WHAT IS CLAIMED:

1. A method of controlling blood glucose in a subject by continuous subcutaneous insulin infusion (CSII) therapy, comprising:

a) administering a composition comprising a hyaluronan-degrading enzyme to the subject; and then

b) continuously infusing a fast-acting insulin by CSII to the subject, wherein the difference in insulin absorption is minimized or reduced over the course of infusion set life compared to CSII performed in the absence of the hyaluronan-degrading enzyme.

2. The method of claim 1, wherein:

the hyaluronan-degrading enzyme is in an amount that effects an ultra-fast insulin response at the outset of infusion set life in the subject; or

the hyaluronan-degrading enzyme is in an amount sufficient to catalyze the hydrolysis of hyaluronic acid to increase tissue permeability.

3. The method of claim 1 or claim 2, wherein in step b) the continuous infusion is effected by a continuous infusion device that comprises an insulin pump, a reservoir containing the fast-acting insulin, an optional glucose monitor, and an infusion set for subcutaneous infusion of the composition.

4. The method of claim 3, wherein the continuous infusion device comprises an insulin pump, a reservoir containing the fast-acting insulin, a glucose monitor, and an infusion set for subcutaneous infusion of the composition.

5. The method of any of claim 3 or claim 4, wherein the continuous infusion device provides an open-loop or closed-loop system.

6. The method of any of claims 1-5, wherein:

the step b) of continuously infusing a fast-acting insulin by CSII continues for a predetermined interval; and

at the end of each interval steps a) and b) are repeated.

7. The method of claim 6, wherein after the end of each interval the infusion set is replaced.

8. The method of claim 6 or claim 7, wherein each predetermined interval is more than a day or is several days.

9. The method of claim 8, wherein several days is 2 days to 4 days.

10. The method of any of claims 1-9, wherein in step a) the hyaluronan-degrading enzyme is administered at or near the site of infusion of the composition in step b).

11. The method of any of claims 1-10, wherein the hyaluronan-degrading enzyme in step a) and the fast-acting insulin composition in step b) are administered through the same injection site.

12. The method of any of claims 1-10, wherein the hyaluronan-degrading enzyme in step a) and the fast-acting insulin composition in step b) are administered through different injection sites.

13. The method of any of claims 1-12, wherein the hyaluronan-degrading enzyme is administered 1 minute to 12 hours, 5 minutes to 6 hours, 30 minutes to 3 hours, 1 hour to 2 hours, 15 seconds to 1 hour, 30 seconds to 30 minutes or 1 minute to 15 minutes prior to infusion of the fast-acting insulin.

14. The method of any of claims 1-13, wherein the hyaluronan-degrading enzyme in step a) is administered no more than 2 hours before infusion of the fast-acting insulin.

15. The method of any of claims 1-14, wherein the hyaluronan-degrading enzyme is a hyaluronidase.

16. The method of any of claims 1-15, wherein the hyaluronan-degrading enzyme is a hyaluronidase that is active at neutral pH.

17. The method of any of claims 1-16, wherein:

the hyaluronan-degrading enzyme lacks a glycosylphosphatidylinositol (GPI) anchor or is not membrane-associated when expressed from a cell; or

the hyaluronan-degrading enzyme contains C-terminal truncations of one or more amino acid residues to remove all or part of a GPI anchor.

18. The method of any of claims 1-17, wherein the hyaluronan-degrading enzyme is a hyaluronidase that is a PH20 or a C-terminally truncated fragment thereof.

19. The method of any of claims 1-18, wherein the hyaluronan-degrading enzyme is a PH20 polypeptide that has the sequence of amino acids set forth in any of SEQ ID NOS: 4-9, 47-48, 234-254, and 267-273, or a sequence of amino acids that exhibits at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%,

94%, 95%, 96%, 97%, 98%, 99% or more sequence identity to any of SEQ ID NOS: 4-9, 47-48, 234-254, and 267-273.

20. The method of any of claims 1-19, wherein the hyaluronan-degrading enzyme is a C-terminal truncated PH20 that comprises a sequence of amino acids set forth in any of SEQ ID NOS: 4-9.

21. The method of any of claims 1-20, wherein:

the hyaluronan-degrading enzyme in step a) is administered in an amount that is functionally equivalent to between or about between 1 Unit to 200 Units, 5 Units to 150 Units, 10 Units to 150 Units, 50 Units to 150 Units or 1 Unit to 50 Units; or

the hyaluronan-degrading enzyme in step a) is administered in an amount that is between or about between 8 ng to 2 μg, 20 ng to 1.6 μg, 80 ng to 1.25 μg or 200 ng to 1 μg.

22. The method of any of claims 1-21, wherein the fast-acting insulin is a regular insulin.

23. The method of claim 22, wherein the regular insulin is a human insulin or pig insulin.

24. The method of claim 22 or claim 23, wherein the regular insulin is an insulin with an A chain having a sequence of amino acids set forth in SEQ ID NO:103 and a B chain having a sequence of amino acids set forth in SEQ ID NO:104 or an insulin with an A chain with a sequence of amino acids set forth as amino acid residue positions 88-108 of SEQ ID NO:123 and a B chain with a sequence of amino acids set forth as amino acid residue positions 25-54 of SEQ ID NO:123.

25. The method of any of claims 1-24, wherein the fast-acting insulin is an insulin analog.

26. The method of any of claims 1-25, wherein the fast-acting insulin is an insulin analog selected from among insulin lispro, insulin aspart or insulin glulisine.

27. The method of claim 25 or claim 26, wherein the insulin analog is selected from among an insulin having an A chain with a sequence of amino acids set forth in SEQ NOS:103 and a B chain having a sequence of amino acids set forth in any of SEQ NOS:147-149.

28. The method of any of claims 1-27, wherein:

the insulin composition comprises insulin in an amount that is between or about between 10 U/mL to 1000 U/mL; or

the insulin composition comprises insulin in an amount that is between or about between 0.35 mg/mL to 35 mg/mL.

29. The method of any of claims 1-28, wherein the insulin in the composition is at least or is about at least or is 100 U/mL.

30. The method of any of claims 1-29, wherein the composition in step b) comprises a fast-acting insulin analog and a hyaluronan-degrading enzyme.

31. The method of claim 30, wherein:

the amount of fast-acting insulin analog in the composition is between or about between 10 U/mL to 1000 U/mL; and

the amount of a hyaluronan-degrading enzyme in the composition is functionally equivalent to between or about between 1 U/mL to 10,000 U/mL.

32. A continuous subcutaneous insulin infusion (CSII) dosage regimen method for controlling blood glucose in a subject, comprising:

a) performing CSII to deliver a composition comprising a super fast-acting insulin composition to a subject in accord with a programmed basal rate and bolus dose of insulin; and

b) at least once during the course of treatment, increasing the amount of basal insulin and/or bolus insulin administered by at least 1% compared to the programmed basal rate and bolus dose of insulin administered in the absence of a hyaluronan-degrading enzyme thereby increasing insulin action.

33. The method of claim 32, wherein the basal insulin and/or bolus insulin administered are increased at least once per day.

34. The method of claim 32 or claim 33, wherein the super-fast acting insulin composition comprises:

a therapeutically effective amount of a fast-acting insulin analog for controlling blood glucose levels; and

an amount of a hyaluronan-degrading enzyme sufficient to render the composition a super fast-acting insulin composition.

35. The method of claim 34, wherein:

the amount of fast-acting insulin is from or from about 10 U/mL to 1000 U/mL; and the sufficient amount of a hyaluronan-degrading enzyme to render the composition super fast-acting is functionally equivalent to 1 U/mL to 10,000 U/mL, or

the amount of fast-acting insulin is from or from about 0.35 mg/mL to 35 mg/mL; and the sufficient amount of a hyaluronan-degrading enzyme to render the composition super fast-acting is functionally equivalent to 8 ng/mL to 80 μg/mL.

36. The method of any of claims 1-35, wherein the subject has diabetes.

37. The method of claim 36, wherein the diabetes is selected from among type 1 diabetes mellitus, type 2 diabetes mellitus and gestational diabetes.

38. A composition, comprising a hyaluronan-degrading enzyme for use for minimizing the change in insulin absorption that occurs over a course of continuous subcutaneous insulin infusion (CSII) for treatment of diabetes.

39. Use of a hyaluronan-degrading enzyme composition for minimizing the change in insulin absorption that occurs over a course of continuous subcutaneous insulin infusion for treatment of diabetes.

40. A composition for use as a leading edge in continuous subcutaneous insulin infusion (CSII) therapy for treatment of diabetes, wherein:

a leading edge therapeutic for insulin therapy is a composition that is administered prior to infusion of an insulin composition by CSII; and

the composition comprises a hyaluronan-degrading enzyme that is formulated for direct administration in an amount that minimizes changes in insulin absorption that occurs over a course of continuous subcutaneous insulin infusion (CSII).

41. Use of a composition as a leading edge in continuous subcutaneous insulin infusion (CSII) therapy for treatment of diabetes, wherein:

a leading edge therapeutic for insulin therapy is a composition that is administered prior to infusion of an insulin composition by CSII; and

the composition comprises a hyaluronan-degrading enzyme that is formulated for direct administration in an amount that minimizes changes in insulin absorption that occurs over a course of continuous subcutaneous insulin infusion (CSII).

42. The composition or use of any of claims 38-41, wherein the hyaluronan-degrading enzyme is in a therapeutically effective amount sufficient to catalyze the hydrolysis of hyaluronic acid to increase tissue permeability.

43. The composition or use of any of claims 38-42, wherein the hyaluronan-degrading enzyme is a hyaluronidase.

44. The composition or use of any of claims 38-43, wherein the hyaluronan-degrading enzyme is a hyaluronidase that is active at neutral pH.

45. The composition or use of any of claims 38-44, wherein:

the hyaluronan-degrading enzyme lacks a glycosylphosphatidylinositol (GPI) anchor or is not membrane-associated when expressed from a cell; or

the hyaluronan-degrading enzyme contains C-terminal truncations of one or more amino acid residues and lacks all or part of a GPI anchor.

46. The composition or use of any of claims 38-45, wherein the hyaluronan-degrading enzyme is a hyaluronidase that is a PH20 or a C-terminally truncated fragment thereof.

47. The composition or use of any of claims 38-46, wherein the hyaluronan-degrading enzyme is a PH20 polypeptide that has the sequence of amino acids set forth in any of SEQ ID NOS: 4-9, 47-48, 234-254, and 267-273, or a sequence of amino acids that exhibits at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity to any of SEQ ID NOS: 4-9, 47-48, 234-254, and 267-273.

48. The composition or use of any of claims 38-47, wherein the hyaluronan-degrading enzyme is a C-terminal truncated PH20 that comprises a sequence of amino set forth in any of SEQ ID NOS: 4-9, or a sequence of amino acids that exhibits at least 85% sequence identity to the sequence of amino acids set forth in any one of SEQ ID NOS:4-9.

49. The composition or use of any of claims 38-48, wherein the PH20 has a sequence of amino acids set forth in any one of SEQ ID NOS:4-9.

50. The composition or use of any of claims 38-49, wherein:

the hyaluronan-degrading enzyme in the composition is in an amount that is functionally equivalent to between or about between 1 Unit to 200 Units, 5 Units to 150 Units, 10 Units to 150 Units, 50 Units to 150 Units or 1 Unit to 50 Units; or

the hyaluronan-degrading enzyme in the composition is in an amount that is between or about between 8 ng to 2 μg, 20 ng to 1.6 μg, 80 ng to 1.25 μg or 200 ng to 1 μg.

51. The composition or use of any of claims 38-50, wherein the hyaluronan-degrading enzyme in the composition is in an amount between or about between 10 Units/mL to 20,000 Units/mL, 30 Units/mL to 3000 U/mL, 100 U/mL to 1000 U/mL, 300 U/mL to 2000 U/mL, 600 U/mL to 2000 U/mL or 600 U/mL to 1000 U/mL.

52. The use or composition of any of claims 38-51, wherein the insulin composition for use in continuous subcutaneous insulin infusion (CSII) therapy comprises a fast-acting insulin.

53. The use or composition of claim 52, wherein the fast-acting insulin is a regular insulin.

54. The use or composition of claim 53, wherein the regular insulin is a human insulin or pig insulin.

55. The use or composition of claim 53 or claim 54, wherein the regular insulin is an insulin with an A chain having a sequence of amino acids set forth in SEQ ID NO:103 and a B chain having a sequence of amino acids set forth in SEQ ID NO:104 or an insulin with an A chain with a sequence of amino acids set forth as amino acid residue positions 88-108 of SEQ ID NO:123 and a B chain with a sequence of amino acids set forth as amino acid residue positions 25-54 of SEQ ID NO:123.

56. The use or composition of claim 52, wherein the fast-acting insulin is an insulin analog.

57. The use or composition of claim 56, wherein the fast-acting insulin analog is insulin aspart, insulin lispro or insulin glulisine.

58. The use or composition of claim 57, wherein the insulin analog is selected from among an insulin having an A chain with a sequence of amino acids set forth in SEQ NOS:103 and a B chain having a sequence of amino acids set forth in any of SEQ NOS:147-149.

59. The use or composition of any of claims 52-58, wherein the fast-acting insulin is formulated in the composition in an amount that is from or from about 100 u/mL to 1000 U/mL or 500 U/mL to 1000 U/mL.

60. The composition or use of any of claims 38-59 for use 15 seconds to 1 hour, 30 seconds to 30 minutes, 1 minute to 15 minutes, 1 minute to 12 hours, 5 minutes to 6 hours, 30 minutes to 3 hours, or 1 hour to 2 hours prior to infusion of the insulin composition.

61. The use or composition of any of claims 38-60 for use no more than 2 hours before infusion of the insulin composition.

62. A composition, comprising a bolus insulin for use in ameliorating the decrease in total insulin action caused by a continuous subcutaneous insulin infusion of a super-fast acting insulin composition.

63. Use of a bolus insulin for ameliorating the decrease in total insulin action caused by a continuous subcutaneous insulin infusion of a super-fast acting insulin composition.

64. The composition or use of claim 62 or claim 63, wherein the super-fast acting insulin composition comprises:

a therapeutically effective amount of a fast-acting insulin analog for controlling blood glucose levels; and

an amount of a hyaluronan-degrading enzyme sufficient to render the composition a super fast-acting insulin composition.

65. The use or composition of claim 64, wherein:

the amount of fast-acting insulin is from or from about 10 U/mL to 1000 U/mL; and

the sufficient amount of a hyaluronan-degrading enzyme to render the composition super fast-acting is functionally equivalent to 1 U/mL to 10,000 U/mL.

66. The use or composition of any one of claims 62-65, wherein:

the amount of fast-acting insulin is from or from about 0.35 mg/mL to 35 mg/mL; and

the sufficient amount of a hyaluronan-degrading enzyme to render the composition super fast-acting is functionally equivalent to 8 ng/mL to 80 μg/mL.

67. The use or composition of any of claims 62-66, wherein the fast-acting insulin bolus is a fast-acting insulin.

68. The use or composition of claim 67, wherein the fast-acting insulin bolus is a regular insulin or an insulin analog.

69. The use or composition of any of claims 62-68, wherein the amount of bolus insulin in the composition is increased at least 1% compared to the programmed insulin dose of insulin administered under the same prandial conditions and/or for correction for a hyperglycemic event in the absence of a hyaluronan-degrading enzyme.

CLAIMS:

1. A composition, comprising a hyaluronidase for use in the treatment of diabetes in combination with continuous subcutaneous insulin infusion (CSII) therapy of an insulin composition, wherein:

the composition comprising the hyaluronidase is formulated for administration separately from the CSII therapy for administration prior to infusion of an insulin composition by CSII; and

the composition comprising the hyaluronidase is formulated for direct administration in an amount that minimizes changes in insulin absorption that occurs over a course of continuous subcutaneous insulin infusion (CSII).

2. Use of a composition comprising a hyaluronidase for manufacture of a medicament for treatment of diabetes in combination with continuous subcutaneous insulin infusion (CSII) therapy of an insulin composition, wherein:

the composition comprising the hyaluronan-degrading enzyme is formulated for administration separately from insulin in the CSII therapy for administration prior to infusion of the insulin composition by CSII; and

the composition comprising the hyaluronan-degrading enzyme is formulated for direct administration in an amount that minimizes changes in insulin absorption that occurs over a course of continuous subcutaneous insulin infusion (CSII).

3. The composition or use of claim 1 or claim 2, wherein the hyaluronidase is in a therapeutically effective amount sufficient to catalyze the hydrolysis of hyaluronic acid to increase tissue permeability.

4. The composition or use of any of claims 1-3, wherein the hyaluronidase is active at neutral pH.

5. The composition or use of any of claims 1-4, wherein:

the hyaluronidase lacks a glycosylphosphatidylinositol (GPI) anchor or is not membrane-associated when expressed from a cell; or

the hyaluronidase contains C-terminal truncations of one or more amino acid residues and lacks all or part of a GPI anchor.

6. The composition or use of any of claims 1-5, wherein the hyaluronidase is a PH20 or a C-terminally truncated fragment thereof.

7. The composition or use of any of claims 1-6, wherein the hyaluronidase is a PH20 polypeptide that has the sequence of amino acids set forth in any of SEQ ID NOS: 4-9, 47-48, 234-254, and 267-273, or a sequence of amino acids that exhibits at least 85% sequence identity to any of SEQ ID NOS: 4-9, 47-48, 234-254, and 267-273 and retains hyaluronidase activity.

8. The composition or use of any of claims 1-7, wherein the hyaluronidase is a C-terminal truncated PH20 that comprises the sequence of amino set forth in any of SEQ ID NOS: 4-9, or a sequence of amino acids that exhibits at least 85% sequence identity to the sequence of amino acids set forth in any one of SEQ ID NOS:4-9 and retains hyaluronidase activity.

9. The composition or use of any of claims 1-8, wherein the PH20 has the sequence of amino acids set forth in any one of SEQ ID NOS:4-9.

10. The composition or use of any of claims 1-9, wherein:

the hyaluronidase in the composition is in an amount that is functionally equivalent to between or about between 1 Unit to 200 Units, 5 Units to 150 Units, 10 Units to 150 Units, 50 Units to 150 Units or 1 Unit to 50 Units; or

the hyaluronidase in the composition is in an amount that is between or about between 8 ng to 2 µg, 20 ng to 1.6 µg, 80 ng to 1.25 µg or 200 ng to 1 µg.

11. The composition or use of any of claims 1-10, wherein the hyaluronidase in the composition is in an amount between or about between 10 Units/mL to 20,000 Units/mL, 30 Units/mL to 3000 U/mL, 100 U/mL to 1000 U/mL, 300 U/mL to 2000 U/mL, 600 U/mL to 2000 U/mL or 600 U/mL to 1000 U/mL.

12. The composition or use of any of claims 1-11, wherein the insulin composition for use in continuous subcutaneous insulin infusion (CSII) therapy comprises a fast-acting insulin.

13. The composition or use of claim 12, wherein the fast-acting insulin is a regular insulin.

14. The composition or use of claim 13, wherein the regular insulin is a human insulin or pig insulin.

15. The composition or use of claim 13 or claim 14, wherein the regular insulin is an insulin with an A chain having the sequence of amino acids set forth in SEQ ID NO:103 and a B chain having the sequence of amino acids set forth in SEQ ID NO:104 or an insulin with an A chain with the sequence of amino acids set forth as amino acid residue positions 88-108 of SEQ ID NO:123 and a B chain with the sequence of amino acids set forth as amino acid residue positions 25-54 of SEQ ID NO:123.

16. The composition or use of claim 12, wherein the fast-acting insulin is an insulin analog.

17. The composition or use of claim 16, wherein the fast-acting insulin analog is insulin aspart, insulin lispro or insulin glulisine.

18. The composition or use of claim 17, wherein the insulin analog is selected from among an insulin having an A chain with the sequence of amino acids set forth in SEQ NOS:103 and a B chain having the sequence of amino acids set forth in any of SEQ NOS:147-149.

19. The composition or use of any of claims 12-18, wherein the fast-acting insulin is formulated in the insulin composition for CSII in an amount that is from or from about 100 u/mL to 1000 U/mL or 500 U/mL to 1000 U/mL.

20. The composition or use of any of claims 1-19, wherein the composition comprising the hyaluronidase is formulated for use 15 seconds to 1 hour, 30 seconds to 30 minutes, 1 minute to 15 minutes, 1 minute to 12 hours, 5 minutes to 6 hours, 30 minutes to 3 hours, or 1 hour to 2 hours prior to infusion of the insulin composition by CSII.

21. The composition or use of any of claims 1-20, wherein the composition comprising the hyaluronidase is formulated for use no more than 2 hours before infusion of the insulin composition by CSII.