insulin analog conjugate.

Still another object of the present invention is to provide a method for preparing the insulin analog conjugate.

Still another object of the present invention is to provide a method for increasing in vivo half-life using the insulin analog or the insulin analog conjugate prepared by linking the insulin analog to the carrier.

Still another object of the present invention is to provide a method for treating insulin-related diseases, including the step of administering the insulin analog or the insulin analog conjugate to a subject in need thereof.

[Technical Solution]

In one aspect to achieve the above objects, the present invention provides an insulin analog having a reduced insulin titer, compared to the native form, in which an amino acid of B chain or A chain is modified.

In one specific embodiment, the present invention provides an insulin analog having a reduced insulin receptor binding affinity.

In another specific embodiment, the present invention provides a non-native insulin analog, in which 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 ~~14^{th}~~ 19^{th} amino acid of A chain is

substituted with alanine, or in which 14th amino acid of A chain is substituted with glutamic acid or asparagine in the insulin analog according to the present invention.

In still another specific embodiment, the present invention provides an insulin analog, in which the insulin analog according to the present invention is selected from the group consisting of SEQ ID NOs. 20, 22, 24, 26, 28, 30, 32, 34 and 36.

In another aspect, the present invention provides an insulin analog conjugate that is prepared by linking the above described insulin analog to a carrier capable of prolonging half-life.

In one specific embodiment, the present invention provides an insulin analog conjugate, in which the insulin analog conjugate is prepared by linking (i) the above described insulin analog and (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 alcohols, polysaccharides, dextran, polyvinyl ethyl ether, biodegradable polymers, lipid polymers, chitins, hyaluronic acid, and combination thereof.

In still another aspect, the present invention provides a long-acting insulin formulation including the above described insulin analog conjugate, in which in vivo duration and

invention.

The insulin fragment of the present invention denotes the type of insulin in which one or more amino acids are added or deleted, and the added amino acids may be non-native amino acids (e.g., D-type amino acid). Such insulin fragments retain the function of controlling blood glucose in the body.

The insulin variant of the present invention denotes a peptide which differs from insulin in one or more amino acid sequences, and retains the function of controlling blood glucose in the body.

The respective methods for preparation of insulin agonists, derivatives, fragments and variants of the present invention can be used independently or in combination. For example, peptides of which one or more amino acid sequences differ from those of insulin and which have deamination at the amino-terminal amino acid residue and also have the function of controlling blood glucose in the body are included in the present invention.

Specifically, the insulin analog may be an insulin analog in which one or more amino acids 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~~ 14^{th} amino acid and 19^{th} amino acid of A chain are substituted with other amino acid, and preferably, in which one or more amino acids 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 are substituted with alanine or in which 14^{th} amino acid of A chain is substituted with glutamic acid or asparagine. In addition, the insulin analog may be selected from the group consisting of SEQ ID NOs. 20, 22, 24, 26, 28, 30, 32, 34 and 36, but may include any insulin analog having a reduced insulin receptor binding affinity without limitation.

According to one embodiment of the present invention, the insulin analogs of SEQ ID NOs. 20, 22, 24, 26, 28, 30, 32, 34 and 36, in particular, the representative insulin analogs, 7, 8, and 9 (SEQ ID NOs. 32, 34, and 36) were found to have reduced insulin receptor binding affinity in vitro, compared to the native form (Table 4).

In another aspect, the present invention provides an insulin analog conjugate that is prepared by linking the insulin analog and a carrier.

As used herein, the term "carrier" denotes a substance capable of increasing in vivo half-life of the linked insulin analog. The insulin analog according to the present invention is characterized in that it has a remarkably reduced insulin receptor binding affinity, compared to the native form, and avoids receptor-mediated clearance or renal clearance. Therefore, if a carrier known to increase in vivo half-life when linked to the known various physiologically active polypeptides is linked with the insulin analog, it is apparent that in vivo half-life can be improved and the resulting

[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.

[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 ~~14^{th}~~—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]

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]

An insulin analog conjugate, prepared by linking (i) the insulin analog according to any one of claims 1 to 4; and (ii) one biocompatible material selected from the group consisting of polyethylene glycol, fatty acid, cholesterol, albumin and