

ESM Table 1. Characteristics of trials

Trial (year of publication) [reference]	Patients with type 2 diabetes (n=275)	Non-diabetic control subjects (n=279)	Type of test(s)	Duration of test (hours)
Bagger et al (2011) [1]	8	8	25g-OGTT 75g-OGTT 125g-OGTT	4
Bose et al (2009) [2]	11	8	50g-OGTT	3
Brown et al (2012) [3]	10	25	75g-OGTT	3
Greenfield et al (2009) [4]	8	8	75g-OGTT	2
Højberg et al (2008) [5]	9	9	2248 kJ (537 kcal)-meal ^a	4
Jørgensen et al (2012) [6]	13	12	1256 kJ (300 kcal)-meal ^b	4
Knop et al (2007 Aug) [7]	10	10	50g-OGTT	4
Knop et al (2007 Jan) [8]	8	8	50g-OGTT	4
Korosi et al (2001) [9]	10	10	40g/m ² -OGTT	3
Kozawa et al (2010) [10]	9	5	1926 kJ (460 kcal)-meal ^a	3
Laferrère et al (2007) [11]	8	7	50g-OGTT	3
Muscelli et al (2008) [12]	10	24	75g-OGTT	3
Raddatz et al (2008) [13]	10	10	2093 kJ (500 kcal)-meal ^{b,c}	3
Rijkelijkhuijzen et al (2009) [14]	18	6	1926 kJ (460 kcal)-meal ^a 2847 kJ (680 kcal)-meal ^a 3488 kJ (833 kcal)-meal ^a	2
Romero et al (2012) [15]	5	5	1666 kJ (398 kcal)-meal ^b	2
Ryskjaer et al (2006) [16]	8	8	2730 kJ (652 kcal)-meal ^a	3
Theodorakis et al (2006) [17]	17	36	75g-OGTT	2
Toft-Nielsen et al (2001) [18]	54	33	2248 kJ (537 kcal)-meal ^a	4
Vaag et al (1996) [19]	12	13	75g-OGTT	3
Vilsbøll et al (2001) [20]	12	12	2370 kJ (566 kcal)-meal ^a	3
Vilsbøll et al (2003) [21]	8	8	1090 kJ (260 kcal)-meal ^a 2177 kJ (520 kcal)-meal ^a	3
Vollmer et al (2008) [22]	17	14	75g-OGTT 3433 kJ (820 kcal)-meal ^a	4

^aSolid mixed meal test

^bLiquid mixed meal test

^cGLP-1, glucagon-like peptide-1, responses evaluated both in portal and in peripheral circulations

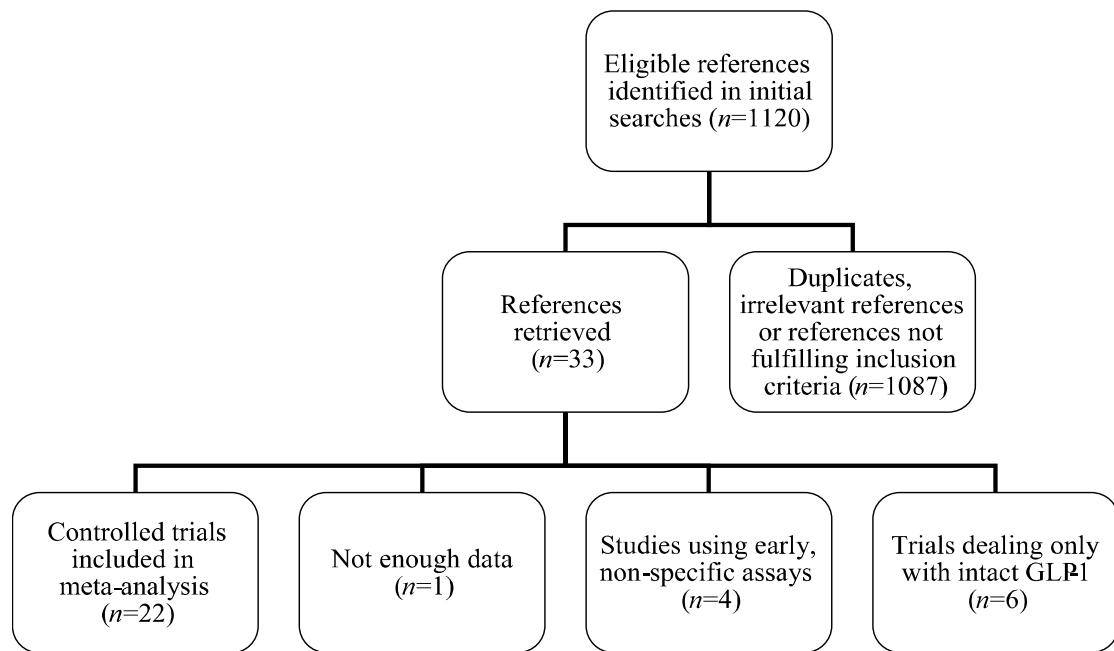
References

1. Bagger JI, Knop FK, Lund A, Vestergaard H, Holst JJ, Vilsbøll T (2011) Impaired regulation of the incretin effect in patients with type 2 diabetes. *J Clin Endocrinol Metab* 96(3):737–745
2. Bose M, Teixeira J, Olivan B, Bawa B, Arias S, Machineni S, Pi-Sunyer FX, Scherer PE, Laferrère B (2010) Weight loss and incretin responsiveness improve glucose control independently after gastric bypass surgery. *J Diabetes* 2(1):47–55
3. Brown RJ, Walter M, Rother KI (2012) Effects of diet soda on gut hormones in youths with diabetes. *Diabetes Care* 35(5):959–964
4. Greenfield JR, Farooqi IS, Keogh JM, Henning E, Habib AM, Blackwood A, Reimann F, Holst JJ, Gribble FM (2009) Oral glutamine increases circulating glucagon-like peptide 1, glucagon, and insulin concentrations in lean, obese, and type 2 diabetic subjects. *Am J Clin Nutr* 89(1):106–113
5. Højberg PV, Vilsbøll T, Zander M, Knop FK, Krarup T, Vølund A, Holst JJ, Madsbad S (2008) Four weeks of near-normalization of blood glucose has no effect on postprandial GLP-1 and GIP secretion, but augments pancreatic B-cell responsiveness to a meal in patients with Type 2 diabetes. *Diabet Med* 25(11):1268–1275
6. Jørgensen NB, Jacobsen SH, Dirksen C, et al (2012) Acute and long-term effects of Roux-en-Y gastric bypass on glucose metabolism in subjects with Type 2 diabetes and normal glucose tolerance. *Am J Physiol Endocrinol Metab* 303(1):E122–131

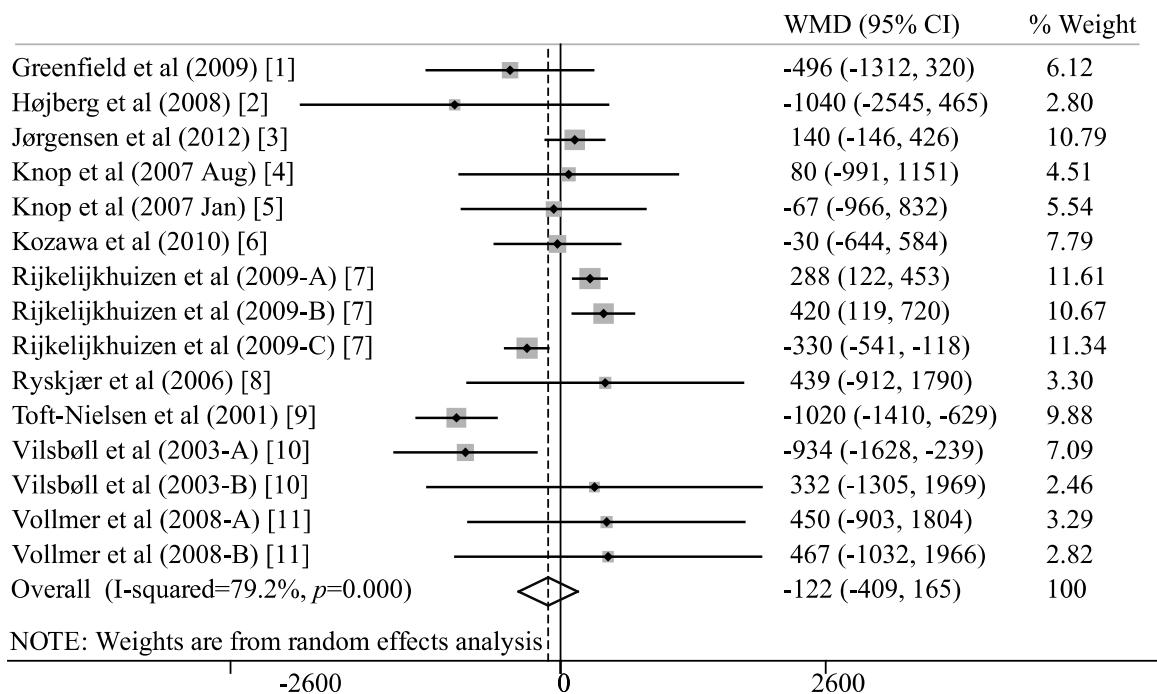
7. Knop FK, Vilsbøll T, Højberg PV, Larsen S, Madsbad S, Vølund A, Holst JJ, Krarup T (2007) Reduced incretin effect in type 2 diabetes: cause or consequence of the diabetic state? *Diabetes* 56(8):1951–1959
8. Knop FK, Vilsbøll T, Madsbad S, Holst JJ, Krarup T (2007) Inappropriate suppression of glucagon during OGTT but not during isoglycaemic i.v. glucose infusion contributes to the reduced incretin effect in type 2 diabetes mellitus. *Diabetologia* 50(4):797–805
9. Korosi J, McIntosh CH, Pederson RA, Demuth HU, Habener JF, Gingerich R, Egan JM, Elahi D, Meneilly GS (2001) Effect of aging and diabetes on the enteroinsular axis. *J Gerontol A Bio Sci Med Sci* 56(9):M575–579
10. Kozawa J, Okita K, Imagawa A, Iwahashi H, Holst JJ, Yamagata K, Shimomura I (2010) Similar incretin secretion in obese and non-obese Japanese subjects with type 2 diabetes. *Biochem Biophys Res Commun* 393(3):410–413
11. Laferrère B, Heshka S, Wang K, Khan Y, McGinty J, Teixeira J, Hart AB, Olivan B (2007) Incretin levels and effect are markedly enhanced 1 month after Roux-en-Y gastric bypass surgery in obese patients with type 2 diabetes. *Diabetes Care* 30(7):1709–1716
12. Muscelli E, Mari A, Casolaro A, Camastra S, Seghieri G, Gastaldelli A, Holst JJ, Ferrannini E (2008) Separate impact of obesity and glucose tolerance on the incretin effect in normal subjects and type 2 diabetic patients. *Diabetes* 57(5):1340–1348
13. Raddatz D, Nolte W, Rossbach C, Leonhardt U, Buchwald A, Scholz KH, Ramadori G (2008) Measuring the effect of a study meal on portal

- concentrations of glucagon-like peptide 1 (GLP-1) in non diabetic and diabetic patients with liver cirrhosis: transjugular intrahepatic portosystemic stent shunt (TIPSS) as a new method for metabolic measurements. *Exp Clin Endocrinol Diabetes* 116(8):461–467
14. Rijkelijkhuisen JM, McQuarrie K, Girman CJ, Stein PP, Mari A, Holst JJ, Nijpels G, Dekker JM (2010) Effects of meal size and composition on incretin, alpha-cell, and beta-cell responses. *Metab Clin Exp* 59(4):502–511
 15. Romero F, Nicolau J, Flores L, Casamitjana R, Ibarzabal A, Lacy A, Vidal J (2012) Comparable early changes in gastrointestinal hormones after sleeve gastrectomy and Roux-En-Y gastric bypass surgery for morbidly obese type 2 diabetic subjects. *Surgical endoscopy*. doi: 10.1007/s00464-012-2166-y
 16. Ryskjær J, Deacon CF, Carr RD, Krarup T, Madsbad S, Holst J, Vilbøll T (2006) Plasma dipeptidyl peptidase-IV activity in patients with type-2 diabetes mellitus correlates positively with HbA_{1c} levels, but is not acutely affected by food intake. *Eur J Endocrinol* 155(3):485–493
 17. Theodorakis MJ, Carlson O, Michopoulos S, Doyle ME, Juhaszova M, Petraki K, Egan JM (2006) Human duodenal enteroendocrine cells: source of both incretin peptides, GLP-1 and GIP. *Am J Physiol Endocrinol Metab* 290(3):E550–559
 18. Toft-Nielsen MB, Damholt MB, Madsbad S, Hilsted LM, Hughes TE, Michelsen BK, Holst JJ (2001) Determinants of the impaired secretion of glucagon-like peptide-1 in type 2 diabetic patients. *J Clin Endocrinol Metab* 86(8):3717–3723

19. Vaag AA, Holst JJ, Vølund A, Beck-Nielsen HB (1996) Gut incretin hormones in identical twins discordant for non-insulin-dependent diabetes mellitus (NIDDM)--evidence for decreased glucagon-like peptide 1 secretion during oral glucose ingestion in NIDDM twins. *Eur J Endocrinol* 135(4):425–432
20. Vilsbøll T, Krarup T, Deacon CF, Madsbad S, Holst JJ (2001) Reduced postprandial concentrations of intact biologically active glucagon-like peptide 1 in type 2 diabetic patients. *Diabetes* 50(3):609–613
21. Vilsbøll T, Krarup T, Sonne J, Madsbad S, Vølund A, Juul AG, Holst JJ (2003) Incretin secretion in relation to meal size and body weight in healthy subjects and people with type 1 and type 2 diabetes mellitus. *J Clin Endocrinol Metab* 88(6):2706–2713
22. Vollmer K, Holst JJ, Baller B, Ellrichmann M, Nauck MA, Schmidt WE, Meier JJ (2008) Predictors of incretin concentrations in subjects with normal, impaired, and diabetic glucose tolerance. *Diabetes* 57(3):678–687



ESM Fig. 1 Flow chart for identification and selection of included trials. Inclusion criteria included controlled studies of adult patients with type 2 diabetes (and control subjects without diabetes) evaluating postprandial or post oral glucose glucagon-like peptide-1 (GLP-1) responses by providing peak plasma levels, integrated responses and/or integrated incremental plasma responses of total GLP-1



ESM Fig. 2 Meta-analysis of plasma total glucagon-like peptide-1 (GLP-1) responses during oral glucose or meal test evaluated from incremental AUC (iAUC) using random effects model. WMD: weighted mean difference with 95% CI in brackets

References

1. Greenfield JR, Farooqi IS, Keogh JM, Henning E, Habib AM, Blackwood A, Reimann F, Holst JJ, Gribble FM (2009) Oral glutamine increases circulating glucagon-like peptide 1, glucagon, and insulin concentrations in lean, obese, and type 2 diabetic subjects. *Am J Clin Nutr* 89(1):106–113
2. Højberg PV, Vilsbøll T, Zander M, Knop FK, Krarup T, Vølund A, Holst JJ, Madsbad S (2008) Four weeks of near-normalization of blood glucose has no effect on postprandial GLP-1 and GIP secretion, but augments pancreatic B-cell responsiveness to a meal in patients with Type 2 diabetes. *Diabet Med* 25(11):1268–1275
3. Jørgensen NB, Jacobsen SH, Dirksen C, et al (2012) Acute and long-term effects of Roux-en-Y gastric bypass on glucose metabolism in subjects with Type 2 diabetes and normal glucose tolerance. *Am J Physiol Endocrinol Metab* 303(1):E122–131
4. Knop FK, Vilsbøll T, Madsbad S, Holst JJ, Krarup T (2007) Inappropriate suppression of glucagon during OGTT but not during isoglycaemic i.v. glucose infusion contributes to the reduced incretin effect in type 2 diabetes mellitus. *Diabetologia* 50(4):797–805
5. Knop FK, Vilsbøll T, Højberg PV, Larsen S, Madsbad S, Vølund A, Holst JJ, Krarup T (2007) Reduced incretin effect in type 2 diabetes: cause or consequence of the diabetic state? *Diabetes* 56(8):1951–1959

6. Kozawa J, Okita K, Imagawa A, Iwahashi H, Holst JJ, Yamagata K, Shimomura I (2010) Similar incretin secretion in obese and non-obese Japanese subjects with type 2 diabetes. *Biochem Biophys Res Commun* 393(3):410–413
7. Rijkelijkhuizen JM, McQuarrie K, Girman CJ, Stein PP, Mari A, Holst JJ, Nijpels G, Dekker JM (2010) Effects of meal size and composition on incretin, alpha-cell, and beta-cell responses. *Metab Clin Exp* 59(4):502–511
8. Ryskjær J, Deacon CF, Carr RD, Krarup T, Madsbad S, Holst J, Vilsbøll T (2006) Plasma dipeptidyl peptidase-IV activity in patients with type-2 diabetes mellitus correlates positively with HbA_{1c} levels, but is not acutely affected by food intake. *Eur J Endocrinol* 155(3):485–493
9. Toft-Nielsen MB, Madsbad S, Holst JJ (1999) Continuous subcutaneous infusion of glucagon-like peptide 1 lowers plasma glucose and reduces appetite in type 2 diabetic patients. *Diabetes Care* 22(7):1137–1143
10. Vilsbøll T, Krarup T, Sonne J, Madsbad S, Vølund A, Juul AG, Holst JJ (2003) Incretin secretion in relation to meal size and body weight in healthy subjects and people with type 1 and type 2 diabetes mellitus. *J Clin Endocrinol Metab* 88(6):2706–2713
11. Vollmer K, Holst JJ, Baller B, Ellrichmann M, Nauck MA, Schmidt WE, Meier JJ (2008) Predictors of incretin concentrations in subjects with normal, impaired, and diabetic glucose tolerance. *Diabetes* 57(3):678–687