~4~~3]

The insulin analog according to claim 1, wherein the insulin analog is selected from the group consisting of SEQ ID NOs. ~~20,~~ 22, 24, 26, 28, 30, 32, 34 and 36.

[Claim ~~5~~4]

An insulin analog conjugate, ~~prepared by linking~~in which (i) the insulin analog according to any one of claims 1 to ~~4~~3~~; and~~ 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 ~~6~~5]

The insulin analog conjugate according to claim ~~5~~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 ~~7~~6]

The insulin analog conjugate according to claim ~~5~~4, wherein the FcRn-binding material is an immunoglobulin Fc region.

[Claim ~~8~~7]

The insulin analog conjugate according to claim ~~6~~5, wherein ~~the insulin analog conjugate is prepared by linking~~ (i) the insulin analog according to any one of claims 1 to ~~4~~3~~, and~~

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 ~~9~~8]

The insulin analog conjugate according to claim ~~8~~7, wherein the non-peptidyl linker is linked to the N-terminus of B chain of the insulin analog.

[Claim ~~10~~9]

The insulin analog conjugate according to claim ~~8~~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 ~~11~~10]

The insulin analog conjugate according to claim ~~8~~7, wherein the immunoglobulin Fc region is aglycosylated.

[Claim ~~12~~11]

The insulin analog conjugate according to claim ~~8~~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 ~~13~~12]

The insulin analog conjugate according to claim ~~8~~7, wherein the immunoglobulin Fc region is an Fc region derived from IgG, IgA, IgD, IgE or IgM.

[Claim ~~14~~13]

The insulin analog conjugate according to claim ~~13~~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 ~~15~~14]

The insulin analog conjugate according to claim ~~8~~7, wherein the immunoglobulin Fc region further includes a hinge region.

[Claim ~~16~~15]

The insulin analog conjugate according to claim ~~13~~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 ~~17~~16]

The insulin analog conjugate according to claim ~~13~~12, wherein the immunoglobulin Fc region is an IgG4 Fc region.

[Claim ~~18~~17]

The insulin analog conjugate according to claim ~~17~~16,

wherein the immunoglobulin Fc region is a human IgG4-derived aglycosylated Fc region.

[Claim ~~19~~18]

The insulin analog conjugate according to claim ~~8~~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 ~~20~~19]

The insulin analog conjugate according to claim ~~19~~18, wherein the succinimide derivative is succinimidyl propionate, succinimidyl carboxymethyl, hydroxy succinimidyl, or succinimidyl carbonate.

[Claim ~~21~~20]

The insulin analog conjugate according to claim ~~8~~7, wherein the non-peptidyl linker has reactive aldehyde groups at both ends thereof.

[Claim ~~22~~21]

A long-acting insulin formulation having improved in vivo duration and stability, comprising the insulin analog conjugate of claim ~~6~~4.

[Claim ~~23~~22]

The long-acting insulin formulation according to claim ~~22~~21, wherein the formulation is a therapeutic agent for diabetes.

[Claim ~~24~~23]

A method for preparing the insulin analog conjugate of claim ~~6~~4, comprising:

(i) preparing an insulin analog;

(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 ~~an FcRn-binding material, fatty acid, polyethylene glycol, an amino acid fragment, and albumin~~; and

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