**Supplementary information 1: Methods used for the systematic review**

**Four systematic reviews were performed in this study:**

1. Insulin receptor knockout

2. Insulin degrading enzyme

3. Insulin suppression by diazoxide

4. Insulin suppression by octreotide

**Keywords:** The keywords used for the four meta-analyses are given the following table

|  |  |  |
| --- | --- | --- |
| **Sr. No.**  | **Meta-analysis for**  | **Keywords** |
| 1. | Insulin receptor knockout | “insulin receptor knockout” |
| 2 | Insulin degrading enzyme  | “insulin degrading enzyme” |
| 3. | Insulin suppression by diazoxide | “diazoxide and diabetes”; “insulin suppression” |
| 4. | Insulin suppression by octreotide  | “octreotide and diabetes”; “insulin suppression |

**Data-bases:** We have used the PubMed/MEDLINE database (and not the data bases which report clinical trials data) since the experiments we were searching for are predominantly experiments in basic research in life sciences as opposed to clinical studies. Majority of the studies which were searching for were rodent studies and not human studies.

**Timeline for inclusion of papers in the search:** The first search was performed in August 2017 and the papers until 31st July 2017 were included in the primary search.

**Inclusion and exclusion criteria:** Given in the tables 2,3 and 4 of the main paper

**Details of the papers:** Tables 2,3,4,5 below

**Methods of data extraction:** Data was extracted from the shortlisted papers using the software WebPlotDigitizer (Author: Ankit Rohatgi

Website: <https://automeris.io/WebPlotDigitizer>, Version: 4.1, January, 2018, E-Mail: ankitrohatgi@hotmail.com, Location: Austin, Texas, USA)

**Principal summary measures:** The data extracted from each shortlisted paper was the difference of means of blood/plasma glucose levels between the ‘control’ and the ‘treated’ along with the 95% confidence intervals.

**Methods of handling data and combining results of studies:** These differences in the means between the control and treated from all the respective shortlisted papers were compiled. These differences were compared across different timepoints using the non-parametric chi-square test.

**Details of the papers shortlisted for the four meta-analyses:**

**Table 2:** Details of the 16 papers used in the Insulin Receptor Knock-Out (IRKO) analysis. All of these studies were carried out on rodent models.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Sr. No.**  | **Reference**  | **Type of IRKO** | **Method used to make the knockout** | **Fasting duration before the GTT (Glucose tolerance test)**  | **Glucose concentration/ mode of glucose infusion used in GTT**  | **Sample size**  |
| 1 | Sakaguchi et al., 2017 | inducible-BATIRKO (brown adipose tissue IRKO) | Cre-loxP system |  6 hours | 2g/kg dextrose given orally  | Control n=13, IRKO, n=12 |
| 2 | Softic et al., 2016 | FIRKO (Fat IRKO) (12 weeks old male mice)  | Cre-loxP system | Overnight (ON) | Random fed  | n=12 to 30 for each group  |
| FIRKO (52 weeks old male mice) | n=5 to 6 for each group |
| 3 | Haas et al., 2012 | LIRKO (Liver IRKO) | Cre-loxP system | ON | 1g/kg dextrose i.p.(intraperitoneal) | n=3 to 5 for each group |
| 4 | Kawamori et al., 2009  | αIRKO (α-cell IRKO) (2, 5, 12-month-old mice)  | Cre-loxP system | 16 hours | Random fed  | n=6 to 8 for each group |
| αIRKO (2,5-month-old mice) | 16 hours | 1g/kg dextrose i.p. | n=3 to 12 for each group |
| 5 | Escribano et al., 2009 | inducible LIRKO | Cre-loxP system | 16 hours  | 2g/kg dextrose i.p. | n=10 to 20 for each group |
| 6 | Ealey et al., 2008 | MIRKO (Muscle IRKO) | Cre-loxP system | ON | 2g/kg dextrose i.p. | n=7 to 13 for each group |
| 7 | Okada et al., 2007 | βIRKO (β-cell IRKO), LIRKO and βIRKO-LIRKO (4-5 weeks old male mice) | Cre-loxP system | ON | 2g/kg dextrose i.p. | n=8 for each group |
| βIRKO (20 weeks old, male mice; chow and HFD) | n=9 to 16 for each group |
| 8 | Cohen et al., 2004 | LIRKO (2-month-old mice)  | Cre-loxP system | 16 hours  | 2g/kg dextrose i.p. | n=17 for control n=25 for LIRKO |
| 9 | Otani, 2003 | βIRKO-Non-diabetic (ND) | Cre-loxP system  | 4 hours | 2g/kg dextrose i.p. | n= 35 for control, n=28 for βIRKO(ND)  |
| βIRKO-Diabetic (D) | n=10 for βIRKO(D) |
| 10 | Blüher et al., 2002 | FIRKO (2 month and 10-month-old mice) | Cre-loxP system  | 16 hours  | 2g/kg dextrose i.p. | n=8 for each group |
| 11 | Guerra et al., 2001 | BATIRKO (3,6 and 9-month-old male and female mice) | Cre-loxP system  | ON  | 2g/kg dextrose i.p. | n=10 to 20 for each group |
| 12 | Lauro et al., 1998 | Insulin receptor (Ins R) and Ins R K1030 mutatnt | Cre-loxP system,  | ON | 2g/kg dextrose i.p. | n=8 for each group |
| 13 | Mauvais-Jarvis et al., 2000  | MIRKO, βIRKO and βIRKO-MIRKO (2 and 6-month-old mice  | Cre-loxP system  | ON  | 2g/kg dextrose i.p. | n=28 to 32 for each group |
| 14 |  Dodson Michael et al., 2000 | LIRKO (2 and 6-month-old mice)  | Cre-loxP system  | 16 hours  | 2g/kg dextrose i.p. | n=8 for each group |
| 15 | Wojtaszewski et al., 1999 | MIRKO | Cre-loxP system  | ON | 2g/kg dextrose i.p. | n= 7 to 8 for each group |
| 16 |  Brüning et al., 1998 | MIRKO | Cre-loxP system  | ON | 2g/kg dextrose i.p. | n=8 for each group |

**Table 3:** Details of the 6 papers used in the Insulin Degrading Enzyme (IDE) inhibition analysis. All studies were carried out on rodent models.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Sr. No.**  | **Reference**  | **Method used to inhibit IDE**  | **Fasting duration before the GTT** | **Glucose concentration/ mode of glucose infusion used in GTT**  | **Sample size**  |
| 1 | Villa-Pérez et al., 2018 | Liver specific IDE knockout | 16 hours | 2g/kg dextrose given i.p. | n= 9 to 13 for each group |
| 2 | Deprez-Poulain et al., 2015 | Inhibition of catalytic site of IDE using the inhibitor BDM44768  | 6 hours  | 1.5g/kg glucose for IPGTT and 2 or 3g/kg glucose for OGTT | n= 4 to 7 for each group |
| 3 | Durham et al., 2015 | Inhibition of IDE using an N-terminal exosite (NTE)  | ON  | 2g/kg dextrose given orally  | n=6 for each group |
| 4 | Maianti et al., 2014 | Inhibition of IDE using a non-catalytic site binding inhibitor  | 14 hours  | 1.5g/kg glucose for IPGTT and 3g/kg glucose for OGTT | n=5 to 7 for each group |
| 5 | Abdul-Hay et al., 2011 | IDE-KO created by Cre-lox recombination | 6 to 9 hours  | 1g/kg dextrose given i.p.  | n=10 to 12 for each group |
| 6 | Farris et al., 2003 | IDE-/- mice created by gene trapping method | ON | 2g/kg dextrose given i.p. | n=6 (IDE-/-)n=4 (Control) |

**Table 4:** Details of the 8 papers used in the Diazoxide (DZX) analysis.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Sr. No.**  | **Study reference**  | **Concentration of diazoxide used**  | **Details of subjects/model** | **Fasting duration** | **GTT details** | **Sample size for GTT (placebo, treatment)** |
| **Studies on human subjects**  |
| 1 | Brauner et al., 2016 | 3.2 to 4.2 mg/kg/d for 6months  | Children over the age of 6 with hyperinsulinemia and obesity  | ON | 75g glucose given to patients orally | n=12 to 17 for each group |
| 2 | Ramanathan et al., 2011 | 6mg/kg diazoxide  | Healthy, young adults | ON | Mixed meal  | n=11 for each group |
| 3 | van Boekel et al., 2008 | 50mg t.i.d (thrice in a day) for 4 weeks and then dose increased till 300mg t.i.d, total duration: 6 months  | Obese, men, age 30 to 50 years | ON | Standardized mixed meal  | n=18 for each group |
| 4 | Due et al., 2007 | 2mg/kg/day DZX or placebo for 8 weeks  | 35 Overweight and obese men, age 23-54 years  | ON | 75g glucose in 300m water given orally  | n=13 (DZX) and n=18 (placebo) |
| 5 |  Schreuder et al., 2005 | 50/75/100 mg t.i.d for 6 days  | Healthy obese and non-obese men, age 30-50 years | ON | Standardized mixed meal  | n=5 (non-obese) and n=12 (obese) |
| 6 | Wigand & Blackard, 1979 | 5mg/kg/d, 7 days  | Obese, non-diabetic subjects, age 18-33 | ON | 40g/m2 body surface area glucose given orally | n=10 |
| **Studies on rodent models**  |
| 7 |  Matsuda et al., 2002 | 30mg/kg/day for 6 weeks | Male Wistar rats, control and STZ induced diabetes  | 12 hours  | 2g/kg glucose i.p | n=7 for each group |
| 8 | Leahy et al., 1994 | 30mg/kg/day, twice a day, for 8-12 days  | Male Sprague-Dawley rats, 3 groups-sham, Pancreatectomised rats treated with water, pancreatectomised rats treated DZX | ON | 3.5g/kg oral gavage  | n=4 for each group |

**Table 5:** Details of the 10 papers used in the Octreotide (OCT) analysis. All the papers included studies on human subjects.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Sr. No.**  | **Study reference**  | **Concentration of octreotide used**  | **Details of subjects/model** | **Fasting duration** | **GTT details** | **Sample size for GTT (placebo, treatment)** |
| 1 | Madsen et al., 2011 | Somatostatin analog (SA) alone: OCT 10-30mg/4weeks ORLanreotide 80mg/4weeks Co-treatment: OCT 6.7-20mg/4weeks ORLanreotide 24-60mg/4weeks AND Pegvisomat 30-60mg/4weeks | 18 Acromegalic patients (age 54±3 years) | ON | 75g glucose given orally  | n=6 SA only n=12 SA+P  |
| 2 | Breckenridge et al., 2007 | OCT (30ng/kg.min) with GH + 1. Saline (treatment for our purpose) 2. Insulin (control for our purpose) | 14 Healthy adults (BMI 23 ± 2.9; Age 29 ± 5 years) | ON | 22.5µmol/kg | n=8 malen=6 female  |
| 3 | Ronchi et al., 2002 | 1. Lanreotide (Slow Release)-30mg im injection every 14 days for 19±16 months 2. OCT (Long Acting Release)-20mg im injection every 28 days for 21±10 months | 10 acromegalic patients (6 men and 4 women; age 46±16 years; BMI 29±5)  | ON | not mentioned  | n=6 malen=4 female  |
| 4 | Parkinson et al., 2002 | 1. OCT (50µg sc t.i.d) for 7 days 2. Pegvisomant (20mg/day sc) for 7 days  | 6 healthy, male volunteers (age 21-63 years), studied on 3 separate occasions  | ON | 75g glucose given orally  | n=6 male  |
| 5 | Giustina et al., 1991 | T2D patients received either of the four treatments a. Insulin 0.1U/kg b. OCT 25µg c. OCT 50µg d. OCT 100µg with insulin  | 8 overweight/obese T2D patients (age 53.4 ± 4.2 years) | ON  | Mixed meal  | n=8 (7 female and 1 male) |
| 6 | Candrina et al., 1988 | Type 2 diabetes patients received 0.5U/kg/day divided into 2 subcutaneous injections  | 5 T2D patients (age 56 ± 4 years), duration of diabetes ranged from 13 to 25 years  | ON | 300 kcal breakfast  | n=5 (3 male and 2 female) |
| 7 | Williams et al., 1988 | Type 2 diabetes patients received 50µg OCT, thrice a day, subcutaneously, for 3 days  | 7 T2D patients (age 51-73 years, mean 67 years), duration of diabetes ranged from (6 months to 4 years, mean 2.5 years) | ON | Standardised breakfast  | n=7 (4 males and 3 females) |
| 8 | Johnston et al., 1986 | 50 µg OCT administered subcutaneously, twice a day in diabetic and nondiabetic patients | 6 normal and 5 type 2 diabetic subjects (age range not given) | ON  | Standardised meals  | n=6 (normal, male)n=5 (T2D) |
| 9 | Davies et al., 1986 | 50 µg OCT administered subcutaneously, twice a day in diabetic patients | 5 T2D patients (mean age 49 years; duration of diabetes ranged from 3 to 10 years, with a mean of 6 years) | ON  | Standardised breakfast  | n=5 (male, diabetic)  |
| 10 | Williams et al., 1986 | 5-100µg OCT administered subcutaneously in T2D patients twice a dayConcentrations used: 50 µg in normal 5,100 µg in T2D | 5 normal and 5 T2D patients (age 50 to 65 years | ON  | Standardised breakfast  | n=5 (normal)n=5 (T2D) |

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