8: 3143-3148). Wei et al. discloses that both genetic and pharmacologic FGF21 gain of function lead to a striking decrease in bone mass in mice. Furthermore, Wei et al. states that the FGF21 loss of function leads to a reciprocal high-bone-mass phenotype and that mechanistically FGF21 inhibits osteoblastogenesis and stimulates adipogenesis from bone marrow mesenchymal stem cells by potentiating the activity of peroxisome proliferator-activated receptor γ (PPAR-γ).

The present examples demonstrate that a FGF21 protein delivered *in vivo* results in an increase of the osteoid deposition in or on a bone. Furthermore, the present examples demonstrate in transgenic mice that overexpression of human FGF21 results in an increase of the mineral content of a bone, when normalized for body weight and compared to wild-type mice. Together these results illustrate that a FGF21 protein may be used in the treatment of hypo-ostosis and/or hypo-osteoidosis. Thus, an objective of the present ~~invention~~embodiments disclosed herein is to provide novel therapeutic uses of FGF21 proteins.

The present ~~invention~~disclosure provides a method of increasing bone formation and/or bone deposition in a patient, comprising administering to the patient an effective amount of the FGF21 protein of SEQ ID NO: 1.

Furthermore, the present ~~invention~~disclosure provides a method of treating hypo-ostosis in a patient, comprising administering to the patient an effective amount of the FGF21 protein of SEQ ID NO: 1.

In a further ~~aspect~~embodiment, the present ~~invention~~disclosure provides a method of accelerating the healing of a bone fracture, orthotic procedure, prosthetics implant, dental implant, and/or spinal fusion in a patient, comprising administering to the patient an effective amount of the FGF21 protein of SEQ ID NO: 1.

In a further ~~aspect~~embodiment, the present ~~invention~~disclosure provides a method of increasing the mineral density of a bone in a patient, comprising administering to the patient an effective amount of the FGF21 protein of SEQ ID NO: 1.

Furthermore, the present ~~invention~~disclosure provides a method of increasing the mineral content of a bone in a patient, comprising administering to the patient an effective amount of the FGF21 protein of SEQ ID NO: 1.

In a further ~~aspect~~embodiment, the present ~~invention~~disclosure provides a method of increasing the osteoid deposition in or on a bone in a patient, comprising administering to the patient an effective amount of the FGF21 protein of SEQ ID NO: 1.

Furthermore, the present ~~invention~~disclosure provides a method of treating hypo-osteoidosis in a patient, comprising administering to the patient an effective amount of the FGF21 protein of SEQ ID NO: 1.

Furthermore, the present ~~invention~~disclosure provides a method of delaying, slowing, and/or preventing bone loss in a patient, comprising administering to the patient an effective amount of the FGF21 protein of SEQ ID NO: 1.

In a further ~~aspect~~embodiment, the present ~~invention~~disclosure provides a method of preventing and/or treating osteoporosis in a patient, comprising administering to the patient an effective amount of the FGF21 protein of SEQ ID NO: 1.

Furthermore, the present disclosure~~invention~~ provides a method of preventing and/or treating high risk of fracture due to poor bone quality and/or bone loss in a patient, comprising administering to the patient an effective amount of the FGF21 protein of SEQ ID NO: 1.

The present ~~invention~~disclosure provides a use of the FGF21 protein of SEQ ID NO: 1 in the manufacture of a medicament for increasing bone formation and/or bone deposition.

In a further ~~aspect~~embodiment, the present ~~invention~~disclosure provides a use of the FGF21 protein of SEQ ID NO: 1 in the manufacture of a medicament for treating hypo-ostosis.

In a further ~~aspect~~embodiment, the present ~~invention~~disclosure provides a use of the FGF21 protein of SEQ ID NO: 1 in the manufacture of a medicament for accelerating the healing of a bone fracture, orthotic procedure, prosthetics implant, dental implant, and/or spinal fusion.

In a further ~~aspect~~embodiment, the present ~~invention~~disclosure provides a use of the FGF21 protein of SEQ ID NO: 1 in the manufacture of a medicament for increasing the mineral density of a bone.

Furthermore, the present ~~invention~~disclosure provides a use of the FGF21 protein of SEQ ID NO: 1 in the manufacture of a medicament for increasing the mineral content of a bone.

Furthermore, the present ~~invention~~disclosure provides a use of the FGF21 protein of SEQ ID NO: 1 in the manufacture of a medicament for increasing the osteoid deposition in or on a bone.

In a further ~~aspect~~embodiment, the present ~~invention~~disclosure provides a use of the FGF21 protein of SEQ ID NO: 1 in the manufacture of a medicament for treating hypo-osteoidosis.

In a further ~~aspect~~embodiment, the present ~~invention~~disclosure provides a use of the FGF21 protein of SEQ ID NO: 1 in the manufacture of a medicament for delaying, slowing, and/or preventing bone loss.

Furthermore, the present ~~invention~~disclosure provides a use of the FGF21 protein of SEQ ID NO: 1 in the manufacture of a medicament for preventing and/or treating osteoporosis.

Furthermore, the present ~~invention~~disclosure provides a use of the FGF21 protein of SEQ ID NO: 1 in the manufacture of a medicament for preventing and/or treating high risk of fracture due to poor bone quality and/or bone loss.

In one aspect, ~~T~~the present ~~invention~~disclosure provides the FGF21 protein of SEQ ID NO: 1 for use in increasing bone formation and/or bone deposition.

In a further aspect, the present ~~invention~~disclosure provides the FGF21 protein of SEQ ID NO: 1 for use in treating hypo-ostosis.

In a further aspect, the present ~~invention~~disclosure provides the FGF21 protein of SEQ ID NO: 1 for use in accelerating the healing of a bone fracture, orthotic procedure, prosthetics implant, dental implant, and/or spinal fusion.

In a further aspect, the present ~~invention~~disclosure provides the FGF21 protein of SEQ ID NO: 1 for use in increasing the mineral density of a bone.

~~Furthermore~~In another aspect, the present ~~invention~~disclosure provides the FGF21 protein of SEQ ID NO: 1 for use in increasing the mineral content of a bone.

~~Furthermore~~In another aspect, the present ~~invention~~disclosure provides the FGF21 protein of SEQ ID NO: 1 for use in increasing the osteoid deposition in or on a bone.

~~Furthermore~~In another aspect, the present ~~invention~~disclosure provides the FGF21 protein of SEQ ID NO: 1 for use in treating hypo-osteoidosis.

In a further aspect, the present ~~invention~~disclosure provides the FGF21 protein of SEQ ID NO: 1 for use in delaying, slowing, and/or preventing bone loss.

In a further aspect, the present ~~invention~~disclosure provides the FGF21 protein of SEQ ID NO: 1 for use in preventing and/or treating osteoporosis.

In a further aspect, the present ~~invention~~disclosure provides the FGF21 protein of SEQ ID NO: 1 for use in preventing and/or treating high risk of fracture due to poor bone quality and/or bone loss.

The FGF21 protein of SEQ ID NO: 1 may be used, as described herein, as a single agent and/or in combination with another agent or agents that promotes bone mineralization, bone formation, and/or decreases bone resorption. Agents include, but are not limited to, FORTEO®, EVISTA®, FOSAMAX®, ACTONEL®, and BONIVA®, zolendronate, denosumab, blososumab, CDP7851/AMG 785. In another aspect, there is provided a combination of the FGF21 protein of SEQ ID NO: 1 with another agent or agents that promotes bone mineralization, bone formation, and/or decreases bone resorption for any of the uses as defined above.

The present ~~invention~~disclosure provides a method of increasing bone formation and/or bone deposition in a patient, comprising administering to the patient an effective amount of the FGF21 protein of SEQ ID NO: 3.

Furthermore, the present ~~invention~~disclosure provides a method of treating hypo-ostosis in a patient, comprising administering to the patient an effective amount of the FGF21 protein of SEQ ID NO: 3.

In a further ~~aspect~~embodiment, the present ~~invention~~disclosure provides a method of accelerating the healing of a bone fracture, orthotic procedure, prosthetics implant, dental implant, and/or spinal fusion in a patient, comprising administering to the patient an effective amount of the FGF21 protein of SEQ ID NO: 3.

In a further ~~aspect~~embodiment, the present ~~invention~~disclosure provides a method of increasing the mineral density of a bone in a patient, comprising administering to the patient an effective amount of the FGF21 protein of SEQ ID NO: 3.

Furthermore, the present ~~invention~~disclosure provides a method of increasing the mineral content of a bone in a patient, comprising administering to the patient an effective amount of the FGF21 protein of SEQ ID NO: 3.

In a further ~~aspect~~embodiment, the present ~~invention~~disclosure provides a method of increasing the osteoid deposition in or on a bone in a patient, comprising administering to the patient an effective amount of the FGF21 protein of SEQ ID NO: 3.

Furthermore, the present ~~invention~~disclosure provides a method of treating hypo-osteoidosis in a patient, comprising administering to the patient an effective amount of the FGF21 protein of SEQ ID NO: 3.

Furthermore, the present ~~invention~~disclosure provides a method of delaying, slowing, and/or preventing bone loss in a patient, comprising administering to the patient an effective amount of the FGF21 protein of SEQ ID NO: 3.

In a further ~~aspect~~embodiment, the present ~~invention~~disclosure provides a method of preventing and/or treating osteoporosis in a patient, comprising administering to the patient an effective amount of the FGF21 protein of SEQ ID NO: 3.

Furthermore, the present ~~invention~~disclosure provides a method of preventing and/or treating high risk of fracture due to poor bone quality and/or bone loss in a patient, comprising administering to the patient an effective amount of the FGF21 protein of SEQ ID NO: 3.

The present ~~invention~~disclosure provides a use of the FGF21 protein of SEQ ID NO: 3 in the manufacture of a medicament for increasing bone formation and/or bone deposition.

In a further ~~aspect~~embodiment, the present ~~invention~~disclosure provides a use of the FGF21 protein of SEQ ID NO: 3 in the manufacture of a medicament for treating hypo-ostosis.

In a further ~~aspect~~embodiment, the present ~~invention~~disclosure provides a use of the FGF21 protein of SEQ ID NO: 3 in the manufacture of a medicament for accelerating the healing of a bone fracture, orthotic procedure, prosthetics implant, dental implant, and/or spinal fusion.

In a further ~~aspect~~embodiment, the present ~~invention~~disclosure provides a use of the FGF21 protein of SEQ ID NO: 3 in the manufacture of a medicament for increasing the mineral density of a bone.

Furthermore, the present ~~invention~~disclosure provides a use of the FGF21 protein of SEQ ID NO: 3 in the manufacture of a medicament for increasing the mineral content of a bone.

Furthermore, the present ~~invention~~disclosure provides a use of the FGF21 protein of SEQ ID NO: 3 in the manufacture of a medicament for increasing the osteoid deposition in or on a bone.

In a further ~~aspect~~embodiment, the present ~~invention~~disclosure provides a use of the FGF21 protein of SEQ ID NO: 3 in the manufacture of a medicament for treating hypo-osteoidosis.

In a further ~~aspect~~embodiment, the present ~~invention~~disclosure provides a use of the FGF21 protein of SEQ ID NO: 3 in the manufacture of a medicament for delaying, slowing, and/or preventing bone loss.

Furthermore, the present ~~invention~~disclosure provides a use of the FGF21 protein of SEQ ID NO: 3 in the manufacture of a medicament for preventing and/or treating osteoporosis.

Furthermore, the present ~~invention~~disclosure provides a use of the FGF21 protein of SEQ ID NO: 3 in the manufacture of a medicament for preventing and/or treating high risk of fracture due to poor bone quality and/or bone loss.

The present ~~invention~~disclosure provides the FGF21 protein of SEQ ID NO: 3 for use in increasing bone formation and/or bone deposition.

In a further ~~aspect~~embodiment, the present ~~invention~~disclosure provides the FGF21 protein of SEQ ID NO: 3 for use in treating hypo-ostosis.

In a further ~~aspect~~embodiment, the present ~~invention~~disclosure provides the FGF21 protein of SEQ ID NO: 3 for use in accelerating the healing of a bone fracture, orthotic procedure, prosthetics implant, dental implant, and/or spinal fusion.

In a further ~~aspect~~embodiment, the present ~~invention~~disclosure provides the FGF21 protein of SEQ ID NO: 3 for use in increasing the mineral density of a bone.

Furthermore, the present ~~invention~~disclosure provides the FGF21 protein of SEQ ID NO: 3 for use in increasing the mineral content of a bone.

Furthermore, the present ~~invention~~disclosure provides the FGF21 protein of SEQ ID NO: 3 for use in increasing the osteoid deposition in or on a bone.

Furthermore, the present ~~invention~~disclosure provides the FGF21 protein of SEQ ID NO: 3 for use in treating hypo-osteoidosis.

In a further ~~aspect~~embodiment, the present ~~invention~~disclosure provides the FGF21 protein of SEQ ID NO: 3 for use in delaying, slowing, and/or preventing bone loss.

In a further ~~aspect~~embodiment, the present ~~invention~~disclosure provides the FGF21 protein of SEQ ID NO: 3 for use in preventing and/or treating osteoporosis.

In a further ~~aspect~~embodiment, the present ~~invention~~disclosure provides the FGF21 protein of SEQ ID NO: 3 for use in preventing and/or treating high risk of fracture due to poor bone quality and/or bone loss.

The FGF21 protein of SEQ ID NO: 3 may be used, as described herein, as a single agent and/or in combination with another agent or agents that promotes bone mineralization, bone formation, and/or decreases bone resorption. Agents include, but are not limited to, FORTEO®, EVISTA®, FOSAMAX®, ACTONEL®, and BONIVA®, zolendronate, denosumab, blososumab, CDP7851/AMG 785.

The present ~~invention~~disclosure provides a method of increasing bone formation and/or bone deposition in a patient, comprising administering to the patient an effective amount of the FGF21 protein, wherein the amino acid sequence is SEQ ID NO: 4.

Furthermore, the present ~~invention~~disclosure provides a method of treating hypo-ostosis in a patient, comprising administering to the patient an effective amount of the FGF21 protein, wherein the amino acid sequence is SEQ ID NO: 4.

In a further ~~aspect~~embodiment, the present ~~invention~~disclosure provides a method of accelerating the healing of a bone fracture, orthotic procedure, prosthetics implant, dental implant, and/or spinal fusion in a patient, comprising administering to the patient an effective amount of the FGF21 protein, wherein the amino acid sequence is SEQ ID NO: 4.

In a further ~~aspect~~embodiment, the present ~~invention~~disclosure provides a method of increasing the mineral density of a bone in a patient, comprising administering to the patient an effective amount of the FGF21 protein, wherein the amino acid sequence is SEQ ID NO: 4.

Furthermore, the present ~~invention~~disclosure provides a method of increasing the mineral content of a bone in a patient, comprising administering to the patient an effective amount of the FGF21 protein, wherein the amino acid sequence is SEQ ID NO: 4.

In a further ~~aspect~~embodiment, the present ~~invention~~disclosure provides a method of increasing the osteoid deposition in or on a bone in a patient, comprising administering to the patient an effective amount of the FGF21 protein, wherein the amino acid sequence is SEQ ID NO: 4.

Furthermore, the present ~~invention~~disclosure provides a method of treating hypo-osteoidosis in a patient, comprising administering to the patient an effective amount of the FGF21 protein, wherein the amino acid sequence is SEQ ID NO: 4.

Furthermore, the present ~~invention~~disclosure provides a method of delaying, slowing, and/or preventing bone loss in a patient, comprising administering to the patient an effective amount of the FGF21 protein, wherein the amino acid sequence is SEQ ID NO: 4.

In a further ~~aspect~~embodiment, the present ~~invention~~disclosure provides a method of preventing and/or treating osteoporosis in a patient, comprising administering to the patient an effective amount of the FGF21 protein, wherein the amino acid sequence is SEQ ID NO: 4.

Furthermore, the present ~~invention~~disclosure provides a method of preventing and/or treating high risk of fracture due to poor bone quality and/or bone loss in a patient, comprising administering to the patient an effective amount of the FGF21 protein, wherein the amino acid sequence is SEQ ID NO: 4.

The present ~~invention~~disclosure provides a use of the FGF21 protein, wherein the amino acid sequence is SEQ ID NO: 4 in the manufacture of a medicament for increasing bone formation and/or bone deposition.

In a further ~~aspect~~embodiment, the present ~~invention~~disclosure provides a use of the FGF21 protein, wherein the amino acid sequence is SEQ ID NO: 4 in the manufacture of a medicament for treating hypo-ostosis.

In a further ~~aspect~~embodiment, the present ~~invention~~disclosure provides a use of the FGF21 protein, wherein the amino acid sequence is SEQ ID NO: 4 in the manufacture of a medicament for accelerating the healing of a bone fracture, orthotic procedure, prosthetics implant, dental implant, and/or spinal fusion.

In a further ~~aspect~~embodiment, the present ~~invention~~disclosure provides a use of the FGF21 protein, wherein the amino acid sequence is SEQ ID NO: 4 in the manufacture of a medicament for increasing the mineral density of a bone.

Furthermore, the present ~~invention~~disclosure provides a use of the FGF21 protein, wherein the amino acid sequence is SEQ ID NO: 4 in the manufacture of a medicament for increasing the mineral content of a bone.

Furthermore, the present ~~invention~~disclosure provides a use of the FGF21 protein, wherein the amino acid sequence is SEQ ID NO: 4 in the manufacture of a medicament for increasing the osteoid deposition in or on a bone.

In a further ~~aspect~~embodiment, the present ~~invention~~disclosure provides a use of the FGF21 protein, wherein the amino acid sequence is SEQ ID NO: 4 in the manufacture of a medicament for treating hypo-osteoidosis.

In a further ~~aspect~~embodiment, the present ~~invention~~disclosure provides a use of the FGF21 protein, wherein the amino acid sequence is SEQ ID NO: 4 in the manufacture of a medicament for delaying, slowing, and/or preventing bone loss.

Furthermore, the present ~~invention~~disclosure provides a use of the FGF21 protein, wherein the amino acid sequence is SEQ ID NO: 4 in the manufacture of a medicament for preventing and/or treating osteoporosis.

Furthermore, the present ~~invention~~disclosure provides a use of the FGF21 protein, wherein the amino acid sequence is SEQ ID NO: 4 in the manufacture of a medicament for preventing and/or treating high risk of fracture due to poor bone quality and/or bone loss.

In another aspect, ~~T~~the present ~~invention~~disclosure provides the FGF21 protein of~~, wherein the amino acid sequence is~~ SEQ ID NO: 4 for use in increasing bone formation and/or bone deposition.

In a further aspect, the present ~~invention~~disclosure provides the FGF21 protein~~, wherein the amino acid sequence is~~ of SEQ ID NO: 4 for use in treating hypo-ostosis.

In a further aspect, the present ~~invention~~disclosure provides the FGF21 protein~~, wherein the amino acid sequence is~~ of SEQ ID NO: 4 for use in accelerating the healing of a bone fracture, orthotic procedure, prosthetics implant, dental implant, and/or spinal fusion.

In a further aspect, the present ~~invention~~disclosure provides the FGF21 protein~~, wherein the amino acid sequence is~~ of SEQ ID NO: 4 for use in increasing the mineral density of a bone.

~~Furthermore~~In another aspect, the present ~~invention~~disclosure provides the FGF21 protein~~, wherein the amino acid sequence is~~ of SEQ ID NO: 4 for use in increasing the mineral content of a bone.

In another aspect~~Furthermore~~, the present ~~invention~~disclosure provides the FGF21 protein~~, wherein the amino acid sequence is~~of SEQ ID NO: 4 for use in increasing the osteoid deposition in or on a bone.

In another aspect~~Furthermore~~, the present ~~invention~~disclosure provides the FGF21 protein~~, wherein the amino acid sequence is~~ of SEQ ID NO: 4 for use in treating hypo-osteoidosis.

In a further aspect, the present ~~invention~~disclosure provides the FGF21 protein~~, wherein the amino acid sequence is~~ of SEQ ID NO: 4 for use in delaying, slowing, and/or preventing bone loss.

In a further aspect, the present ~~invention~~disclosure provides the FGF21 protein~~, wherein the amino acid sequence is~~ of SEQ ID NO: 4 for use in preventing and/or treating osteoporosis.

In a further aspect, the present ~~invention~~disclosure provides the FGF21 protein~~, wherein the amino acid sequence is~~ of SEQ ID NO: 4 for use in preventing and/or treating high risk of fracture due to poor bone quality and/or bone loss.

The FGF21 protein of SEQ ID NO: 4 may be used, as described herein, as a single agent and/or in combination with another agent or agents that promotes bone mineralization, bone formation, and/or decreases bone resorption. Agents include, but are not limited to, FORTEO®, EVISTA®, FOSAMAX®, ACTONEL®, and BONIVA®, zolendronate, denosumab, blososumab, CDP7851/AMG 785. In another aspect, there is provided a combination of the FGF21 protein of SEQ ID NO: 4 with another agent or agents that promotes bone mineralization, bone formation, and/or decreases bone resorption for any of the uses as defined above.

The methods and uses of the present ~~invention~~disclosure comprise a preferred FGF21 protein of SEQ ID NO: 4, wherein the FGF21 protein is selected from the group consisting of SEQ ID NO: 1 and SEQ ID NO: 3. The most preferred FGF21 protein is SEQ ID NO: 1.

The term "treating" (or "treat" or "treatment") means slowing, stopping, reducing, or reversing the progression or severity of a sign, symptom, disorder, condition, or disease.

The term "preventing" (or "prevent" or "prevention") refers to a decrease in the occurrence or severity of a sign, symptom, disorder, condition, or disease or decrease in the risk of acquiring a sign, symptom, disorder, condition, or disease or its associated signs and/or symptoms in a subject.

A "patient" is a human.

The term "effective amount" refers to the amount or dose of the FGF21 protein of SEQ ID NO: 1, SEQ ID NO: 3, and/or SEQ ID NO: 4 that provides the desired treatment upon single or multiple dose administration to a patient.

The following examples may be performed essentially as described below.