X30 is Lys, Gly, Pro or absent;
X31 is Gly, Pro, Ser, Glu or absent;
X32 is Lys, Ser or absent;
X33 is Lys, Ser, Glu or absent;
X34 is Asn, Gly, Ala, Lys or absent;
X35 is Asp, Ala, Pro, Glu or absent;
X36 is Trp, Pro, Lys or absent;
X37 is Lys, Pro, Glu or absent;
X38 is His, Pro, Ser, Lys or absent;
X39 is Asn, Ser or absent;
X40 is Ile or absent;
X41 is Thr or absent;
X42 is Gln or absent; and
R^2 is $-NH_2$ or -OH.

[0008] In an ~~aspect~~embodiment, a GIP analogue of the present disclosure is represented by the general Formula I':

R^1- Tyr-X2-X3-Gly-Thr-Phe-X7-Ser-X9-X10-X11-X12-X13-X14-X15-X16-Lys-Ala-X19-X20-X21-X22-X23-X24-Trp-Leu-X27-X28-X29-X30-X31-X32-X33-X34-X35-X36-X37-X38-X39-X40-X41-X42- R^2 (I') (SEQ ID NO 61)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

R^1 is Hy-, Ac or pGlu;
X2 is Ala, Aib or Gly;
X3 is Glu or Asp;
X7 is Thr, Ser or Ile;
X9 is Asp or Glu;
X10 is Tyr, Leu or Ser;
X11 is Ser or Leu;
X12 is Ile or Lys;
X13 is Ala, Tyr or Aib;
X14 is Met, Leu or Ser;
X15 is Asp or Glu;
X16 is Lys, Gly, Ser or Glu;
X19 is Gln, Ala, Glu or Lys;
X20 is Gln, Lys, Arg or His;

X19 is Gln, Lys, Ala or Glu;

X20 is Lys or Arg;

X21 is Ala or Glu;

X23 is Val or Ile;

X24 is Asn or Glu;

X27 is Leu, Glu, Ser, Lys or Val;

X28 is Aib, Ala, Ser or Arg;

X29 is Aib, Glu, Gly or Lys;

X30 is Lys, Gly or absent;

Y1 is Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser or absent; and

R^2 is $-NH_2$ or -OH.

[0014] In another ~~aspect~~embodiment, a GIP analogue of the present disclosure is represented by the general Formula II':

R^1- Tyr- X2-Glu-Gly-Thr-Phe-X7-Ser-Asp-X10-X11-X12-X13-Leu-X15-X16-Lys-Ala-X19-X20-X21-Phe-X23-X24-Trp-Leu-X27-X28- X29-X30-Y1-R^2 (II')

(SEQ ID NO 64)

wherein

R^1 is Hy-, Ac or pGlu;

X2 is Aib or Gly;

X7 is Thr, Ile or Ser;

X10 is Tyr or Leu;

X11 is Ser or Leu;

X12 is Ile or Lys;

X13 is Ala, Tyr or Aib;

X15 is Asp or Glu;

X16 is Ser, Glu or Lys;

X19 is Gln or Ala;

X20 is Lys, His or Arg;

X21 is Ala, Asp or Glu;

X23 is Val or Ile;

X24 is Asn, Lys or Glu;

X27 is Leu, Glu, Val or Ile;

[0020] In other embodiments, a GIP analogue of the present disclosure is represented by the general Formula II(d):

R^1- Tyr- Aib-Glu-Gly-Thr-Phe-X7-Ser-Asp-Tyr-Ser-Ile-X13-Leu-X15-X16-Lys-Ala-Gln-X20-Ala-Phe-Val-Glu-Trp-Leu-X27-Ala-Gln-X30-Y1-R^2 (II(d))

(SEQ ID NO: 68)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

R^1 is Hy-, Ac or pGlu;

X7 is Thr or Ser;

X13 is Aib or Tyr;

X15 is Asp or Glu;

X16 is Glu, Lys or Ser;

X20 is Lys, His or Arg;

X27 is Leu, Glu or Val;

X30 is Lys, Gly or absent;

Y1 is Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser or absent; and

R^2 is -NH_2 or -OH.

In another aspect, there is provided a GIP analogue selected from:

Hy-Y-Aib-EGTFISDYSIYLEKKAAKEFVNWLLAQK-NH_2;

Hy-Y-Aib-EGTFTSDYSI-Aib-LDKKAQRAFVEWLLAQGPSSGAPPPS-NH_2;

Hy-Y-Aib-EGTFTSDYSIALDKIAQRAFVNWLVA-Aib-K-NH_2;

Hy-Y-Aib-EGTFISDYSIYLEKIAAKEFVNWLLAQK-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-K-NH_2,

pGlu-YAEGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-YGEGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFSSDYSIYLDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDLSIYLDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYLIYLDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIALDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYSDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLEKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIALEKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDSKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDEKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDSKAKRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQKEFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVKWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLVA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLKA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLL-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-KYG-1Nal-LDF-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLLAYG-1Nal-LDF-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAEKAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-GPSSGAPPPS-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-GPSSGAPPS-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLEKKAAKEFVNWLLAQK-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDK-K(15-carboxy-pentadecanoyl-isoGlu)-AQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSI-Aib-LDK-K(Hexadecanoyl-isoGlu)-AQRAFVEWLLAQGPSSGAPPPS-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDK-K(hexadecanoyl-isoGlu)-AQRAFVEWLLAQGPSSGAPPPS-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDE-K(hexadecanoyl-isoGlu)-AAKEFIEWLESA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDK-K(hexadecanoyl-isoGlu)-AQRAFVNWLLA-Aib-KPSSGAPPPS-NH_2;

Hy-Y-Aib-EGTFTSDYSIALDK-K(hexadecanoyl-isoGlu)-AQRAFVNWLVA-Aib-KPSSGAPPPS-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLE-KKAAKDFVEWLLSA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLE-KKAAHDFVEWLLSA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLEKKAQKEFVEWLLSA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDEKAAKDFVEWLLSA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLESKAAHDFVEWLLSA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAAHDFVEWLLSA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLEKKAAKEFVEWLLSA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDSKAAHDFVEWLLRA-NH_2;

Hy-Y-Aib-EGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLEK-K(Hexadecanoyl-isoGlu)-AAKEFVEWLLSA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLRA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDE-K(Hexadecanoyl-isoGlu)-AAKDFVEWLESA-NH_2;

Hy-Y-Aib-EGTFTSDYSKYLDE-K(Hexadecanoyl-isoGlu)-AAKDFIEWLESA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDE-K(Hexadecanoyl-isoGlu)-AAKDFIEWLESA-NH_2;

Hy-Y-Aib-EGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLRA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDE-K(Hexadecanoyl-isoGlu)-AAKDFVEWLLSA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLSAGPSSGAPPPS-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLEK-K-(Hexadecanoyl-isoGlu)-AAKEFVEWLLSAGPSSGAPPPS-NH_2; and
Hy-Y-Aib-EGTFTSDYSIYLDSKAAHDFVEWLLSAGPSSGAPPPS-NH_2; and
Hy-Y-Aib-EGTFTSDYSIYLDE-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH_2
or a pharmaceutically acceptable salt or solvate thereof.

In another aspect, there is provided a GIP analogue or pharmaceutically acceptable salt or solvate as disclosed ~~herein~~ above for use in a therapeutic method.

In another aspect, there is provided a pharmaceutical composition comprising a GIP analogue as disclosed ~~herein~~above, or a pharmaceutically acceptable salt or solvate thereof, in admixture with a carrier.

In another aspect, there is provided the use of a GIP analogue or pharmaceutically acceptable salt or solvate as disclosed ~~herein~~ above for the preparation of a medicament for the treatment and/or prevention of diabetes, or a diabetes related disorder selected from insulin resistance, glucose intolerance, increased fasting glucose, pre-diabetes, type 1 diabetes, type 2 diabetes, gestational diabetes hypertension, dyslipidemia, or a combination thereof.

In another aspect, there is provided the use of a GIP analogue or pharmaceutically acceptable salt or solvate as disclosed ~~herein~~ above for the preparation of a medicament for the treatment and/or prevention of obesity, or an obesity related disorder selected from atherosclerosis, arteriosclerosis, coronary heart disease, peripheral artery disease, stroke, obesity linked inflammation, obesity linked gallbladder disease and obesity induced sleep apnea.

In another aspect, there is provided a therapeutic kit comprising a GIP analogue or pharmaceutically acceptable salt or solvate as disclosed ~~herein~~above, optionally in combination with a pharmaceutically acceptable carrier.

In another aspect, there is provided a device comprising a GIP analogue or pharmaceutically acceptable salt or solvate as disclosed above~~according to any one of claims 1 to 23~~, for delivery of the GIP analogue to a subject.

[0021] Without wishing to be bound by any particular theory, the Isoleucine at position 7 of native GIP appears to provide significant selectivity for the GIP receptor. A small polar residue (e.g. Thr or Ser) at position 7 may increase potency and/or selectivity at the GLP-1 receptor.

[0022] Without wishing to be bound by any particular theory, it is believed that substitution of Met found in position 14 of native GIP with a hydrophobic residue like leucine is important for enhancing GLP-1 receptor activity and so increase potency and/or selectivity at the GLP-1 receptor. The substitution of Met at position 14 with leucine also reduces the potential for oxidation, so increasing the chemical stability of the compounds. The non-conservative and non-obvious substitution of Ile for Lys in position 17 may enhance GLP-1 receptor activity and in addition provide a handle for acylation to prolong half life of the peptide.

[0023] Without wishing to be bound by any particular theory, the histidine at position 18 of native GIP appears to provide significant selectivity for the GIP receptor. A non-conservative substitution of histidine in position 18 with a small

Claims:

1. A GIP analogue selected from:

Hy-Y-Aib-EGTFISDYSIYLEKKAAKEFVNWLLAQK-NH_2;

Hy-Y-Aib-EGTFTSDYSI-Aib-LDKKAQRAFVEWLLAQGPSSGAPPPS-NH_2;

Hy-Y-Aib-EGTFTSDYSIALDKIAQRAFVNWLVA-Aib-K-NH_2;

Hy-Y-Aib-EGTFISDYSIYLEKIAAKEFVNWLLAQK-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-K-NH_2,

pGlu-YAEGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-YGEGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFSSDYSIYLDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDLSIYLDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYLIYLDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIALDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYSDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLEKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIALEKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDSKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDEKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDSKAKRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQKEFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVKWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLVA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLKA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLL-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-KYG-1Nal-LDF-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLLAYG-1Nal-LDF-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAEKAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-GPSSGAPPPS-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-GPSSGAPPS-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLEKKAAKEFVNWLLAQK-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDK-K(15-carboxy-pentadecanoyl-isoGlu)-AQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSI-Aib-LDK-K(Hexadecanoyl-isoGlu)-AQRAFVEWLLAQGPSSGAPPPS-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDK-K(hexadecanoyl-isoGlu)-AQRAFVEWLLAQGPSSGAPPPS-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDE-K(hexadecanoyl-isoGlu)-AAKEFIEWLESA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDK-K(hexadecanoyl-isoGlu)-AQRAFVNWLLA-Aib-KPSSGAPPPS-NH_2;

Hy-Y-Aib-EGTFTSDYSIALDK-K(hexadecanoyl-isoGlu)-AQRAFVNWLVA-Aib-KPSSGAPPPS-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLE-KKAAKDFVEWLLSA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLE-KKAAHDFVEWLLSA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLEKKAQKEFVEWLLSA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDEKAAKDFVEWLLSA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLESKAAHDFVEWLLSA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAAHDFVEWLLSA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLEKKAAKEFVEWLLSA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDSKAAHDFVEWLLRA-NH_2;

Hy-Y-Aib-EGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLEK-K(Hexadecanoyl-isoGlu)-AAKEFVEWLLSA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLRA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDE-K(Hexadecanoyl-isoGlu)-AAKDFVEWLESA-NH_2;

Hy-Y-Aib-EGTFTSDYSKYLDE-K(Hexadecanoyl-isoGlu)-AAKDFIEWLESA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDE-K(Hexadecanoyl-isoGlu)-AAKDFIEWLESA-NH_2;

Hy-Y-Aib-EGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLRA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDE-K(Hexadecanoyl-isoGlu)-AAKDFVEWLLSA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLSAGPSSGAPPPS-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLEK-K-(Hexadecanoyl-isoGlu)-AAKEFVEWLLSAGPSSGAPPPS-NH_2; and

Hy-Y-Aib-EGTFTSDYSIYLDSKAAHDFVEWLLSAGPSSGAPPPS-NH_2; and

Hy-Y-Aib-EGTFTSDYSIYLDE-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH_2

or a pharmaceutically acceptable salt or solvate thereof.

2. A GIP analogue or pharmaceutically acceptable salt or solvate according to claim 1 for use in a therapeutic method.

3. A pharmaceutical composition comprising a GIP analogue of claim 1, or a pharmaceutically acceptable salt or solvate thereof, in admixture with a carrier.

4. The pharmaceutical composition of claim 3, wherein the GIP analogue is a pharmaceutically acceptable acid addition salt.

5. The pharmaceutical composition of claim 3 or claim 4, which is formulated as a liquid suitable for administration by injection or infusion, or which is formulated to cause slow release of said GIP analogue.

6. Use of a GIP analogue or pharmaceutically acceptable salt or solvate of claim 1 for the preparation of a medicament for the treatment and/or prevention of diabetes, or a diabetes related disorder selected from insulin resistance, glucose intolerance, increased fasting glucose, pre-diabetes, type 1 diabetes, type 2 diabetes, gestational diabetes hypertension, dyslipidemia, or a combination thereof.

7. Use of a GIP analogue or pharmaceutically acceptable salt or solvate of claim 1 for the preparation of a medicament for the treatment and/or prevention of obesity, or an obesity related disorder selected from atherosclerosis, arteriosclerosis, coronary heart disease, peripheral artery disease, stroke, obesity linked inflammation, obesity linked gallbladder disease and obesity induced sleep apnea.

8. A GIP analogue or pharmaceutically acceptable salt or solvate according to claim 1 for use in a method of treatment and/or prevention of diabetes, or a diabetes related disorder selected from insulin resistance, glucose intolerance, increased fasting glucose, pre-diabetes, type 1 diabetes, type 2 diabetes, gestational diabetes hypertension, dyslipidemia, or a combination thereof.

9. A GIP analogue or pharmaceutically acceptable salt or solvate according to claim 1 for use in a method of treatment and/or prevention of any one of claims 1 to 23 for use in a method of treatment and/or prevention of obesity, or an obesity related disorder selected from atherosclerosis, arteriosclerosis, coronary heart

disease, peripheral artery disease, stroke, obesity linked inflammation, obesity linked gallbladder disease and obesity induced sleep apnea.

10. A therapeutic kit comprising a GIP analogue or pharmaceutically acceptable salt or solvate according to claim 1, optionally in combination with a pharmaceutically acceptable carrier.

11. A device comprising a GIP analogue or pharmaceutically acceptable salt or solvate according to claim 1, for delivery of the GIP analogue to a subject.

12. A pharmaceutical composition comprising a GIP analogue or pharmaceutically acceptable salt or solvate according to claim 1 for use in treatment and/or prevention of diabetes, or a diabetes related disorder selected from insulin resistance, glucose intolerance, increased fasting glucose, pre-diabetes, type 1 diabetes, type 2 diabetes, gestational diabetes hypertension, dyslipidemia, or a combination thereof.

13. A pharmaceutical composition comprising a GIP analogue or pharmaceutically acceptable salt or solvate according to claim 1 for use in treatment and/or prevention of obesity, or an obesity related disorder selected from atherosclerosis, arteriosclerosis, coronary heart disease, peripheral artery disease, stroke, obesity linked inflammation, obesity linked gallbladder disease and obesity induced sleep apnea.

Claims:

1. A GIP analogue represented by the general Formula I':

R^1- Tyr-X2-X3-Gly-Thr-Phe-X7-Ser-X9-X10-X11-X12-X13-X14-X15-X16-Lys-Ala-X19-X20-X21-X22-X23-X24-Trp-Leu-X27-X28-X29-X30-X31-X32-X33-X34-X35-X36-X37-X38-X39-X40-X41-X42- R^2 (I') (SEQ ID NO 61)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

R^1 is Hy-, Ac or pGlu;

X2 is Ala, Aib or Gly;

X3 is Glu or Asp;

X7 is Thr, Ser or Ile;

X9 is Asp or Glu;

X10 is Tyr, Leu or Ser;

X11 is Ser or Leu;

X12 is Ile or Lys;

X13 is Ala, Tyr or Aib;

X14 is Met, Leu or Ser;

X15 is Asp or Glu;

X16 is Lys, Gly, Ser or Glu;

X19 is Gln, Ala, Glu or Lys;

X20 is Gln, Lys, Arg or His;

X21 is Asp, Ala or Glu;

X22 is Phe or 1Nal;

X23 is Val, Ile or Leu;

X24 is Asn, Glu, Arg or Lys;

X27 is Leu, Val, Ile, Lys, Glu or Ser;

X28 is Ala, Ser, Arg or Aib;

X29 is Gln, Aib, Lys, Gly or Ala;

X30 is Lys, Gly, Pro or absent;

X31 is Gly, Pro, Ser, Glu or absent;

X32 is Lys, Ser or absent;

X33 is Lys, Ser, Glu or absent;

X34 is Asn, Gly, Ala, Lys or absent;

X35 is Asp, Ala, Pro, Glu or absent;

X36 is Trp, Pro, Lys or absent;

X37 is Lys, Pro, Glu or absent;

X38 is His, Pro, Ser, Lys or absent;

X39 is Asn, Ser or absent;

X40 is Ile or absent;

X41 is Thr or absent;

X42 is Gln or absent; and

R^2 is $-NH_2$ or -OH;

and wherein said analogue has agonist activity at the GIP and GLP-1 receptors.

2. The GIP analogue of claim 1, wherein the GIP analogue is represented by the general Formula I(b)':

R^1- Tyr-X2-X3-Gly-Thr-Phe-X7-Ser-X9-X10-X11-X12-X13-X14-X15-X16-Lys-Ala-X19-X20-X21-Phe-X23-X24-Trp-Leu-X27-X28-X29-X30-X31-X32-X33-X34-X35-X36-X37-X38-X39-X40-X41-X42- R^2 (I(b)') (SEQ ID NO 63)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

R^1 is Hy-, Ac or pGlu;

X2 is Ala, Aib or Gly;

X3 is Glu or Asp;

X7 is Thr or Ser;

X9 is Asp or Glu;

X10 is Tyr or Leu;

X11 is Ser or Leu;

X12 is Ile or Lys;

X13 is Ala, Tyr or Aib;

X14 is Leu or Ser;

X15 is Asp or Glu;

X16 is Lys, Ser or Glu;

X19 is Gln, Ala, Glu or Lys;

X20 is Gln, Lys, Arg or His;

X21 is Asp, Ala or Glu;

X23 is Val, Ile or Leu;

X24 is Asn, Glu, Arg or Lys;

X27 is Leu, Glu, Val or Ile;

X28 is Ala, Ser, Arg or Aib;

X29 is Gln, Gly, Aib or Ala;

X30 is Lys, Gly, Pro or absent;
X31 is Gly, Pro, Ser, Glu or absent;
X32 is Lys, Ser or absent;
X33 is Lys, Ser, Glu or absent;
X34 is Asn, Gly, Ala, Lys or absent;
X35 is Asp, Ala, Pro, Glu or absent;
X36 is Trp, Pro, Lys or absent;
X37 is Lys, Pro, Glu or absent;
X38 is His, Pro, Ser, Lys or absent;
X39 is Asn, Ser or absent;
X40 is Ile or absent;
X41 is Thr or absent;
X42 is Gln or absent; and
R^2 is $-NH_2$ or -OH.

3. A GIP analogue represented by the general Formula II':

R^1- Tyr- X2-Glu-Gly-Thr-Phe-X7-Ser-Asp-X10-X11-X12-X13-Leu-X15-X16-Lys-Ala-X19-X20-X21-Phe-X23-X24-Trp-Leu-X27-X28- X29-X30-Y1-R^2 (II')

(SEQ ID NO 64)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

R^1 is Hy-, Ac or pGlu;
X2 is Aib or Gly;
X7 is Thr, Ile or Ser;
X10 is Tyr or Leu;
X11 is Ser or Leu;
X12 is Ile or Lys;
X13 is Ala, Tyr or Aib;
X15 is Asp or Glu;
X16 is Ser, Glu or Lys;
X17 is Ile or Lys;
X19 is Gln or Ala;
X20 is Lys, His or Arg;
X21 is Ala, Asp or Glu;
X23 is Val or Ile;
X24 is Asn, Lys or Glu;

X27 is Leu, Glu, Val or Ile;
X28 is Aib, Ala, Ser or Arg;
X29 is Gln, Aib, Ala, Gly or Lys;
X30 is Lys, Gly or absent;
Y1 is Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser or absent; and
R^2 is $-NH_2$ or –OH;
and wherein said analogue has agonist activity at the GIP and GLP-1 receptors.

4. The GIP analogue or pharmaceutically acceptable salt or solvate of claim 3, wherein the GIP analogue is represented by the general Formula II(a)':

R^1- Tyr- X2-Glu-Gly-Thr-Phe-X7-Ser-Asp-X10-X11-Ile-X13-Leu-X15-X16-Lys-Ala-X19-X20-X21-Phe-X23-X24-Trp-Leu-X27-X28- X29-X30-Y1-R^2 (II(a)')

(SEQ ID NO 65)

wherein
R^1 is Hy-, Ac or pGlu;
X2 is Aib or Gly;
X7 is Thr, Ile or Ser;
X10 is Tyr or Leu;
X11 is Ser or Leu;
X13 is Ala, Tyr or Aib;
X15 is Asp or Glu;
X16 is Ser, Glu or Lys;
X19 is Gln, Lys, Ala or Glu;
X20 is Lys, His or Arg;
X21 is Ala, Asp or Glu;
X23 is Val or Ile;
X24 is Asn, Lys or Glu;
X27 is Leu, Glu, Val or Ile;
X28 is Aib, Ala, Ser or Arg;
X29 is Gln, Aib, Ala or Gly;
X30 is Lys, Gly or absent;
Y1 is Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser or absent; and

R^2 is -NH_2 or -OH.

5. The GIP analogue of claim 4, wherein the GIP analogue is represented by the general Formula II(b)':

R^1- Tyr- Aib-Glu-Gly-Thr-Phe-X7-Ser-Asp-Tyr-Ser-Ile-X13-Leu-X15-X16-Lys-Ala-Gln-X20-X21-Phe-X23-Glu-Trp-Leu-X27-X28-Ala-X30-Y1-R^2 (II(b)')

(SEQ ID NO: 66)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

R^1 is Hy-, Ac or pGlu;

X7 is Thr or Ser;

X13 is Ala or Tyr;

X15 is Asp or Glu;

X16 is Lys, Glu or Ser;

X20 is Lys, His or Arg;

X21 is Ala, Asp or Glu;

X23 is Val or Ile;

X27 is Leu, Glu or Val;

X28 is Arg or Ser;

X30 is Lys, Gly or absent;

Y1 is Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser or absent; and

R^2 is -NH_2 or -OH.

6. The GIP analogue of claim 4, wherein the GIP analogue is represented by the general Formula II(c):

R^1- Tyr- Aib-Glu-Gly-Thr-Phe-X7-Ser-Asp-Tyr-Ser-Ile-X13-Leu-X15-X16-Lys-Ala-Gln-X20-X21-Phe-Val-X24-Trp-Leu-X27-Ala- X29-X30-Y1-R^2 (II(c))

(SEQ ID NO: 67)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

R^1 is Hy-, Ac or pGlu;

X7 is Thr or Ser;

X13 is Ala, Aib or Tyr ;

X15 is Asp or Glu;
X16 is Glu, Lys or Ser;
X20 is Lys, His or Arg;
X21 is Ala, Asp or Glu;
X24 is Glu or Asn
X27 is Leu, Glu or Val;
X29 is Gln or Aib;
X30 is Lys, Gly or absent;
Y1 is Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser or absent; and
R^2 is $-NH_2$ or -OH.

7. The GIP analogue of claim 5, wherein the GIP analogue is represented by the general Formula II(d):

R^1- Tyr- Aib-Glu-Gly-Thr-Phe-X7-Ser-Asp-Tyr-Ser-Ile-X13-Leu-X15-X16-Lys-Ala-Gln-X20-Ala-Phe-Val-Glu-Trp-Leu-X27-Ala-Gln-X30-Y1-R^2 (II(d))
(SEQ ID NO: 68)
or a pharmaceutically acceptable salt or solvate thereof,
wherein
R^1 is Hy-, Ac or pGlu;
X7 is Thr or Ser;
X13 is Ala, Aib or Tyr;
X15 is Asp or Glu;
X16 is Glu, Lys or Ser;
X20 is Lys, His or Arg;
X27 is Leu, Glu or Val;
X30 is Lys, Gly or absent;
Y1 is Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser or absent; and
R^2 is $-NH_2$ or -OH.

8. A GIP analogue or pharmaceutically acceptable salt or solvate of any one of claims 1 to 7 wherein the amino acid sequence X1-X29 has no more than 6 amino acid differences from the sequence Y-Aib-EGTFTSDYSIYLDKKAQRAFVEWLLAQ (SEQ ID NO: 70).

9. A GIP analogue or pharmaceutically acceptable salt or solvate of any one of claims 1 to 7 wherein the amino acid sequence X1-X29 has no more than 6 amino acid differences from the sequence Y-Aib-EGTFTSDYSIYLEKKAAKEFVEWLLSA (SEQ ID NO: 71).

10. A GIP analogue or pharmaceutically acceptable salt or solvate of any one of claims 1 to 7 wherein the amino acid sequence X1-X29 has no more than 5 amino acid differences from the sequence Y-Aib-EGTFTSDYSIYLDEKAAKEFIEWLESA (SEQ ID NO: 72).

11. A GIP analogue or pharmaceutically acceptable salt or solvate according to any one of claims 1 to 7 wherein X24 is Glu and/or X21 is Ala.

12. A GIP analogue or pharmaceutically acceptable salt or solvate according to any one of claims 1-11, wherein X7 is Thr and X14 is Leu.

13. A GIP analogue or pharmaceutically acceptable salt or solvate according to any one of claims 1-11, wherein X7 is Thr, X14 is Leu and X18 is Ala.

14. A GIP analogue or pharmaceutically acceptable salt or solvate according to any one of claims 1-11, wherein X2 is Aib, X7 is Thr and X14 is Leu.

15. A GIP analogue or pharmaceutically acceptable salt or solvate according to any one of claims 1-11, wherein X2 is Aib, X7 is Thr, X14 is Leu and X13 and/or X29 is Aib.

16. A GIP analogue or pharmaceutically acceptable salt or solvate according to any one of claims 1-11, wherein X2 is Aib, X7 is Thr, X14 is Leu and X24 is Glu,

17. A GIP analogue or pharmaceutically acceptable salt or solvate according to any one of claims 1-11, wherein X2 is Aib, X7 is Thr, X14 is Leu, X24 is Glu and X29 is Gln.

18. A GIP analogue or pharmaceutically acceptable salt or solvate according to any one of claims 1-11, wherein X2 is Aib, X7 is Thr, X14 is Leu, X21 is Ala, X24 is Glu and X29 is Gln.

19. A GIP analogue or pharmaceutically acceptable salt or solvate according to any one of claims 1-11, wherein X2 is Aib, X7 is Thr, X14 is Leu, X24 is Glu, X27 is Leu and X28 is Ser.

20. A GIP analogue or pharmaceutically acceptable salt or solvate according to any one of claims 1-11, wherein X2 is Aib, X7 is Thr, X14 is Leu, X24 is Glu, X27 is Glu and X28 is Ser.

21. A GIP analogue or pharmaceutically acceptable salt or solvate according to any one of claims 1-11, wherein X2 is Aib, X7 is Thr, X14 is Leu, X20 is His, X24 is Glu, X27 is Leu and X28 is Ser.

22. A GIP analogue selected from:

Hy-Y-Aib-EGTFISDYSIYLEKKAAKEFVNWLLAQK-NH_2;

Hy-Y-Aib-EGTFTSDYSI-Aib-LDKKAQRAFVEWLLAQGPSSGAPPPS-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-K-NH_2,

pGlu-YAEGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-YGEGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFSSDYSIYLDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDLSIYLDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYLIYLDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIALDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYSDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLEKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIALEKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDSKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDEKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDSKAKRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQKEFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVKWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLVA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLKA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLL-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAEKAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-GPSSGAPPPS-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-GPSSGAPPS-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLEKKAAKEFVNWLLAQK-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDK-K(15-carboxy-pentadecanoyl-isoGlu)-AQRAFVNWLLA-Aib-K-NH_2;
Hy-Y-Aib-EGTFTSDYSI-Aib-LDK-K(Hexadecanoyl-isoGlu)-AQRAFVEWLLAQGPSSGAPPPS-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLDK-K(hexadecanoyl-isoGlu)-AQRAFVEWLLAQGPSSGAPPPS-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLDE-K(hexadecanoyl-isoGlu)-AAKEFIEWLESA-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLDK-K(hexadecanoyl-isoGlu)-AQRAFVNWLLA-Aib-KPSSGAPPPS-NH_2;
Hy-Y-Aib-EGTFTSDYSIALDK-K(hexadecanoyl-isoGlu)-AQRAFVNWLVA-Aib-KPSSGAPPPS-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLE-KKAAKDFVEWLLSA-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLE-KKAAHDFVEWLLSA-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLEKKAQKEFVEWLLSA-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLDEKAAKDFVEWLLSA-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLESKAAHDFVEWLLSA-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLDKKAAHDFVEWLLSA-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLEKKAAKEFVEWLLSA-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLDSKAAHDFVEWLLRA-NH_2;
Hy-Y-Aib-EGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLEK-K(Hexadecanoyl-isoGlu)-AAKEFVEWLLSA-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLRA-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLDE-K(Hexadecanoyl-isoGlu)-AAKDFVEWLESA-NH_2;
Hy-Y-Aib-EGTFTSDYSKYLDE-K(Hexadecanoyl-isoGlu)-AAKDFIEWLESA-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLDE-K(Hexadecanoyl-isoGlu)-AAKDFIEWLESA-NH_2;
Hy-Y-Aib-EGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLRA-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLDE-K(Hexadecanoyl-isoGlu)-AAKDFVEWLLSA-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLSAGPSSGAPPPS-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLEK-K-(Hexadecanoyl-isoGlu)-AAKEFVEWLLSAGPSSGAPPPS-NH_2; and
Hy-Y-Aib-EGTFTSDYSIYLDSKAAHDFVEWLLSAGPSSGAPPPS-NH_2; and
Hy-Y-Aib-EGTFTSDYSIYLDE-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH_2
or a pharmaceutically acceptable salt or solvate thereof.

23. A GIP analogue or pharmaceutically acceptable salt or solvate according to any one of the preceding claims with a lipophilic substituent conjugated to one or more of positions 15, 16, 17, 19, 20, 24, 27, 28 and 30.

24. A GIP analogue or pharmaceutically acceptable salt or solvate according to any one of the preceding claims for use in a therapeutic method.

25. A pharmaceutical composition comprising a GIP analogue of any one of the preceding claims, or a pharmaceutically acceptable salt or solvate thereof, in admixture with a carrier.

26. The pharmaceutical composition of claim 25, wherein the GIP analogue is a pharmaceutically acceptable acid addition salt.

27. The pharmaceutical composition of claim 25 or claim 26, which is formulated as a liquid suitable for administration by injection or infusion, or which is formulated to cause slow release of said GIP analogue.

28. Use of a GIP analogue or pharmaceutically acceptable salt or solvate of any one of claims 1 to 23 for the preparation of a medicament for the treatment and/or prevention of diabetes, or a diabetes related disorder selected from insulin resistance, glucose intolerance, increased fasting glucose, pre-diabetes, type 1 diabetes, type 2 diabetes, gestational diabetes hypertension, dyslipidemia, or a combination thereof.

29. Use of a GIP analogue or pharmaceutically acceptable salt or solvate of any one of claims 1 to 23 for the preparation of a medicament for the treatment and/or prevention of obesity, or an obesity related disorder selected from atherosclerosis, arteriosclerosis, coronary heart disease, peripheral artery disease, stroke, obesity linked inflammation, obesity linked gallbladder disease and obesity induced sleep apnea.

30. A GIP analogue or pharmaceutically acceptable salt or solvate according to any one of claims 1 to 23 for use in a method of treatment and/or prevention of diabetes, or a diabetes related disorder selected from insulin resistance, glucose intolerance, increased fasting glucose, pre-diabetes, type 1 diabetes, type 2 diabetes, gestational diabetes hypertension, dyslipidemia, or a combination thereof.

31. A GIP analogue or pharmaceutically acceptable salt or solvate according to any one of claims 1 to 23 for use in a method of treatment and/or prevention of obesity, or an obesity related disorder selected from atherosclerosis, arteriosclerosis, coronary heart disease, peripheral artery disease, stroke, obesity linked inflammation, obesity linked gallbladder disease and obesity induced sleep apnea.

32. A therapeutic kit comprising a GIP analogue or pharmaceutically acceptable salt or solvate according to any one of claims 1 to 23, optionally in combination with a pharmaceutically acceptable carrier.

33. A device comprising a GIP analogue or pharmaceutically acceptable salt or solvate according to any one of claims 1 to 23,

for delivery of the GIP analogue to a subject.

34. A pharmaceutical composition comprising a GIP analogue or pharmaceutically acceptable salt or solvate according to any one of claims 1 to 23 for use in treatment and/or prevention of diabetes, or a diabetes related disorder selected from insulin resistance, glucose intolerance, increased fasting glucose, pre-diabetes, type 1 diabetes, type 2 diabetes, gestational diabetes hypertension, dyslipidemia, or a combination thereof.

35. A pharmaceutical composition comprising a GIP analogue or pharmaceutically acceptable salt or solvate according to any one of claims 1 to 23 for use in treatment and/or prevention of obesity, or an obesity related disorder selected from atherosclerosis, arteriosclerosis, coronary heart disease, peripheral artery disease, stroke, obesity linked inflammation, obesity linked gallbladder disease and obesity induced sleep apnea.