Supplementary Material

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|   | **Control group** | **Obese patient without T2D** | **Obese patient with T2D** | **6 months after LSG** | **6 months after RYGB** |
| 1 | 2 | 3 | 4 | 5 |
| **Cholesterol****(< 5.2)****mmol/l** | 4.51 (4.21-5.02) | 5.32 (4.41-6.04)р 1-2 \* | 5.2 (4.33-6.01) | 4.19 (3.63-5.09)р 2-4 \*\*р 3-4 \*\* | 4.46 (4.09-5.07)р 2-5 \*\*р 3-5 \* |
| **Triglycerides****(< 2.53)****mmol/l** | 1.11 (0.75-1.69) | 1.9 (1.25-2.41)р 1-2 \*\*\* | 1.86 (1.41-2.44)р 1-3 \*\*\* | 1.26 (0.76-1.4)р 2-4 \*\*р 3-4 \*\*\* | 1.16 (1-1.37)р 2-5 \*\*\*р 3-5 \*\*\* |
| **High-density lipoproteins (HDL)****(0.78 – 1.81) mmol / l** | 1.19 (1.02-1.38) | 1.23 (0.98-1.45) | 1.09 (0.89-1.24) | 1.05 (0.98-1.29) | 1.04 (0.95-1.18) |
| **Low-density lipoproteins (LDL)****(0.00 – 3.4) mmol / l** | 2.67 (2.3-3.04) | 3.11 (2.67-3.62)р 1-2 \* | 2.99 (2.46-3.55)р 1-3 \* | 2.56 (1.93-2.81)р 2-4 \*\*р 3-4 \* | 2.6(2.28-3.04)р 2-5 \*р 3-5 \* |
| **C-reactive protein****(>6.0)****mg/l** | 1.09 (0.89-1.93) | 9.23 (5.04-15.11)р 1-2 \*\*\* | 4.75 (1.87-9.22)р 1-3 \*\*\*р 2-3 \*\* | 13.86 (9.24-19.29)р 1-4 \*\*\*р 3-4 \*\* | 7.66 (4.99-12)р 1-5 \*\*\*р 4-5 \* |
| **Glucose before breakfast****(3.9-6.4)****mmol/l** | 5.00(4.65-5.42) | 5.55 (5.03-6.24)р 1-2 \*\* | 6.28 (5.64-7.04)р 1-3 \*\*\*р 2-3 \*\* | 6.15 (5.17-9.02)р 1-4 \*\*\* | 8.46 (6.86-10.74)р 1-5 \*\*\*р 2-5 \*\*\*р 3-5 \*\* |
| **Glucose after breakfast****mmol/l** | 5.54 (4.76-5.77) | 6.4 (5.55-7.75)#р 1-2 \* | 8.05 (6.88-9.88)#р 1-3 \*\*\*р 2-3 \*\* | 7.99 (7.86-8.12) | 7.12 (6.16-9.78)р 1-5 \* |

**Supplementary Table 1.** The biochemical parameters of the lipid and protein metabolism. liver enzymes and glucose in the obese patient's serum with and without T2DM.

Note: \*– p<0.05, \*\* – p<0.001, \*\*\* – p<0.0001; # - differences in glucose before and after breakfast; differences in significance level were determined using the Mann-Whitney criterion for two independent samples (Me(Q1–Q3)). 1- Control group; 2- Obese patient without T2D; 3- Obese patient with T2D; 4- 6 months after LSG; 5- 6 months after RYGB.

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| --- | --- | --- | --- | --- | --- | --- |
| Biochemical parameters | Sex | Control groupn=42 | Obese patient without T2DMn=90 | Obese patient with T2DMn=72 | RYGBn=31 | LCGn=23 |
| 1 | 2 | 3 | 4 | 5 |
| Cholesterol | Male(< 5,2) mmol/l | n=174,5 (4,31-5,5) | n=284,14 (3,42-4,83) | n=205,12 (4,31-5,97) | n=74,44 (4,14-5,31) | n=54,96 (4,08-5,08) |
| Female(< 5,2) mmol/l | n=254,98 (4,39-5,2)p=0,2 | n=624,9 (4,21-5,79)p=0,0044 \*\* | n=525,29 (4,35-5,98)p=0,97 | n=244,46 (4-5,18)p=1,0 | n=184,66 (3,73-5,28)p=0,82 |
| Triglycerides | Male (< 2,53) mmol/l | n=170,71 (0,56-1,23) | n=281,26 (0,89-2,34) | n=201,93 (1,42-2,9) | n=71,29 (0,82-1,52) | n=51,39 (1,13-1,78) |
| Female(< 2,53) mmol/l | n=250,67 (0,53-0,89)p=0,2 | n=621,46 (1-1,93)p=0,71 | n=521,85 (1,37-2,32)p=0,42 | n=241,14 (1-1,36)p=0,42 | n=181,23 (0,86-1,59)p=0,43 |
| High-density lipoproteins (HDL) | Male (0,78 – 1,81) mmol/l | n=161,23 (1,05-1,41) | n=280,95 (0,81-1,07) | n=200,99 (0,82-1,14) | n=70,95 (0,89-1,11) | n=51,29 (1,02-1,34) |
| Female(0,78 – 2,2) mmol/l | n=251,77 (1,54-2,19)p˂0,0001 \*\*\* | n=621,25 (1,04-1,62)p˂0,0001 \*\*\* | n=521,13 (0,97-1,33)p=0,03 \* | n=241,19 (1,01-1,35)p=0,06 | n=181,13 (0,98-1,3)p=0,53 |
| Low-density lipoproteins (LDL) | Male (˂ 3,4) mmol/l | n=162,67 (2,44-2,92) | n=282,41 (1,84-2,97) | n=203,08 (2,57-3,39) | n=72,65 (2,28-3,35) | n=52,66 (2,44-3,02) |
| Female(˂ 3,4) mmol/l | n=252,77 (2,34-3,01)p=0,65 | n=622,9 (2,38-3,43)p=0,01 \*\* | n=522,99 (2,48-3,54)p=0,86 | n=242,62 (2,32-2,9)p=0,64 | n=182,79 (2,07-3,12)p=0,97 |
| C-reactive protein (CRP) | Male (>6.0) mg/l | n=141,02 (0,47-2,21) | n=176,92 (4,11-12,03) | n=185,78 (3,55-9,2) | n=71,21 (0,7-8,57) | n=54,87 (2,62-6,94) |
| Female(>6.0) mg/l | n=231,08 (0,58-1,89)p=1 | n=416,57 (2,67-9,02)p=0,19 | n=467,16 (2,22-15,51)p=0,39 | n=242,83 (1,5-4,67)p=0,59 | n=183,54 (1,75-5,18)p=0,97 |
| Glucose before breakfast | Male (3,9-6,4) mmol/l | n=175,26 (4,8-5,44) | n=285,68 (5,05-6,48) | n=209,3 (7,23-10,52) | n=75,43 (4,62-6,48) | n=54,47 (3,94-5,21) |
| Female(3,9-6,4) mmol/l | n=255,13 (5,03-5,28)p=0,99 | n=625,35 (4,85-6,09)p=0,42 | n=526,9 (5,57-8,76)p=0,01 \*\* | n=244,86 (4,21-5,64)p=0,38 | n=184,73 (4,13-5,48)p=0,48 |
| Glucose after breakfast | Male | n=44,58 (4,11-5,18) | n=318,04 (6,84-8,66) | n=910,37 (7,96-12,72) | n=76,92 (3,86-7,72) | n=55,81 (5,43-6,43) |
| Female | n=145,5 (4,27-6,48)p=0,26 | n=216,43 (5,6-8,66)p=0,002 \*\* | n=318,04 (6,84-8,66)p=0,04 \* | n=205,93 (4,69-6,6)p=0,93 | n=145,36 (4,77-7,25)p=0,67 |

**Supplementary Table 2.** Sex differences of biochemical parameters in the serum of obese patients with/without T2DM.

Note: \*– p<0.05, \*\* – p<0.001, \*\*\* – p<0.000; differences in significance level were determined using the Mann-Whitney criterion for two independent samples (Me(Q1–Q3)). 1- Control group; 2- Obese patient without T2DM; 3- Obese patient with T2DM; 4- 6 months after LSG; 5- 6 months after RYGB.

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| Indicatorsng/mlStudy groups | Sex | С–peptide | Grelin | GIP | GLP–1 | Glucagon | Insulin | Leptine | PAI–1 | Resistin | Visfatin |
| Control group n=14 | 1 | male | n=2292,7(227,8-357,6) | n=496,73(64,56-119,8) | n=442,16(29,02-50,40) | n=29,95(7,61-12,29) | n=5227,8(292,7-357,6) | n=446,91(28,97-96,03) | n=2145,5 (117,6-173,5) | n=4991,4 (904,3-1109) | n=42135(537,1-2627) | n=21067(938,6-1195) |
| female | n=9306,5 (235,8-346,2)p=0,90 | n=979,45(48,39-93,90)p=0,41 | n=933(23,87-43,54)p=0, 41 | n=913,65(10,81-16,17)p=0,21 | n=9306,5 (235,8-346,2)p=0,69 | n=943,82(34,75-87,67) p=0,93 | n=9427,1(246,1-555,3)p=0,07 | n=91146(892,3-1581)p=0,33 | n=91362(571,8-2581)p=0,71 | n=9998,5 (514,4-1178)p=0,72 |
| 2 | male | n=2483,8(420,7-546,9) | n=558,08(50,2-77,54) | n=5107,4(74,64-135,6) | n=413,50(9,35-15,36) | n=5483,8( 420,7-546,9) | n=599,31(52,08-130,0) | n=5330,1(180,4-501,2) | n=5935,2(759,6-1030) | n=51053(598,3-1707) | n=3608,8(445,8-744,1) |
| female | n=8422,0(356,0-746,8) | n=1061,67(51,14-92,09)p=0,61 | n=10112,1( 63,04-164,5)p=0,61 | n=1014,87(9,563-)p=0,47 | n=10422,0(356,0-746,8)p=0,13 | n=10119,6(49,67-207,6)p=0,45 | n=10399,0 (167,3-582,7)p=0,61 | n=10803,5(690,2-944,8)p=0,38 | n=10959,3(505,5-3979)p=0,70 | n=10636,5(355,0-1237)p=0,98 |
| Obese patient without T2D n=22 | 1 | male | n=4442,9(430,7-452,9) | n=495(54,07-99,18) | n=450,18(33,45-53,91) | n=419,73(8,25-21,97) | n=4442,9(430,7-450,9) | n=442,14(39,50-90,13) | n=423,67(15,73-567,3) | n=41330(1296-1415) | n=41639(1548-1749) | n=42463(969,0-2631) |
| female | n=15584,6(541,5-754,5)p=0,006 | n=1558,2(41,09-92,61) p=0,40 | n=1542,0(26,81-79,85)p=0,73 | n=156,67(4,54-16,89)p=0,17 | n=15584,6( 541,5-754,5)p=0,22 | n=15140,8(57,97-185,0)p=0,02 | n=151623(1259-1759)p=0,001 | n=151581(1423-2152)p=0,02 | n=141545(1248-1811)p=0,79 | n=15569,0(390,2-2326)p=0,06 |
| 2 | male | n=41063(980,5-1093) | n=4101,0(61,36-106,3) | n=4120,5(118,3-273,7) | n=431,41(15,09-36,45) | n=41063(980,5-1093) | n=4151,4(128,4-280,7) | n=418,34(14,23-1088) | n=41152(1036-1784) | n=41264(1193-1900) | n=42200(861,5-2705) |
| female | n=15778,4(527,2-940,6)p=0,08 | n=1554,93(12,73-93,3)p=0,22 | n=1560,34( 20,74-148,5)p=0,08 | n=146,4(2,37-16,36)p=0,01 | n=14778,4( 527,2-940,6)p=0,04 | n=14203,7(99,9-228,8)p=0,95 | n=151428(978,4-1493)p=0,08 | n=151586(1365-2008)p=0,26 | n=131314(522,0-1373)p=0,62 | n=14503,6(323,6-2056)p=0,13 |
| Obese patient with T2Dn=54 | 1 | male | n=11476(251,2-525,5) | n=1064,65(56,79-112,8) | n=1069,47( 22,5-134,1) | n=1011,74(8,11-43,70) | n=10476,0( 251,2-525,5) | n=12182,7(29,99-779,8) | n=111064 (287,2-6437) | n=81811(1030-10499) | n=101086(378,0-6522) | n=101091(800,1-1184) |
| female | n=17466,6(346,4-2404)p=0,25 | n=2097,51(73,91-135,9)p=0,11 | n=1979,26(56,38-175,3)p=0,20 | n=1643,44( 24,58-64,75)p=0,05 | n=20466,6(346,4-2404)p=0,11 | n=20339,4(145,3-643,6) p=0,13 | n=196303(2135-8489)p=0,01 | n=157695(1725-18079)p=0,05 | n=163325(648,2-6936)p=0,38 | n=18890,6(112,80-1287)p=0,75 |
| 2 | male | n=9490(405,1-755 | n=1394,62(58,78-112,3) | n=11174,3(64,8-357,4 | n=1120,88(18,85-27,47) | n=11490,2( 405,1-755,0) | n=11553,4( 78,63-2189) | n=111730(633,8-3360) | n=111664(1592-10024) | n=91737(1039-5123) | n=111470(1181-2233) |
| female | n=18519,6(435,3-4135)p=0,55 | n=2298,57(76,71-138,3)p=0,28 | n=20310(215,7-646,9)p=0,09 | n=2041,46(15,31-67,42)p=0,27 | n=21519,6(435,3-4135)p=0,80 | n=20474,7( 276,1-1708) p=0,63 | n=195363(2996-10004)p=0,002 | n=2010054 (2564-15475)p=0,03 | n=164214(1444-8009)p=0,26 | n=21961,6(320,6-1464)p=0,16 |
| RYGB | 1 | male | n=10 438,4(211,9-438,4) | n=961,33(17,74-105,0) | n=960,25(21,55-111,8) | n=531,65(4,66-63,50) | n=10303,0(146,9-559,0) | n=795,84(48,10-116,0) | n=9648,0(211,0-1667) | n=102080(1099-7882) | n=63109(1481-7295) | n=8827,9(116,0-1890) |
| female | n=17410,3(269,3-877,6)p=0,60 | n=1474,0(58,77-86,16)p=0,78 | n=1464,34(41,73-107,0)p=0,78 | n=139,91(6,56-41,19)p=0,71 | n=17486,1(208,5-666,8)p=0,28 | n=14107,2(48,21-214,6)p=0,58 | n=141056(811,0-3059)p=0,10 | n=153571(1996-7181)p=0,28 | n=92031(783,1-6561)p=0,60 | n=171001(418,8-1803)p=0,62 |
| 2 | male | n=10562,0(291,1-907,7) | n=850,86(16,81-81,20) | n=8133(70,83-205,2) | n=829,26(13,98-44,43) | n=8431,9(204,3-9956) | n=8152,3(70,37-377,8) | n=8387,0(53,26-1286) | n=83627(1661-3627) | n=51667(1118-8237) | n=101244(233,3-5425) |
| female | n=14509,0(362,7-939,6)p=0,93 | n=1364,53(37,53-78,85)p=0,37 | n=12161,2(98,7-236,1)p=0,34 | n=1232,69(15,78-63,25)p=0,52 | n=16462,4(266,2-780,2)p=0,65 | n=12133,7(69,36-305,6)p=0,92 | n=13805,0(528,6-2649)p=0,08 | n=143248(2128-9732)p=0,92 | n=102639(356,3-5160)p=0,85 | n=16797,8(390,5-1639)p=0,69 |
| LCS | 1 | male | n=4 769,0(442,1-4801) | n=326,33(14,71-96,0) | n=3295,5(26,51-456,0) | n=241,30(8,59-74,0) | n=4312,9(111,7-10001) | n=3111,9(96,74-438,5) | n=31599(724,5-2859) | n=34759(1462-7569) | n=23349(130,4-6567) | n=4570(39,36-13326) |
| female | n=22461,5(216,4-838,7)p=0,24 | n=2019,57(15,19-94,07)p=0,95 | n=2050,96(16,53-107,9)p=0,22 | n=1616,21(3,09-40,0)p=0,45 | n=22269,9(171,1-465,9) p=0,64 | n=2075,04(34,64-200,6)p=0,34 | n=211346(365,6-3365)p=0,78 | n=181985(1020-8998)p=0,59 | n=182081(555,9-3448)p=0,84 | n=20p=609,5(298,6-1137)p=0,66 |
| 2 | male | n=5735,6(296,6-4350) | n=445,8(17,11-80,55) | n=354,(102,6-519,4) | n=429,(11,36-67,42) | n=5459,(147,3-6759) | n=4143,3(55,70-534,3) | n=41141(797,2-1861) | n=45478( 1782-18826) | n=25340(3958-6723) | n=51166(423,5-2746) |
| female | n=20641,9(339,1-1273)p=0,96 | n=1936,31(15,67-84,31)p=0,95 | n=18165,4(103,4-254,1)p=0,42 | n=1720,81(5,79-53,43)p=0,62 | n=21278,2(240,0-557,5)p=0,74 | n=18167,1(73,14-280,0)p=0,88 | n=191148(255,3-2860)p=0,95 | n=181761(856,6-5979)p=0,21 | n=121765(1053-5572)p=0,34 | n=20721,4( 378,0-970,3)p=0,39 |

**Supplementary Table 3.** Sex differences of mediators in plasma in obese patients with and without type 2 diabetes before and after the test breakfast

Note: \*– p<0.05, \*\* – p<0.001, \*\*\* – p<0.000; differences in significance level were determined using the Mann-Whitney criterion for two independent samples (Me(Q1–Q3)). 1- Control group; 2- Obese patient without T2DM; 3- Obese patient with T2DM; 4- 6 months after LSG; 5- 6 months after RYGB.

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| **GeneOntology** | **Biological process** |
| GO:0150012 | positive regulation of neuron projection arborization |
| GO:0110135 | Norrin signaling pathway |
| GO:0001553 | luteinization |
| GO:0035929 | steroid hormone secretion |
| GO:0042701 | progesterone secretion |
| GO:0042813 | Wnt-activated receptor activity |
| GO:0061300 | cerebellum vasculature development |
| GO:0061298 | retina vasculature development in camera-type eye |
| GO:0061299 | retina vasculature morphogenesis in camera-type eye |
| GO:0061301 | cerebellum vasculature morphogenesis |
| GO:0061304 | retinal blood vessel morphogenesis |
| GO:0150011 | regulation of neuron projection arborization |

**Supplementary Table 4.** Functional annotation of GHCR (FZD4).

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| **GeneOntology** | **Biological process** |
| GO:0042226 | interleukin-6 biosynthetic process |
| GO:0120058 | positive regulation of small intestinal transit |
| GO:0032095 | regulation of response to food |
| GO:0001616 | growth hormone secretagogue receptor activity |
| GO:0014061 | regulation of norepinephrine secretion |
| GO:0016520 | growth hormone-releasing hormone receptor activity |
| GO:0032096 | negative regulation of response to food |
| GO:0032097 | positive regulation of response to food |
| GO:0032108 | negative regulation of response to nutrient levels |
| GO:0032109 | positive regulation of response to nutrient levels |
| GO:0048243 | norepinephrine secretion |
| GO:1902683 | regulation of receptor localization to synapse |
| GO:0010700 | negative regulation of norepinephrine secretion |
| GO:0032099 | negative regulation of appetite |
| GO:0032100 | positive regulation of appetite |
| GO:0033604 | negative regulation of catecholamine secretion |
| GO:0043134 | regulation of hindgut contraction |
| GO:0045408 | regulation of interleukin-6 biosynthetic process |
| GO:1905562 | regulation of vascular endothelial cell proliferation |
| GO:0099645 | neurotransmitter receptor localization to postsynaptic specialization membrane |
| GO:0098696 | regulation of neurotransmitter receptor localization to postsynaptic specialization membrane |
| GO:0014827 | intestine smooth muscle contraction |
| GO:0015874 | norepinephrine transport |
| GO:0033033 | negative regulation of myeloid cell apoptotic process |
| GO:0036321 | ghrelin secretion |
| GO:0043568 | positive regulation of insulin-like growth factor receptor signaling pathway |
| GO:0045409 | negative regulation of interleukin-6 biosynthetic process |
| GO:0099170 | postsynaptic modulation of chemical synaptic transmission |
| GO:0099633 | protein localization to postsynaptic specialization membrane |
| GO:1904306 | positive regulation of gastro-intestinal system smooth muscle contraction |
| GO:1905564 | positive regulation of vascular endothelial cell proliferation |
| GO:1990314 | cellular response to insulin-like growth factor stimulus |
| GO:1990770 | small intestine smooth muscle contraction |
| GO:0030252 | growth hormone secretion |
| GO:0042536 | negative regulation of tumor necrosis factor biosynthetic process |
| GO:0060123 | regulation of growth hormone secretion |
| GO:1904304 | regulation of gastro-intestinal system smooth muscle contraction |
| GO:2000109 | regulation of macrophage apoptotic process |
| GO:1904347 | regulation of small intestine smooth muscle contraction |
| GO:1904349 | positive regulation of small intestine smooth muscle contraction |
| GO:1904468 | negative regulation of tumor necrosis factor secretion |
| GO:2000110 | negative regulation of macrophage apoptotic process |

**Supplementary Table 5**. Functional annotation of GHSR.

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| **GeneOntology** | **Biological process** |
| GO:0042748 | circadian sleep/wake cycle. non-REM sleep |
| GO:0045187 | regulation of circadian sleep/wake cycle. sleep |
| GO:0045938 | positive regulation of circadian sleep/wake cycle. sleep |
| GO:0016520 | growth hormone-releasing hormone receptor activity |
| GO:0045188 | regulation of circadian sleep/wake cycle. non-REM sleep |
| GO:0046010 | positive regulation of circadian sleep/wake cycle. non-REM sleep |
| GO:0043568 | positive regulation of insulin-like growth factor receptor signaling pathway |
| GO:0021984 | adenohypophysis development |
| GO:0030252 | growth hormone secretion |
| GO:0060123 | regulation of growth hormone secretion |
| GO:0060124 | positive regulation of growth hormone secretion |
| GO:0060126 | somatotropin secreting cell differentiation |
| GO:0060133 | somatotropin secreting cell development |

**Supplementary Table 6.** GHRHR functional annotation.

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| **GeneOntology** | **Biological process** |
| GO:0007190 | Аctivation of adenylate cyclase activity |
| GO:0002029 | Desensitization of G-protein coupled receptor protein signaling pathway |
| GO:0031018 | Endocrine pancreas development |
| GO:0032024 | Positive regulation of insulin secretion |
| GO:0048678 | Response to axon injury |
| GO:0070542 | Response to fatty acid |

**Supplementary Table 7.** GIPR functional annotation.

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|  **GeneOntology** | **Biological process** |
| GO:0007190 | Activation of adenylate cyclase activity |
| GO:0019933 | cAMP-mediated signaling |
| GO:0045777 | Positive regulation of blood pressure |
| GO:0071377 | Cellular response to glucagon stimulus |
| GO:0004967 | glucagon receptor activity |

**Supplementary Table 8.** GLP-1R functional annotation.

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|  **GeneOntology** | **Biological process** |
| KEGG:04024 | cAMP signaling pathway |
| KEGG:04080 | neuroactive ligand-receptor interaction |
| REACTOME:18372 | Secretin family receptors class B/2 |
| REACTOME:18377 | Glucagon-type ligand receptors |
| REACTOME:19327 | G alpha (s) signalling events |
| REACTOME:21340 | GPCR ligand binding |

**Supplementary Table 9.** Signaling pathways of GIPR and GLP-1R involvement.