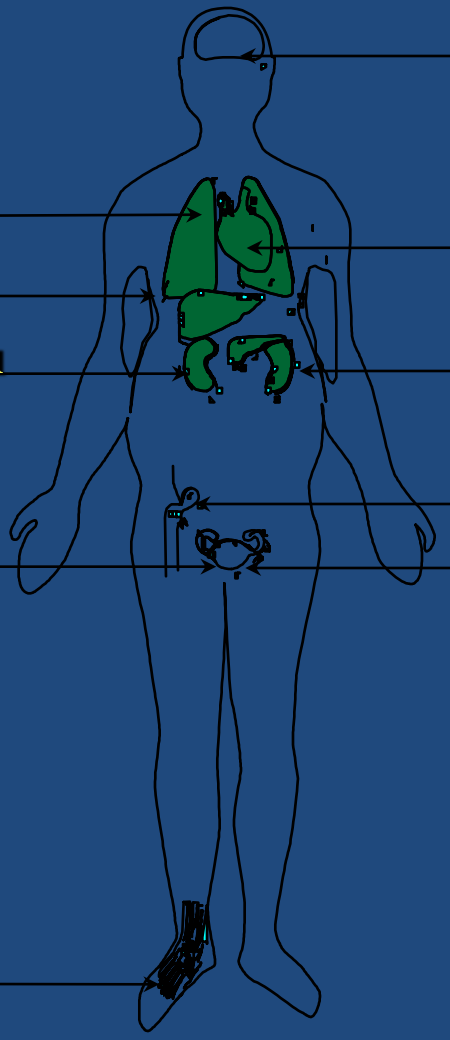
Obezite Tedavisinde yeni farmakolojik yaklasimlar Calismalardan Klinige

Dr.Hasan Ilkova
Istanbul Universitesi
Cerrahpasa Tip Fakultesi

Obezitenin Zararları

- Estetik Kaygılar
- Sağlık Problemleri

Obezitenin Sonuçları



İnme

Solunum hastalıkları

Kalp damar hastalık risk faktörleri

Kalp hastalıkları

Safra kesesi hastalıkları

Diyabet

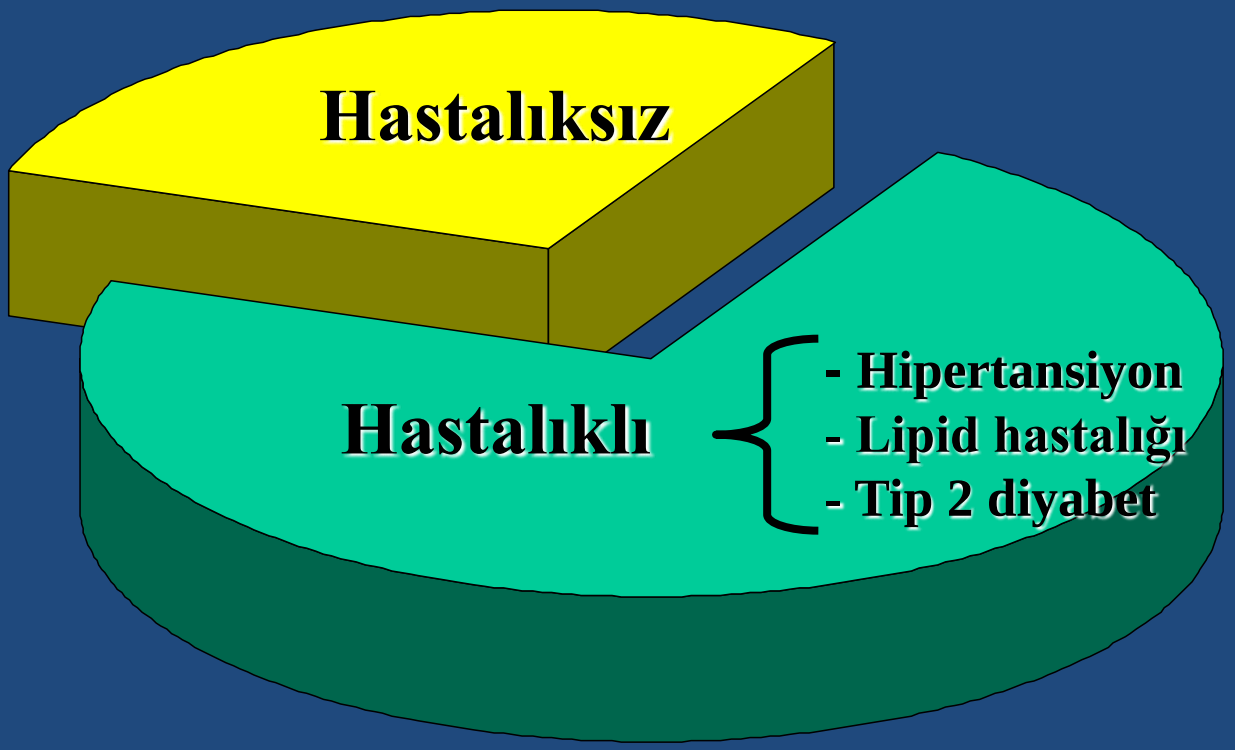
Osteoartrit

Endokrinolojik bozukluklar

Kanser

Hiperürisemi & Gut

Obeziteye Eşlik Eden Hastalıklar

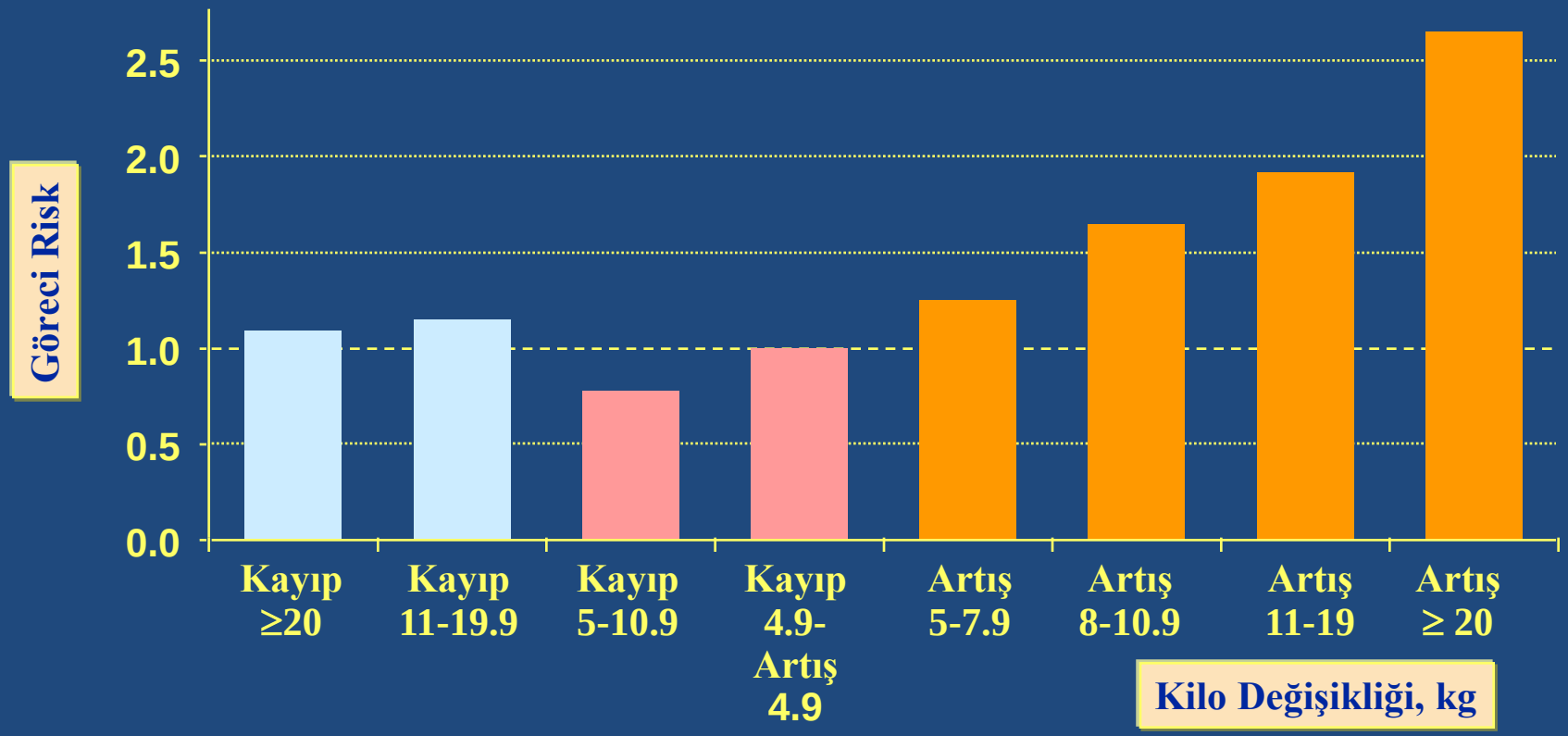


BMI= BKİ göre Diyabet gelişme riski ve insidansı

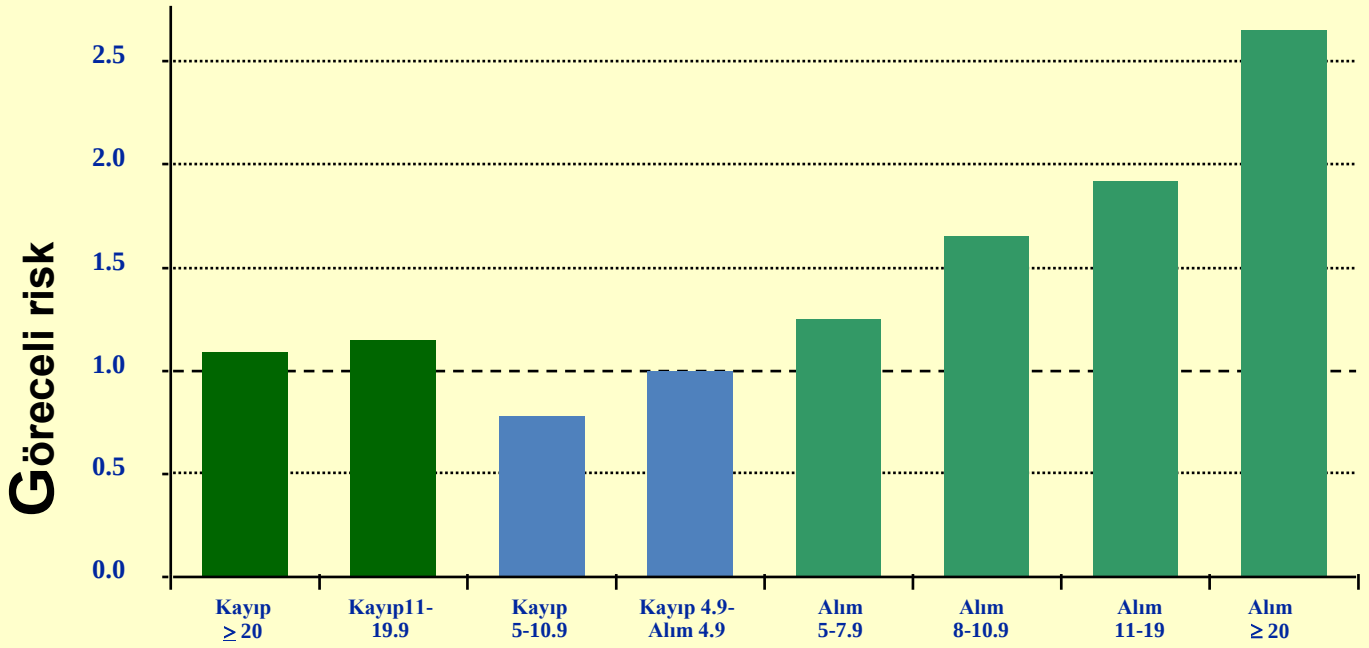
BMI= BKİ	İnsidans (100 000)	Risk
< 22	13	1.0
22-22.9	37.4	2.9
23-23.9	54.9	4.3
24-24.9	62.9	5.0
25-26-9	103.5	8.1
27-28.9	200.4	15.8
29-30.9	354.5	27.6
31-32.9	521.2	40.3
33-34.9	703.6	54.0
> 35	1190.5	93.2

Colditz et al Ann Intern Med 122:481, 1995

Kalp Damar Hastalığı Riski



Obezite – Hipertansiyon (Yüksek Tansiyon)



Diyabetes Mellitus Tedavisi

- Diyet
- Kilo kaybı
- Egzersiz
- Oral hipoglisemik ajanlar
- İnsülin

Tansiyon Yüksekliği Tedavisi

- Kilo kaybı
- Sigarayı bırakma
- Alkolü azaltma
- Stresi azaltma
- Tuz kısıtlanması
- İlaçlar

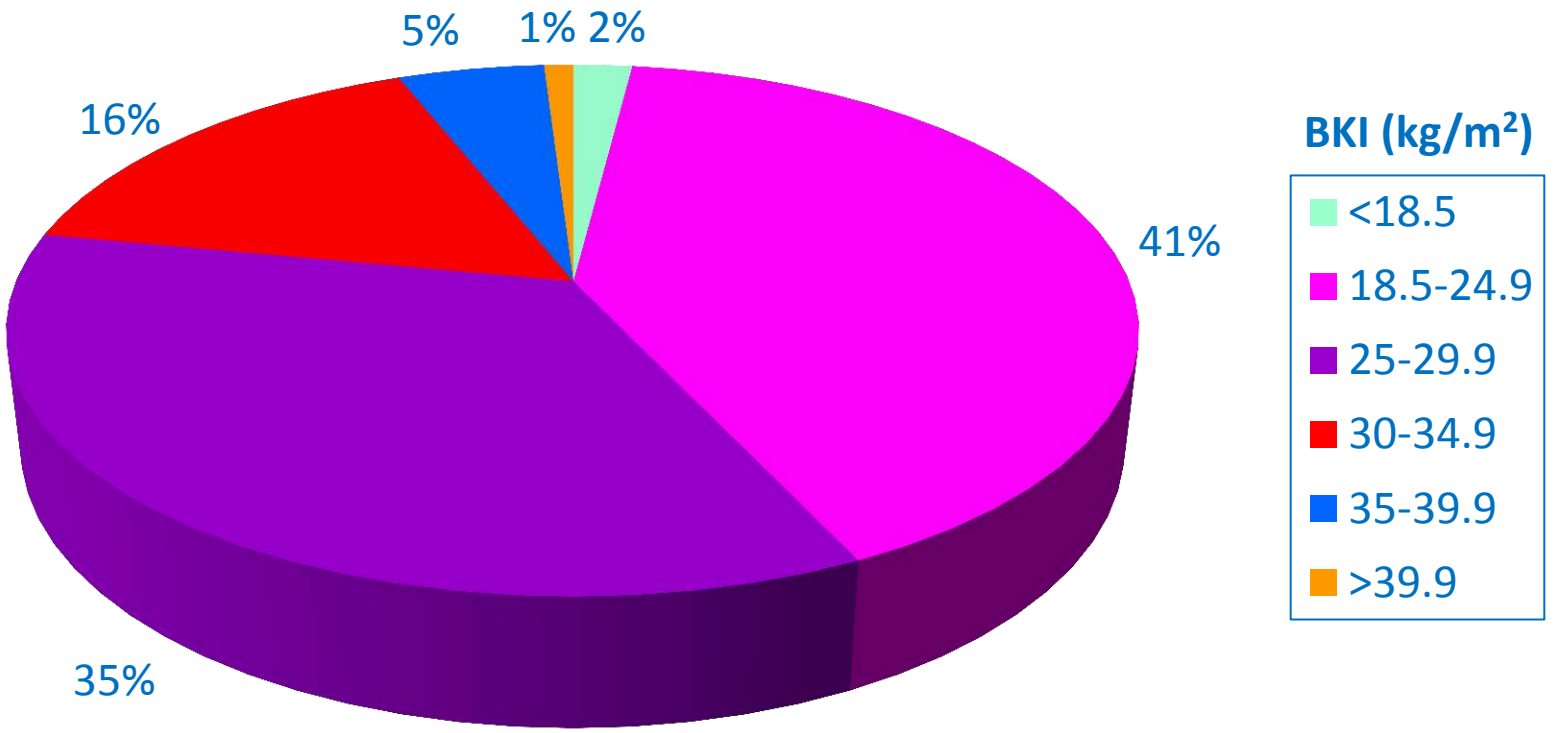
Kolesterol Yüksekliği Tedavisi

- Diyet
- Kilo kaybı
- Egzersiz
- İlaçlar

Kalp Damar Hastalığı Tedavisi

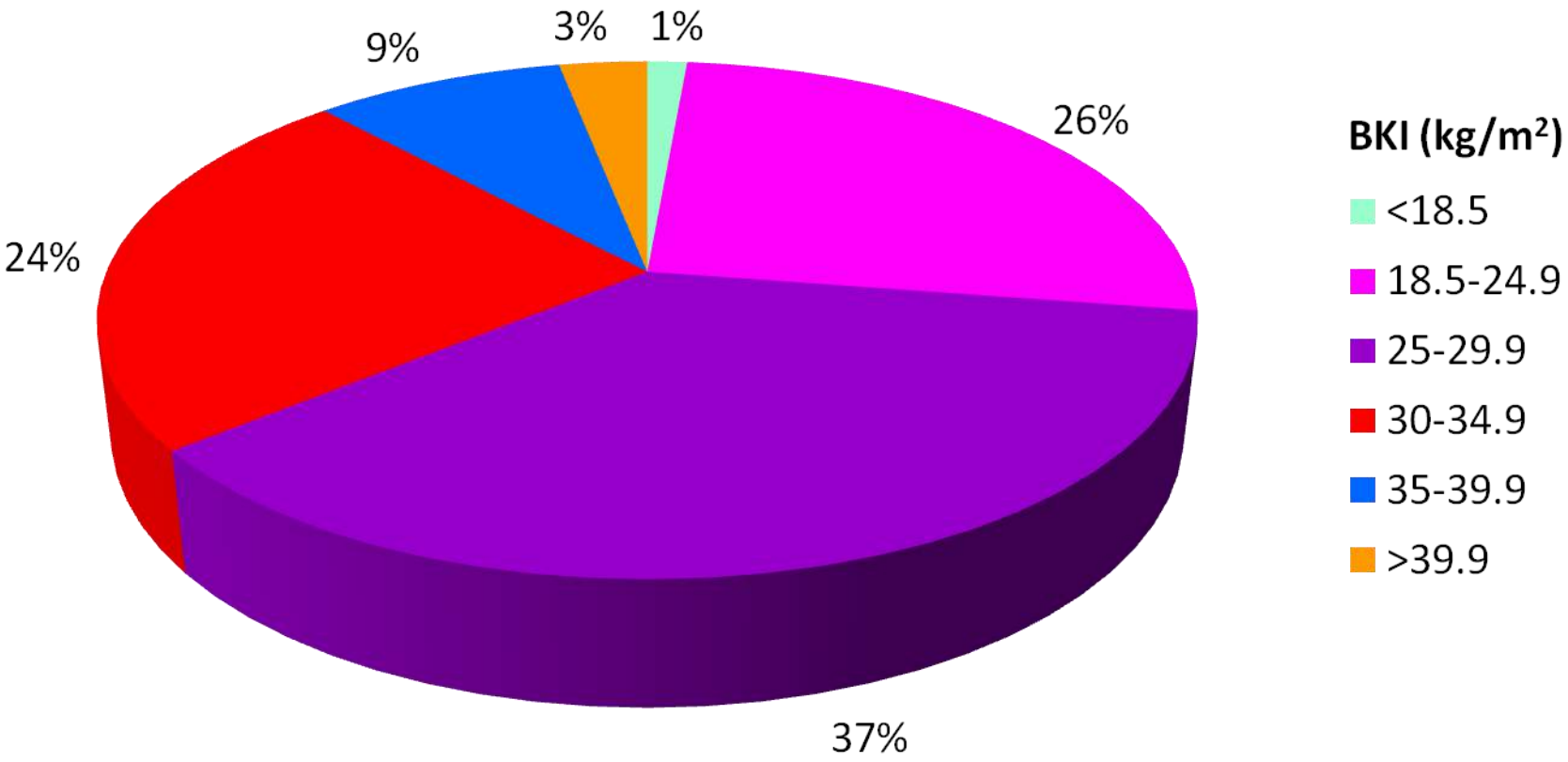
- Diyet
- Kilo kaybı
- Yaşam tarzında değişiklik
- Sigarayı bırakma
- İlaçlar
- Cerrahi

TURDEP-I-(YEAR 1998) : BMI distribution among Turkish Adults



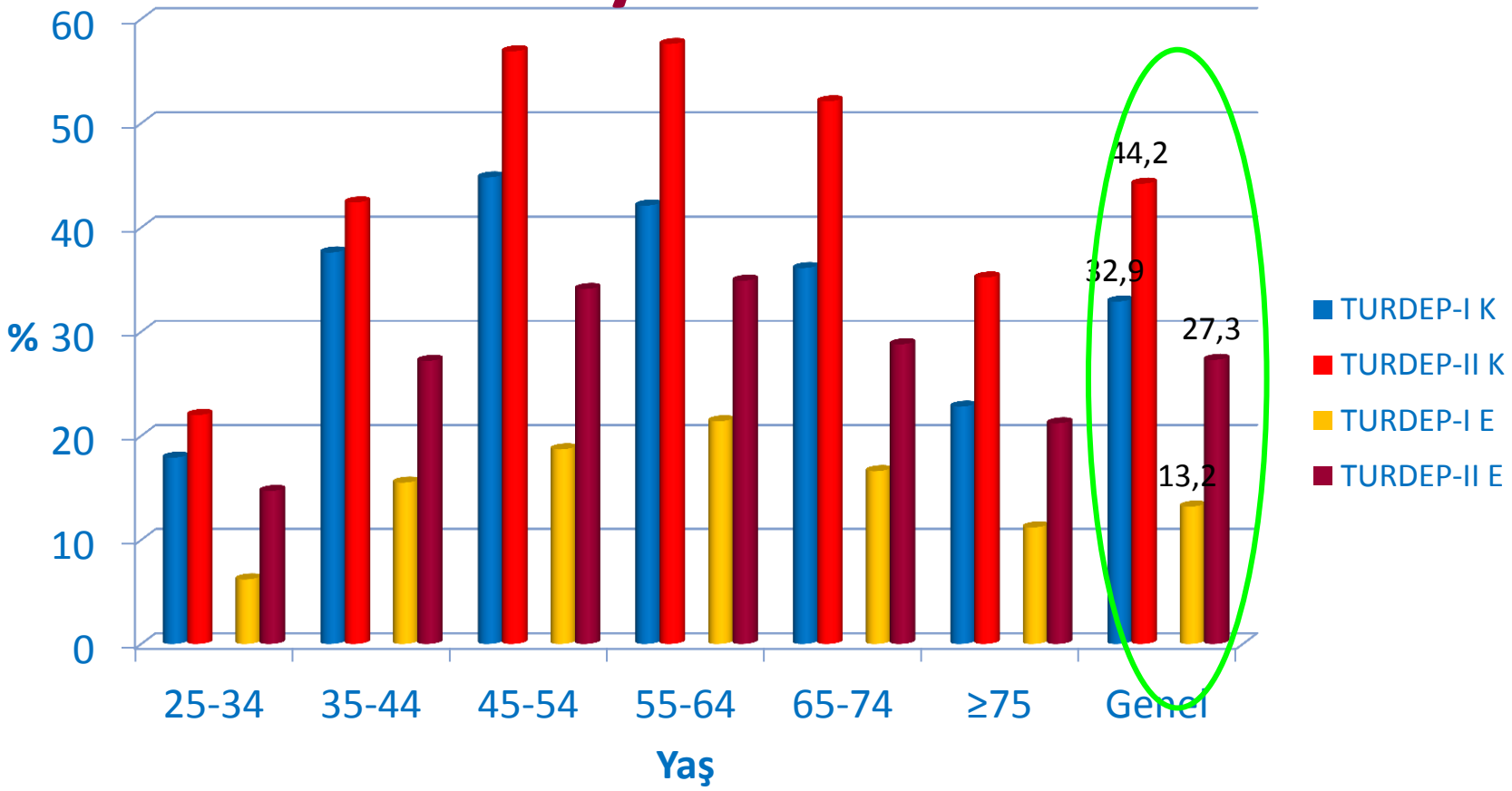
İ Satman ve TURDEP-II Çalışma Grubu 2011

TURDEP-II – (YEAR 2010): BMI distribution among Turkish Adults



İ Satman ve TURDEP-II Çalışma Grubu 2011

Obesity has increased by 34% in women and 107% in men in 12 years



İ Satman ve TURDEP-II Çalışma Grubu 2011

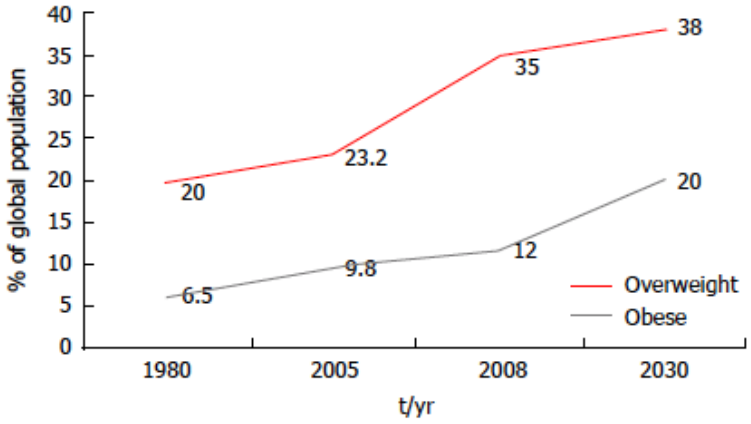
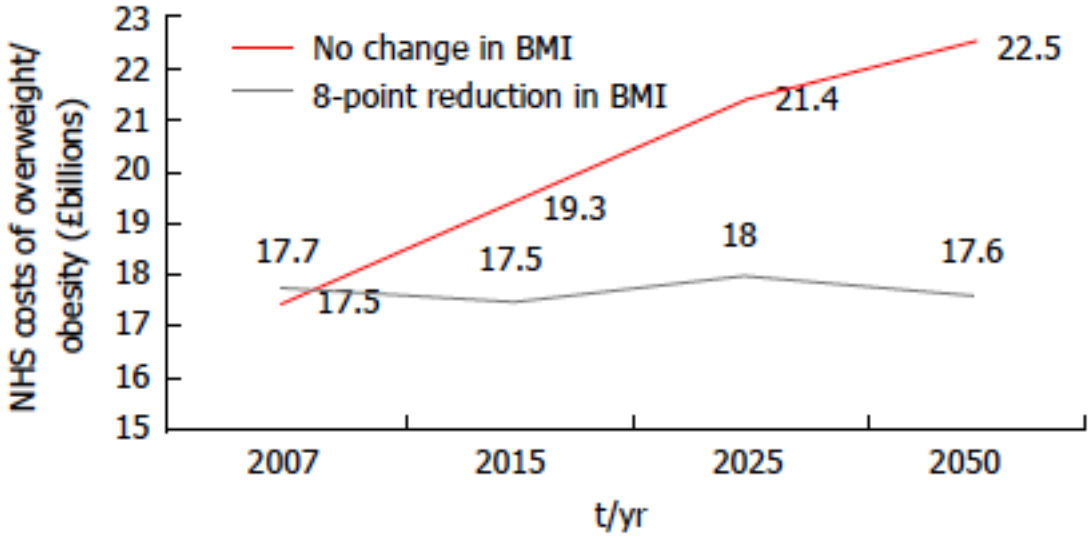


Figure 1 Global overweight and obesity trends and projections. If recent trends continue unabated, by 2030, 38% and 20% of the world's adult population are projected to be overweight or obese respectively[8].



World J Diabetes 2016 December 15; 7(20): 572-598
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Table 1 Current and previously Food and Drug Administration licenced anti-obesity pharmacotherapeutics

Drug	Mechanism	Year	Clinical use and limitations	Suspension reason
Currently FDA licenced drugs				
Diethylpropion	NA releasing agent	1959	FDA approved for short term use (3 mo); not recommended with uncontrolled hypertension or heart disease	-
Phentermine		1959	FDA and EMA approved for long term use; treatment dependent weight loss	-
Orlistat (Xenical)	-	1999		-
Orlistat (Alli)	Pancreatic lipase inhibitor	2007		-
Phentermine-topamirate (Qysmia)	-	-	Approved for long term use; treatment dependent weight loss	-
Lorcaserin (Belviq)	5HT2c-R antagonist	2012	FDA approved for long term use, recommended in those with cardiovascular disease; treatment dependent weight loss	-
Liraglutide (Saxenda)	GLP-1 analogue	2014	FDA and EMA (2015) approved	-
Previously FDA licenced drugs				
Dinitrophenol	Unknown	1938	-	Dermatitis, neuropathy, agranulocytosis, visual impairment, death
Aminorex	Unknown	1968	-	Chronic pulmonary hypertension
Amphetamines	Monoamine reuptake inhibitor	1971	-	Addiction, hypertension, myocardial toxicity
Fenfluramine	Serotonin reuptake inhibitor	1997	-	Valvular heart disease
Phenylpropanolamine	NA-R and DA-R agonist	2000	-	Haemorrhagic stroke
Rimonabant	CB1R antagonist	2009	-	Psychiatric disorders, depression, suicidal ideation
Sibutramine	Serotonin-NA reuptake inhibitor	2010	-	Risk of major cardiovascular events

The pancreatic lipase inhibitor Orlistat and GLP-1 analogue liraglutide are the only currently UK licenced anti-obesity agents). 5HT2c: Serotonin receptor; NA: Noradrenaline; DA: Dopamine; CB1R: Cannabinoid receptor; R: Receptor; FDA: Food and Drug Administration; EMA: European Medical Association.

Yanetkiler ve guvenlik nedeniyle kullanimina son verilen antiobezite ilaclari

Antiobesity drug	FDA approval year	Approval withdrawn	Adverse effects
Amphetamines (dexamphetamine, methamphetamine)	1947	1979	Dependency, abuse potential
Fenfluramine and dexfenfluramine	1973	1997	Valvular abnormalities and pulmonary hypertension
Sibutramine	1997	2010	Increased CV events
Rimonabant	2006 (in Europe only)	2009 (in Europe only)	Anxiety, depression, and suicidal ideation

FDA onayli antiobezite ilaclariyla yapilmis etkinlik ve guvenilirlik calismalari

Medication	Trial	Duration (weeks)	Arms	Weight loss (%)	Most common adverse events (%)
Phentermine/ topiramate ER	EQUIP [18]	56	15/92 mg daily 3.75/23 mg daily placebo	10.9[a] 5.1[a] 1.6	18.8, 17.0, 14.1 4.2, 6.7, 7.9 1.9, 3.7, 6.8 (Paresthesia, dry mouth, constipation)
	CONQUER [19]	56	15/92 mg daily 7.5/46 mg daily placebo	9.8[a] 7.8[a] 1.2	21, 21, 17 13, 14, 15 2, 2, 6 (Dry mouth, paresthesia, constipation)
	SEQUEL [20]	108 (52-week extension of CONQUER trial)	15/92 mg daily 7.5/46 mg daily placebo	10.5[a] 9.3[a] 1.8 data from weeks 0–108	15.3, 9.5, 8.8 17.0, 7.8, 8.5 18.5, 7.9, 11.5 (URI, sinusitis, nasopharyngitis) data from weeks 56–108
Lorcaserin	BLOOM [21]	52	10 mg BID placebo	5.8[a] 2.2	18.0, 14.8, 13.4 11.0, 11.9, 12.0 (Headache, URI, nasopharyngitis)
	BLOSSOM [22]	52	10 mg BID 10 mg daily placebo	5.8[a] 4.7[a] 2.8	15.6, 12.7, 12.5 15.6, 14.6, 11.9 9.2, 12.6, 12.0 (Headache, URI, nasopharyngitis)
	BLOOM-DM [23]	52	10 mg BID 10 mg daily placebo	4.5[a] 5.0[a] 1.5	14.5, 11.7, 11.3 16.8, 8.4, 23.2 7.1, 7.9, 9.9 (Headache, back pain, nasopharyngitis)
Bupropion SR/ naltrexone SR	COR-I [24]	56	16/180 mg BID 8/180 mg BID placebo	6.1[a] 5.0[a] 1.3	29.8, 13.8, 15.7 27.2, 16.0, 15.8 5.3, 9.3, 5.6 (Nausea, headache, constipation)
	COR-II [25]	56	16/180 mg BID placebo	6.4[a] 1.2	29.2, 19.1, 17.5 6.9, 7.1, 8.7 (Nausea, constipation, headache)
	COR-BMOD [26]	56	16/180 mg BID placebo	9.3[a] 5.1	34.1, 23.8, 24.1 10.5, 17.5, 14.0 (Nausea, headache, constipation)
	COR-DIABETES [27]	56	16/180 mg BID placebo	5.0[a] 1.8	42.3, 17.7, 18.3 7.1, 7.1, 3.6 (Nausea, constipation, vomiting)
Liraglutide 3.0 mg	SCALE Obesity and Prediabetes [28]	56	3.0 mg daily placebo	8.0[a] 2.6	40.2, 20.9, 20.0 14.7, 9.3, 8.7 (Nausea, diarrhea, constipation)
	SCALE Diabetes [29]	56	3.0 mg daily 1.8 mg daily placebo	6[a] 4.7[a] 2.0	32.7, 25.6, 16.1 31.4, 17.6, 9.5 13.7, 12.7, 6.1 (Nausea, diarrhea, constipation)
	SCALE Maintain [30]	56 (after initial ≥5 % weight loss with LCD)	3.0 mg daily placebo	6.2[a] 0.2	47.6, 26.9, 17.9 17.1, 12.4, 12.4 (Nausea, constipation, diarrhea)

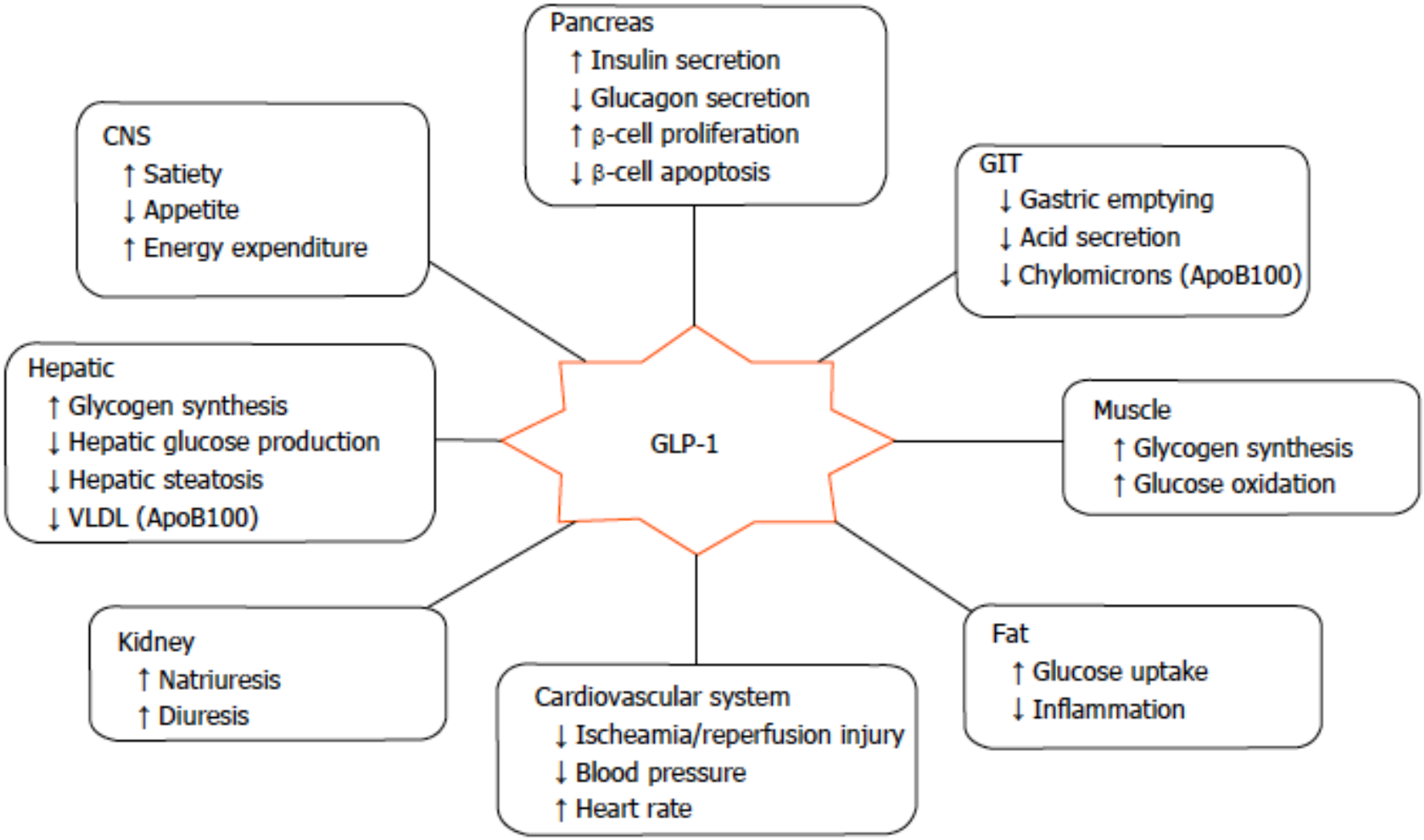
Table 2. Glucagon-like peptide-1 receptor agonists (GLP1-RAs) currently available for treatment of type 2 diabetes.

GLP1-RA (Brand name, manufacturer)	Approval year	Dose	Weight reduction	HbA1c reduction	CV outcome trial
Exenatide (Byetta®, AstraZeneca)	USA 2005, Europe 2006	5–10 µg twice daily	2–3 kg	0.8–1.5%	None
Liraglutide (Victoza®, Novo Nordisk)	USA 2010, Europe 2009	1.2–1.8 mg once daily	2–3 kg	1.1–1.8%	LEADER published
Exenatide LAR (Bydureon®, AstraZeneca)	USA 2012, Europe 2011	2 mg once weekly	2–3 kg	1.3–1.9%	EXSCEL
Lixisenatide (Lyxumia®, Sanofi)	USA – not approved, Europe 2013	10–20 µg once daily	1–3 kg	0.7–1.0%	ELIXA published
Albiglutide (Eperzan®/Tanzeum®, GlaxoSmithKline)	USA 2014, Europe 2014	30–50 mg once weekly	0–0.8 kg	0.8–1.1%	HARMONY
Dulaglutide (Trulicity®, Lilly)	USA 2014, Europe 2014	0.75–1.5 mg once weekly	0.4–3 kg	0.8–1.5%	REWIND

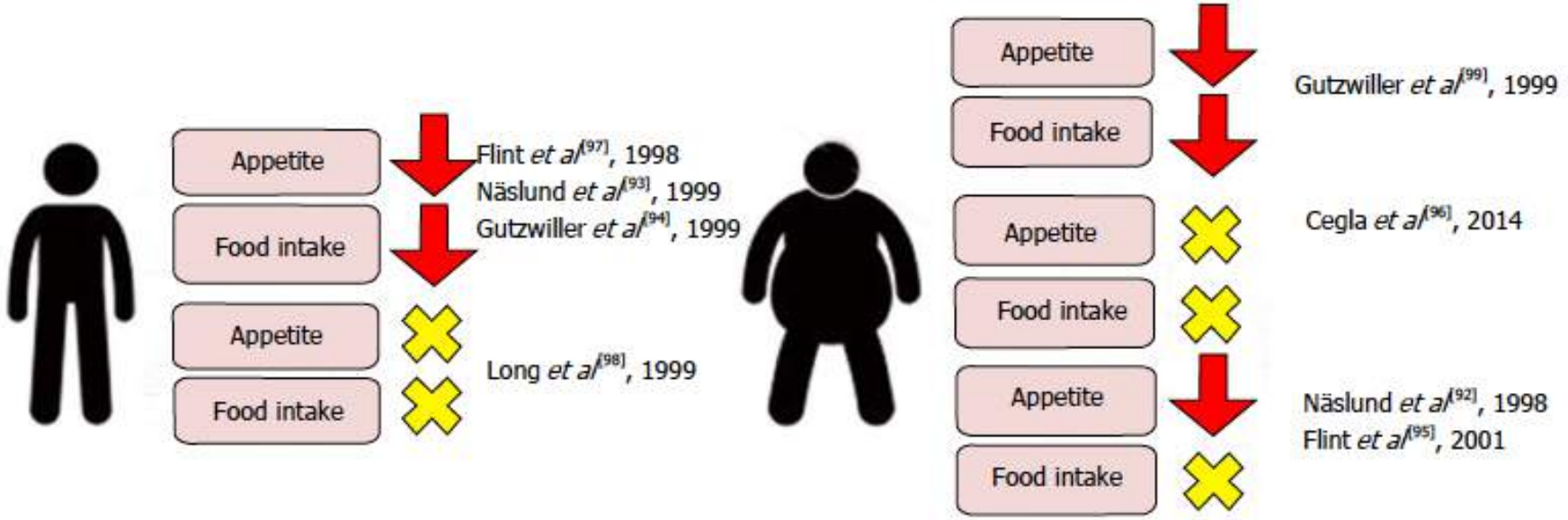
Table 3. Glucagon-like peptide-1 receptor agonists in active Phase II or III development.

GLP1-RA	Developer	Phase	Dosing route and frequency
ITCA 650	Intarcia	Phase III	Continuous subcutaneous pump release of exenatide 40–60 µg daily for up to 12 months
Semaglutide (NN9924/OG217SC)	Novo Nordisk	Phase III	Subcutaneous injection 0.5 mg or 1.0 mg weekly Daily oral dosing
Efpeglenatide (HM11260 C /langlenatide /LAPS-Exendin /LAPS-Exd4)	Hamni Pharmaceuticals	Phase II	Subcutaneous injection weekly or monthly
PB1023 (Glymera)	PhaseBio	Phase II	Subcutaneous injection weekly
TTP273	vTv Therapeutics (formerly TransTech Pharma)	Phase II	Oral daily

GLP 1 in Santral ve Periferik Etkileri



Metanaliz : GLP 1 akut infuzyonu **GIDA ALIMINDA** % 11.7 azalmaya neden olur
(GLP 1 vs Saline)



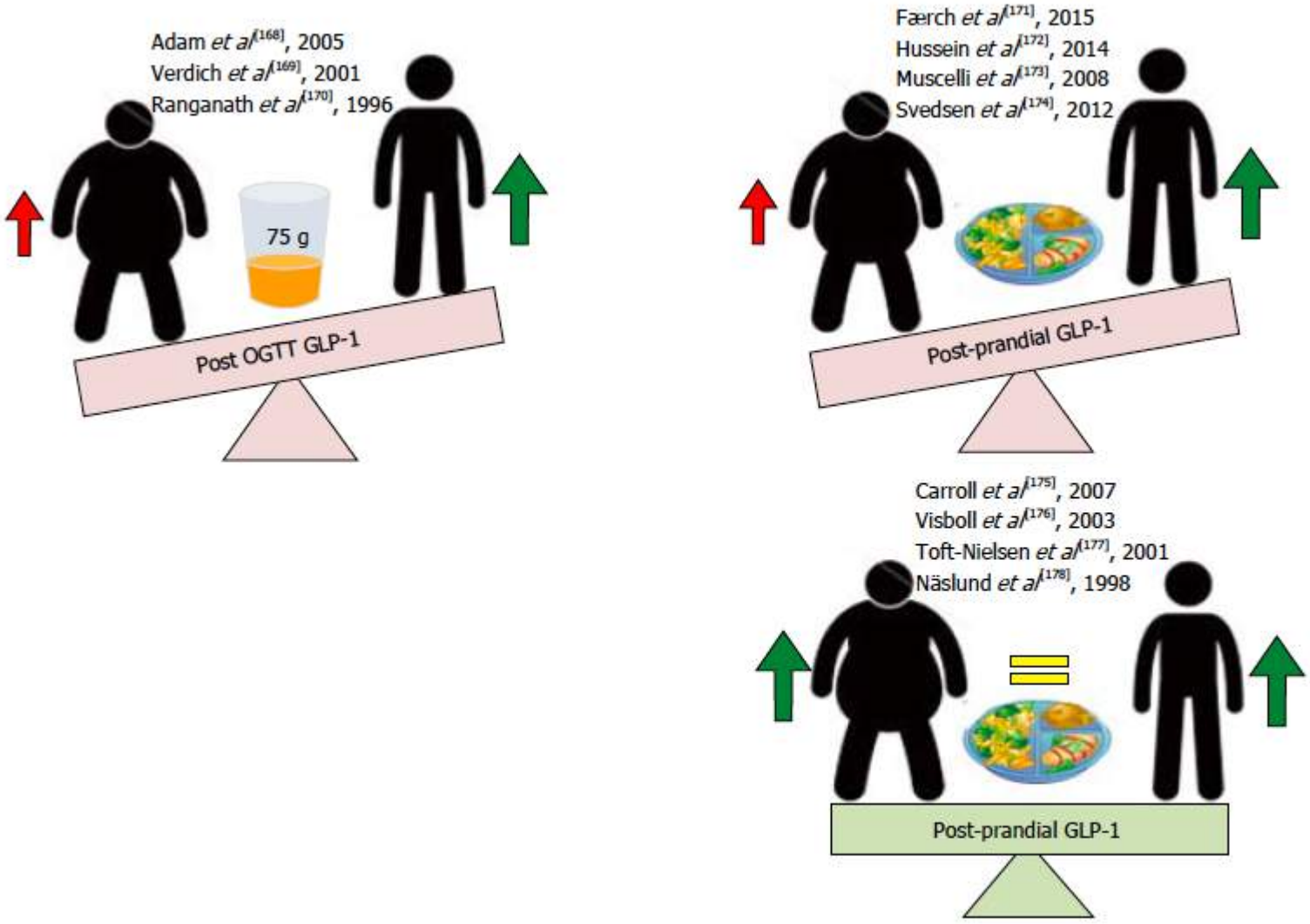
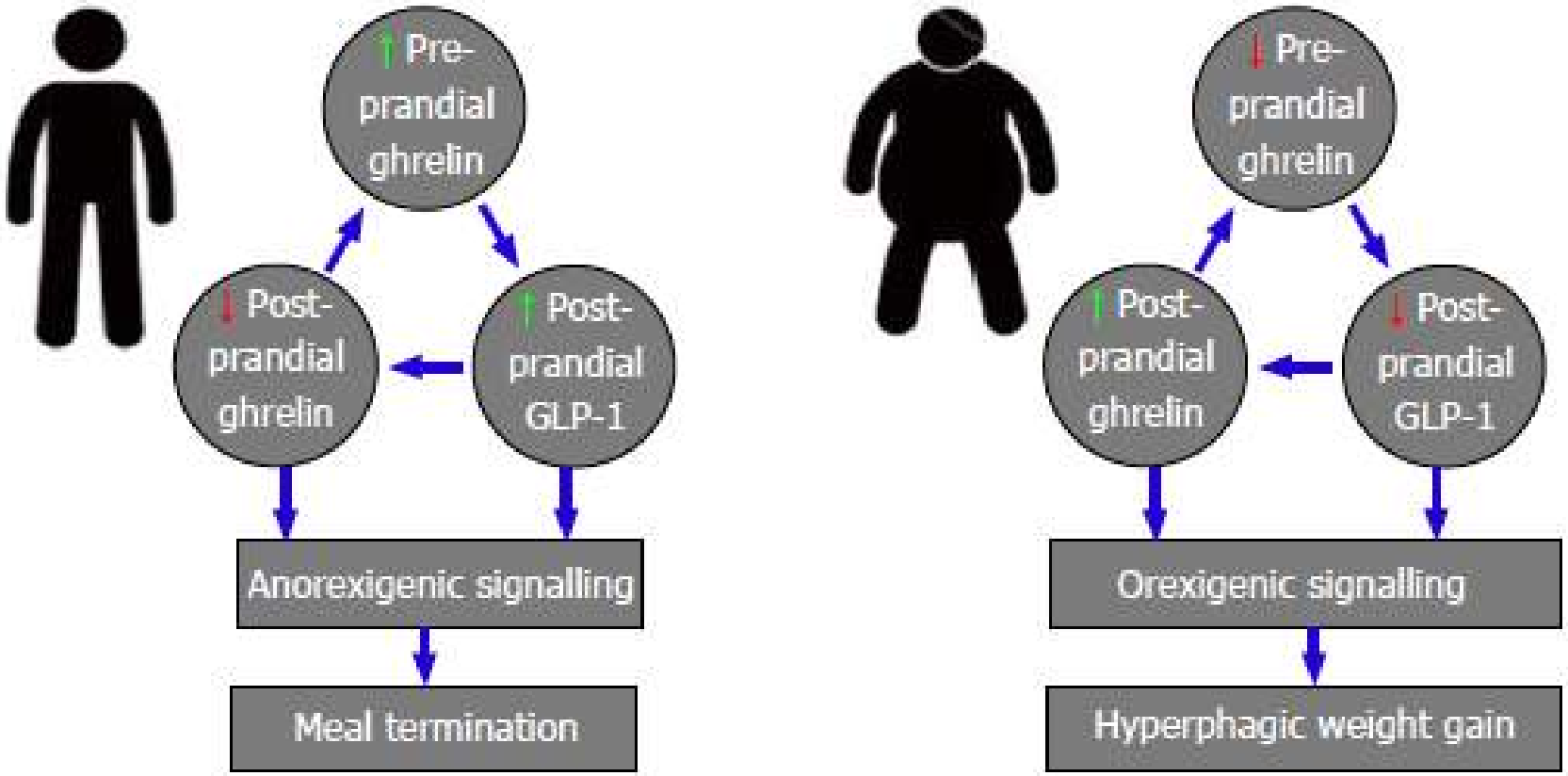
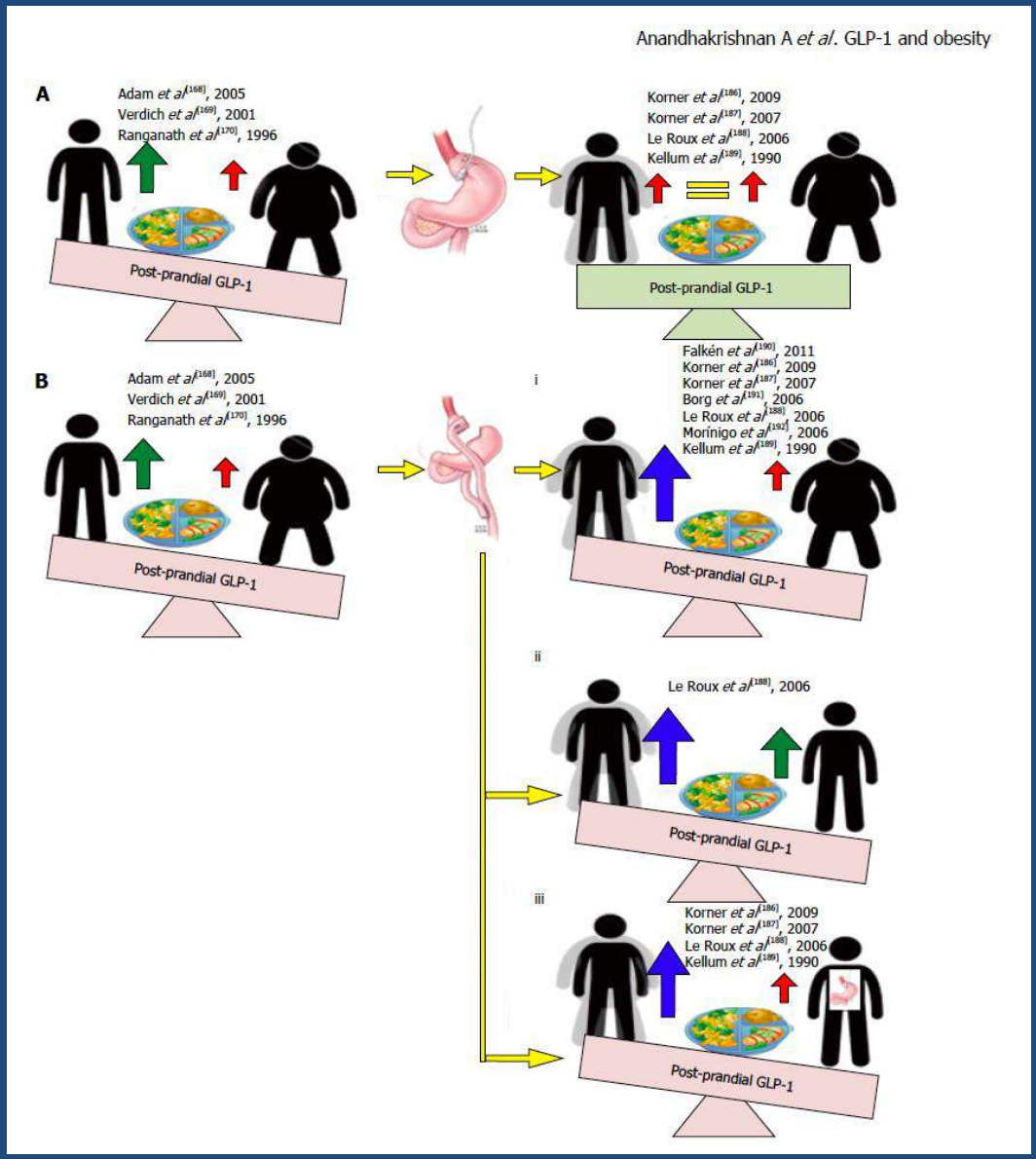


Figure 8 Effects of obesity on glucagon-like peptide 1 responses post oral glucose load and post-prandial. Obese subjects consistently demonstrate reduced glucagon-like peptide 1 (GLP-1) secretory responses following a 75-g oral glucose load compared to lean controls. Post-prandial GLP-1 secretory responses in obese subjects are conflicting, with some studies observing significant reductions and others observing no change[168-178] when compared to lean controls.

Normal ve sisman kisilerde Gherelin (orexigenic) ve GLP 1 (Anorexigenic) arasindaki fizyolojik ve patofizyolojik etkilesimler

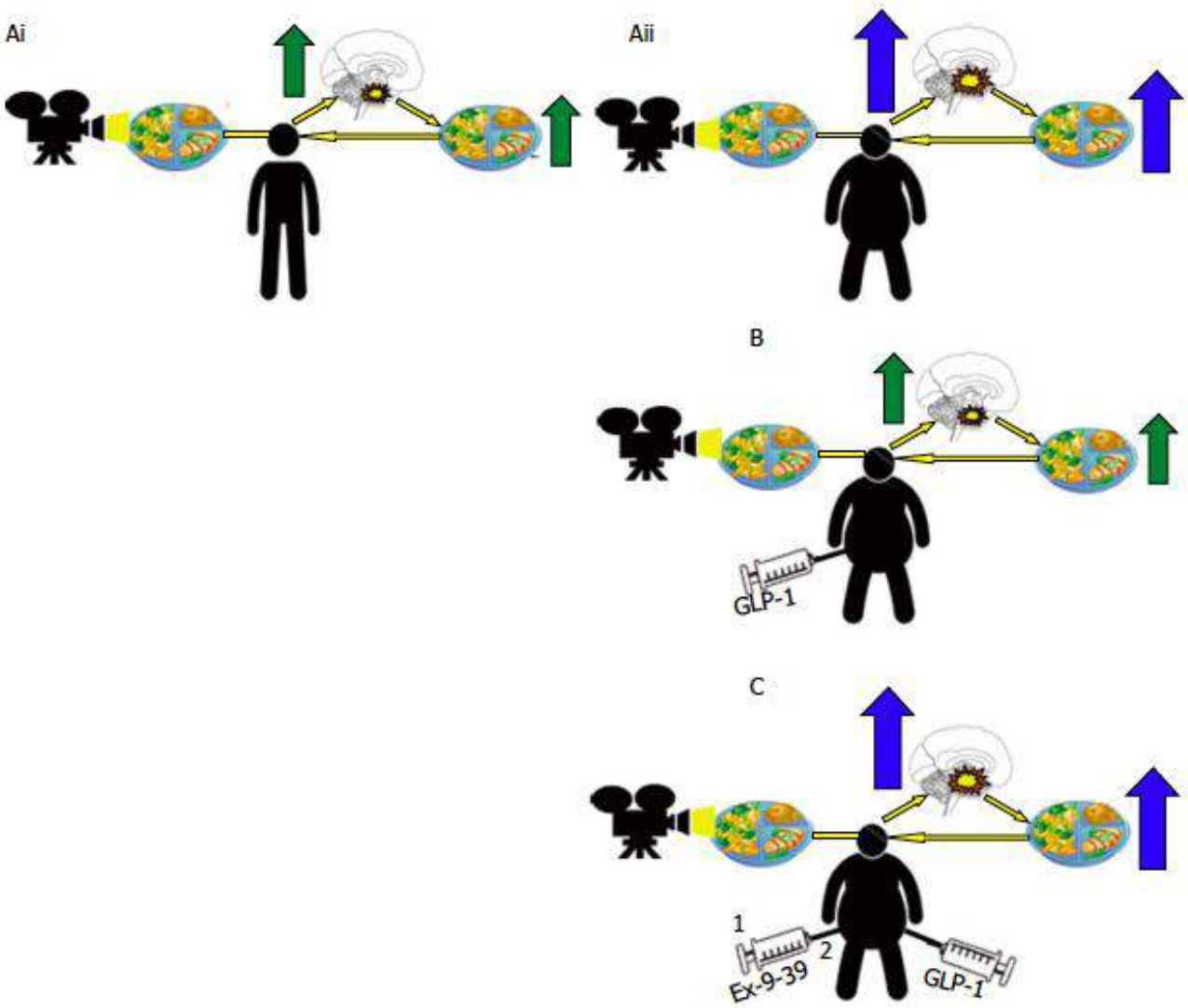


Gastric Banding ve RYGB in Postprandiyal GLP 1 'e etkileri



Obezlerde GLP 1 reseptor aktivasyonunun SSS uzerine etkileri Fonksiyonel MRI calismalari

Anandhakrishnan A *et al*. GLP-1 and obesity



International Journal of Obesity (2015) **39,** 834–841

www.nature.com/ijo

ORIGINAL ARTICLE

Treatment with a GLP-1 receptor agonist diminishes the decrease in free plasma leptin during maintenance of weight loss

EW Iepsen[1,2,3], J Lundgren[1,2,3], C Dirksen[2], J-EB Jensen[2], O Pedersen[1], T Hansen[1], S Madsbad[2], JJ Holst[1] and SS Torekov[1]

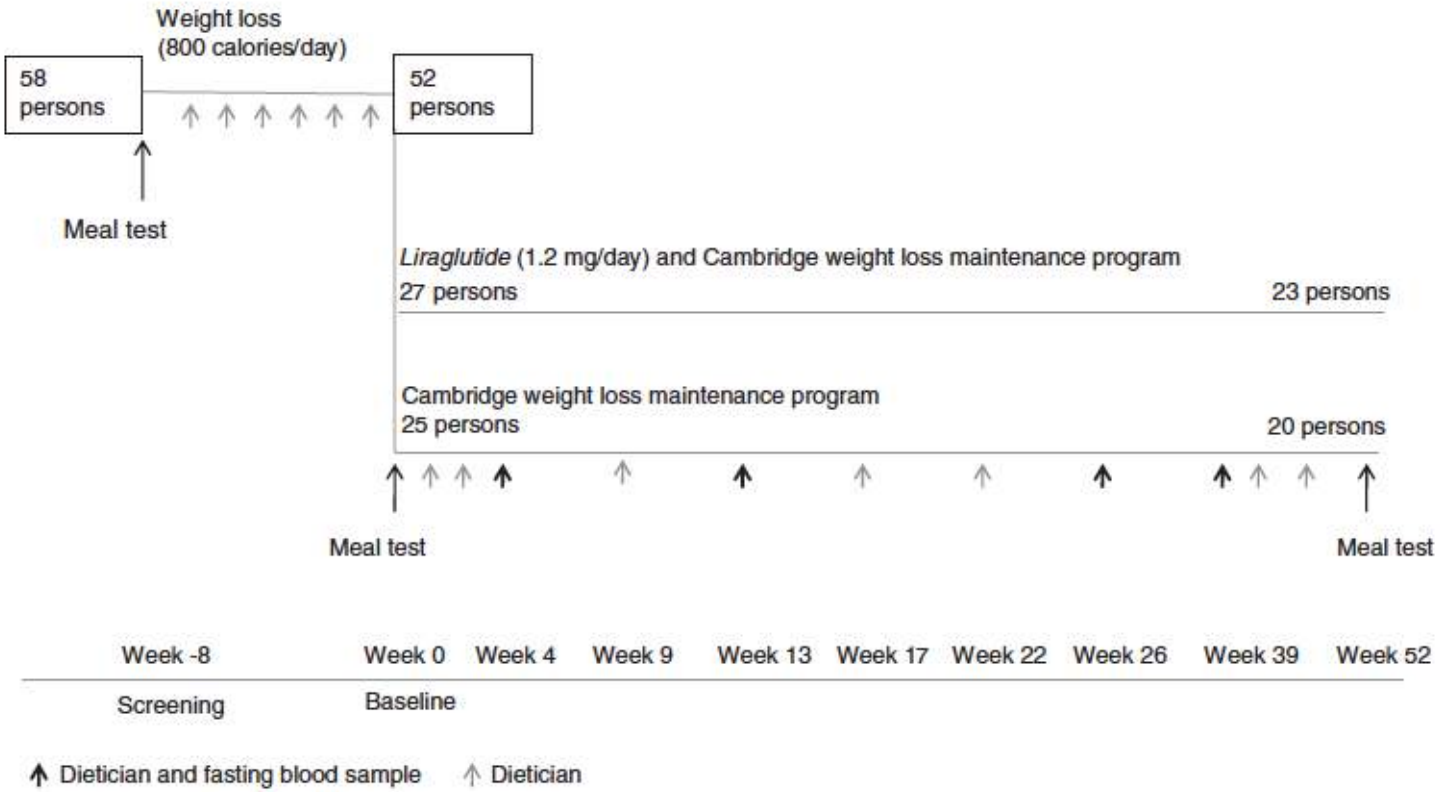


Figure 1. Study design.

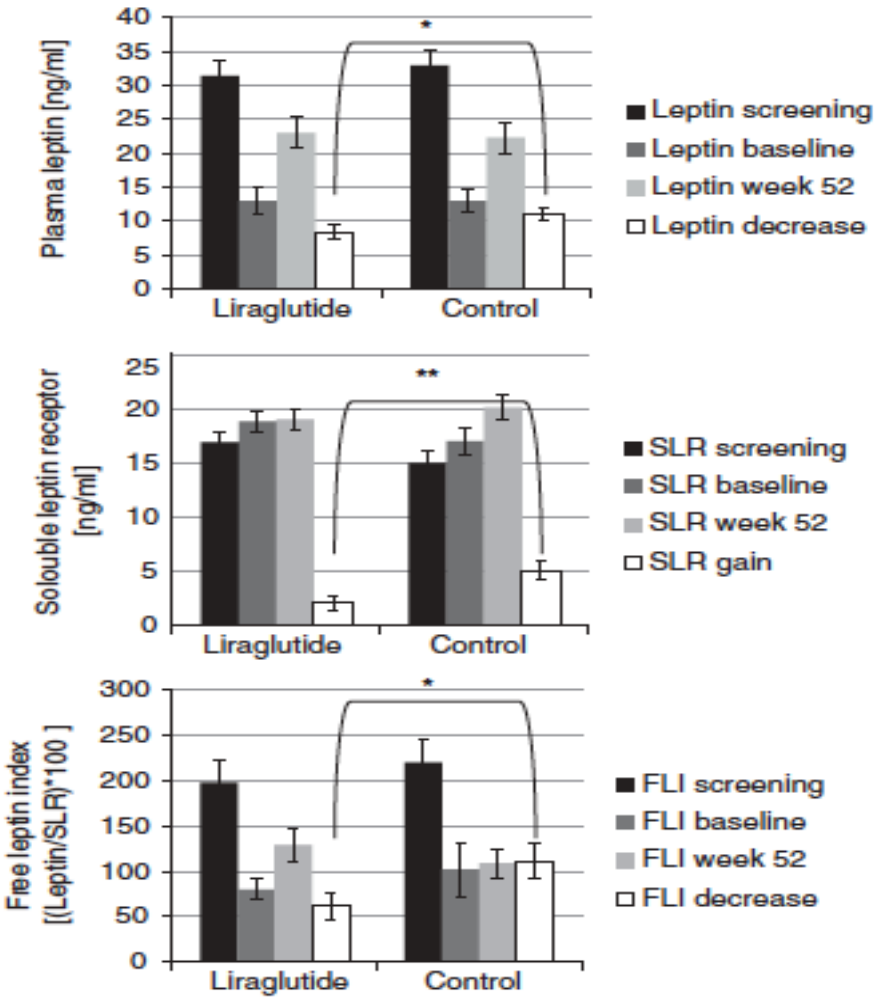
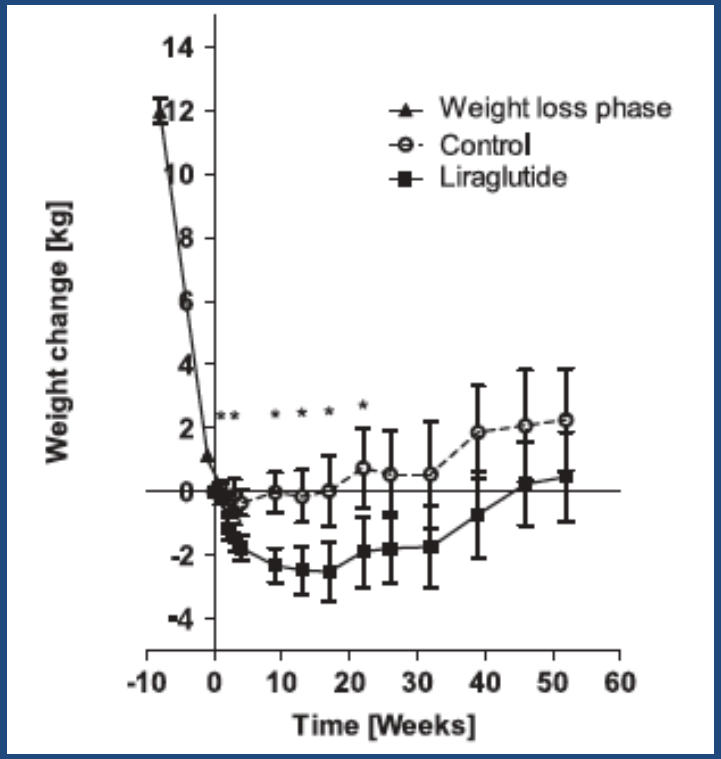
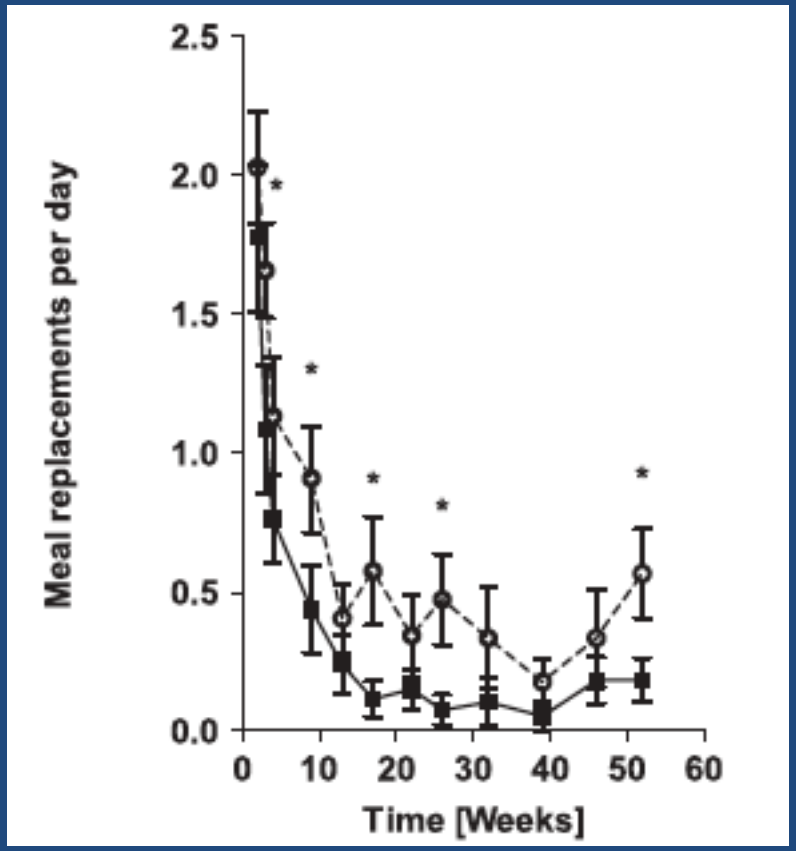
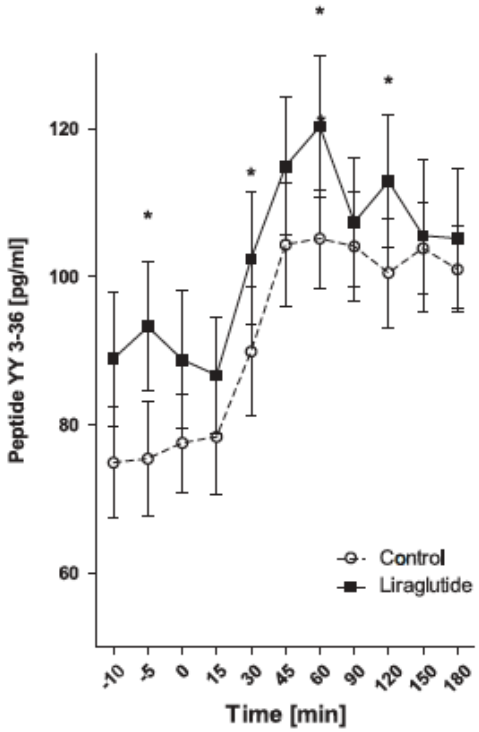
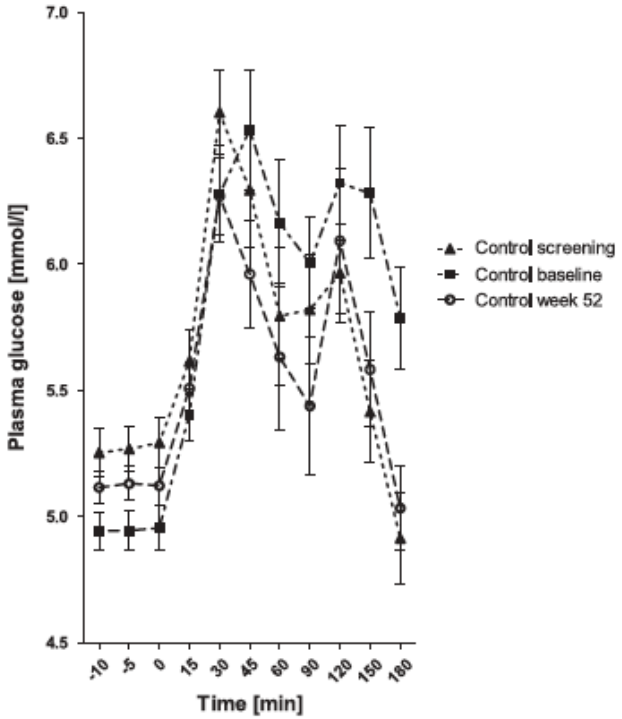


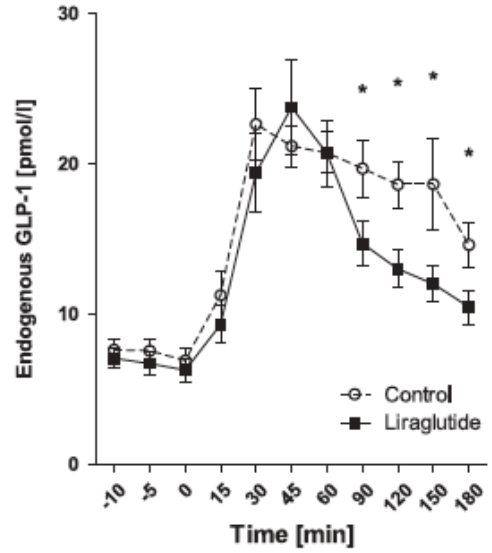
Figure 2. Change in plasma leptin, soluble leptin receptor (SLR) and free leptin index (FLI). Mean ± s.e.m., $*P < 0.05$, $**P < 0.005$.

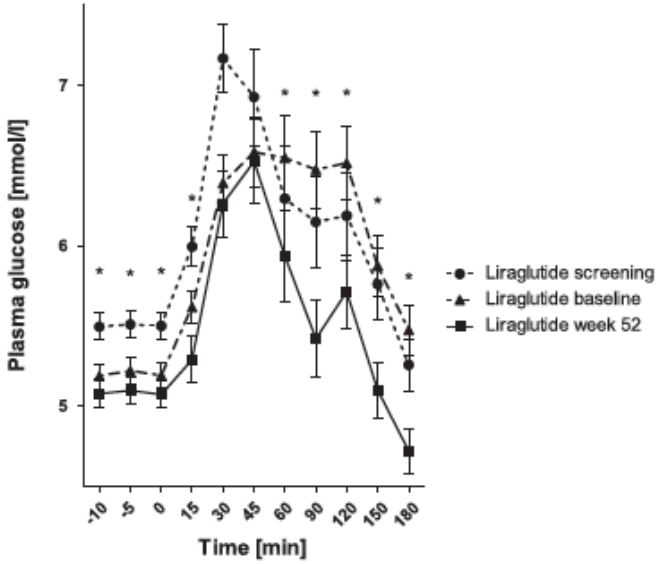

Weight loss phase
Control
Liraglutide
Weight change [kg]
Time [Weeks]
14
12
10
8
6
4
2
0
-2
-4
-10
0
10
20
30
40
50
60
**
*
*
*
*


Meal replacements per day
Time [Weeks]
2.5
2.0
1.5
1.0
0.5
0.0
0
10
20
30
40
50
60
*
*
*
*
*


Peptide YY 3-36 [pg/ml]
120
100
80
60
Control
Liraglutide
-10 -5 0 15 30 45 60 90 120 150 180
Time [min]


Plasma glucose [mmol/l]
7.0
6.5
6.0
5.5
5.0
4.5
Control screening
Control baseline
Control week 52
-10 -5 0 15 30 45 60 90 120 150 180
Time [min]


Endogenous GLP-1 [pmol/l]
30
20
10
0
Control
Liraglutide
-10 -5 0 15 30 45 60 90 120 150 180
Time [min]


Plasma glucose [mmol/l]
7
6
5
Liraglutide screening
Liraglutide baseline
Liraglutide week 52
-10 -5 0 15 30 45 60 90 120 150 180
Time [min]

LEADER - Primary and Secondary Outcomes.

Table 1. Primary and Secondary Outcomes.*

Outcome	Liraglutide (N=4668)	Incidence Rate	Placebo (N=4672)	Incidence Rate	Hazard Ratio (95% CI)	P Value
	no. of patients (%)	*no. of events/ 100 patient-yr*	*no. of patients (%)*	*no. of events/ 100 patient-yr*		
Primary composite outcome†	608 (13.0)	3.4	694 (14.9)	3.9	0.87 (0.78–0.97)	0.01
Expanded composite outcome‡	948 (20.3)	5.3	1062 (22.7)	6.0	0.88 (0.81–0.96)	0.005
Death from any cause	381 (8.2)	2.1	447 (9.6)	2.5	0.85 (0.74–0.97)	0.02
Death from cardiovascular causes	219 (4.7)	1.2	278 (6.0)	1.6	0.78 (0.66–0.93)	0.007
Death from noncardiovascular causes	162 (3.5)	0.9	169 (3.6)	1.0	0.95 (0.77–1.18)	0.66
Myocardial infarction§	292 (6.3)	1.6	339 (7.3)	1.9	0.86 (0.73–1.00)	0.046
Fatal§	17 (0.4)	0.1	28 (0.6)	0.2	0.60 (0.33–1.10)	0.10
Nonfatal	281 (6.0)	1.6	317 (6.8)	1.8	0.88 (0.75–1.03)	0.11
Silent§	62 (1.3)	0.3	76 (1.6)	0.4	0.86 (0.61–1.20)	0.37
Stroke§	173 (3.7)	1.0	199 (4.3)	1.1	0.86 (0.71–1.06)	0.16
Fatal§	16 (0.3)	0.1	25 (0.5)	0.1	0.64 (0.34–1.19)	0.16
Nonfatal	159 (3.4)	0.9	177 (3.8)	1.0	0.89 (0.72–1.11)	0.30
Transient ischemic attack§	48 (1.0)	0.3	60 (1.3)	0.3	0.79 (0.54–1.16)	0.23
Coronary revascularization	405 (8.7)	2.3	441 (9.4)	2.5	0.91 (0.80–1.04)	0.18
Hospitalization for unstable angina pectoris	122 (2.6)	0.7	124 (2.7)	0.7	0.98 (0.76–1.26)	0.87
Hospitalization for heart failure	218 (4.7)	1.2	248 (5.3)	1.4	0.87 (0.73–1.05)	0.14
Microvascular event	355 (7.6)	2.0	416 (8.9)	2.3	0.84 (0.73–0.97)	0.02
Retinopathy	106 (2.3)	0.6	92 (2.0)	0.5	1.15 (0.87–1.52)	0.33
Nephropathy	268 (5.7)	1.5	337 (7.2)	1.9	0.78 (0.67–0.92)	0.003

* Hazard ratios and P values were estimated with the use of a Cox proportional-hazards model with treatment as a covariate.
† The primary composite outcome in the time-to-event analysis consisted of the first occurrence of death from cardiovascular causes (181 patients in the liraglutide group vs. 227 in the placebo group), nonfatal (including silent) myocardial infarction (275 vs. 304), or nonfatal stroke (152 vs. 163). The P value is for superiority.
‡ The expanded composite outcome included death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina pectoris or heart failure.
§ This analysis was not prespecified.

Marso SP et al. N Engl J Med 2016;375:311-322

The NEW ENGLAND JOURNAL of MEDICINE

Original Investigation

Efficacy of Liraglutide for Weight Loss Among Patients With Type 2 Diabetes

The SCALE Diabetes Randomized Clinical Trial

Melanie J. Davies, MD; Richard Bergenstal, MD; Bruce Bode, MD; Robert F. Kushner, MD; Andrew Lewin, MD; Trine Vang Skjøth, MD; Arne Haahr Andreasen, MSc; Christine Bjørn Jensen, MD; Ralph A. DeFronzo, MD; for the NN8022-1922 Study Group

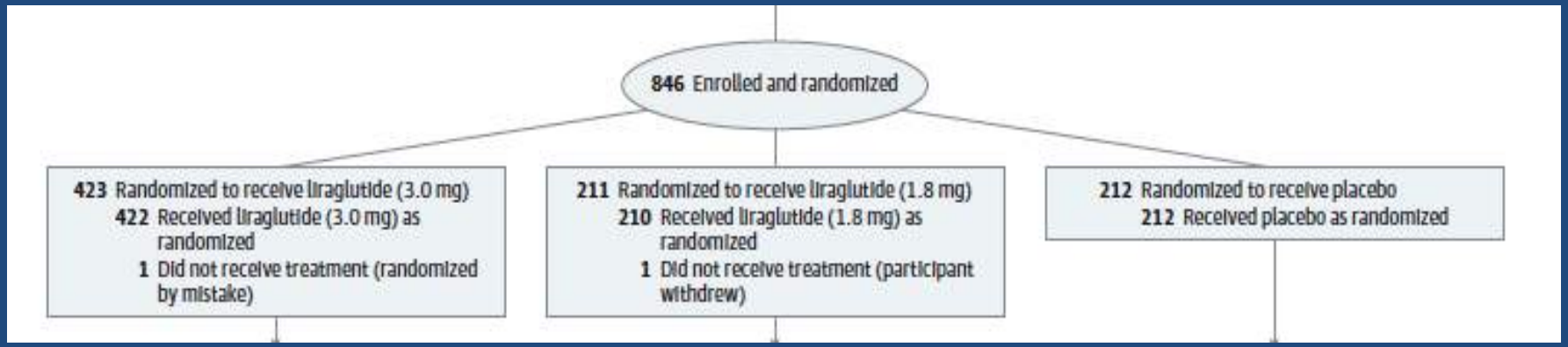
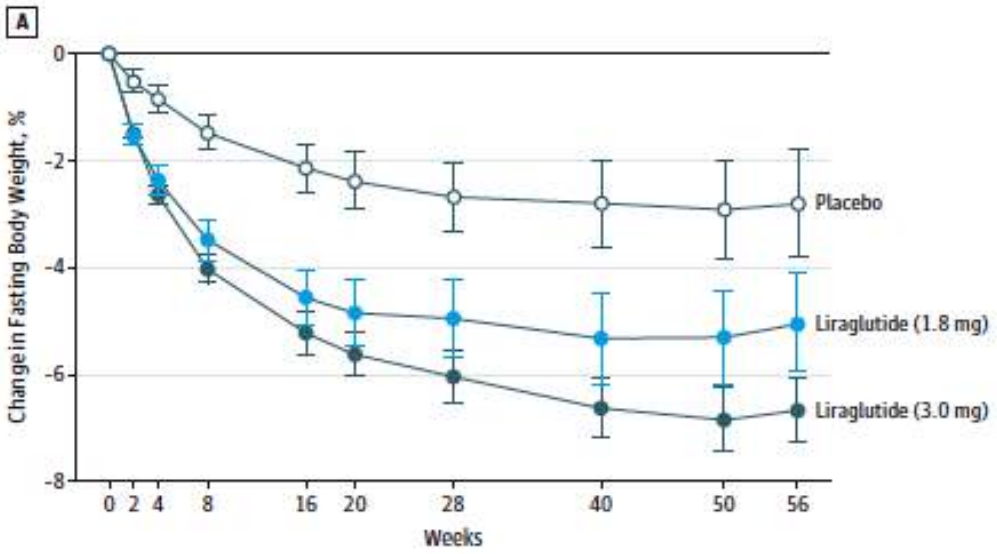
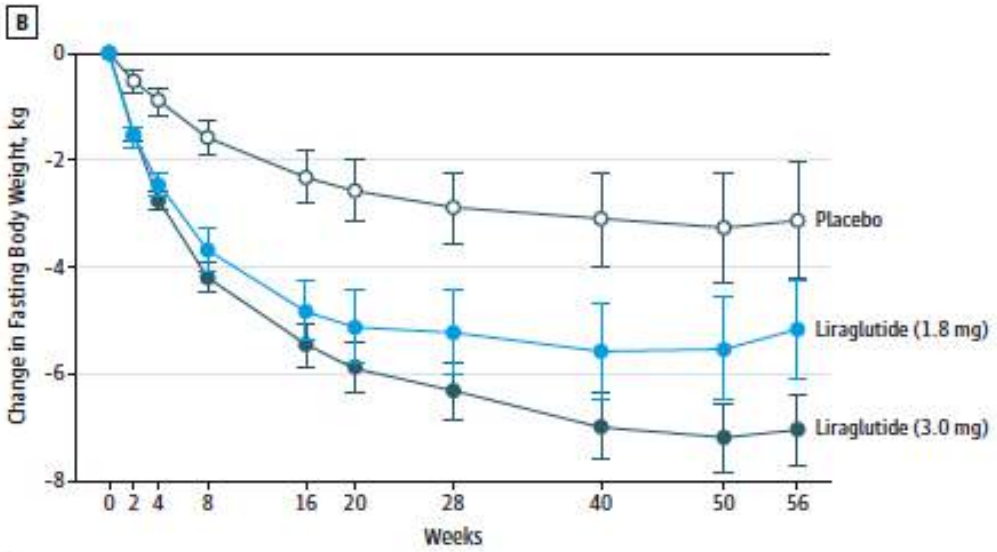


Table 1. Baseline Demographic Characteristics and Secondary Efficacy End Points

	No. (%)		
	Liraglutide		
	3.0 mg	1.8 mg	Placebo
Demographic Characteristics[a]			
Patients, No.	423	211	212
Age, mean (SD), y	55.0 (10.8)	54.9 (10.7)	54.7 (9.8)
Women	203 (48.0)	103 (48.8)	115 (54.2)
Body weight, mean (SD), kg	105.7 (21.9)	105.8 (21.0)	106.5 (21.3)
Body mass index, mean (SD)[c]	37.1 (6.5)	37.0 (6.9)	37.4 (7.1)
Body mass index group[c]			
25.0-29.9 (preobese)	52 (12.3)	34 (16.1)	30 (14.2)
30.0-34.9 (obese class I)	139 (32.9)	62 (29.4)	59 (27.8)
35.0-39.9 (obese class II)	108 (25.5)	50 (23.7)	60 (28.3)
>40.0 (obese class III)	124 (29.3)	65 (30.8)	63 (29.7)
Waist circumference, mean (SD), cm	118.0 (14.4)	117.5 (14.7)	117.3 (14.0)
Duration of diabetes, mean (SD), y	7.5 (5.65)	7.4 (5.16)	6.7 (5.07)

Figure 2. Time Course of Body Weight Loss From Baseline to Week 56 for Liraglutide (3.0 mg), Liraglutide (1.8 mg), and Placebo





No. of patients									
Placebo	211	205	193	165	154	137	124	116	116
Liraglutide (1.8 mg)	204	192	182	179	176	172	165	160	158
Liraglutide (3.0 mg)	412	400	385	365	352	337	329	320	317

3mg.=%6, 6.4kg

1.8mg=%4.7,5kg

Plc= %2.0,2.2kg

Table 2. Summary of Coprimary Efficacy End Points at Week 56[a]

End Point	Baseline Value, Full Analysis Set, Mean (SD), kg	Mean and Categorical Weight Loss at Week 56			Estimated Treatment Difference/Risk Difference (95% CI)			
		Liraglutide			Liraglutide			
		3.0 mg (n = 412)	1.8 mg (n = 204)	Placebo (n = 211)	3.0 mg vs Placebo	*P* Value	1.8 mg vs Placebo	*P* Value
Change from baseline, fasting body weight, %	106.0 (21.5)	-6.0	-4.7	-2.0	−4.00 (-5.10 to -2.90)	<.001	-2.71 (-4.00 to -1.42)	<.001
Observed means, %[b]	106.0 (21.5)	-5.9	-4.6	-2.0	NA	NA	NA	NA
Weight loss ≥5%, %	NA	54.3[c]	40.4[c]	21.4[c]	32.9 (24.6 to 41.2)	<.001	19.0 (9.1 to 28.8)	<.001
Observed proportions, No. (%)[b]	NA	205 (49.9)	72 (35.6)	29 (13.8)	NA	NA	NA	NA
Weight loss, >10%, %	NA	25.2[c]	15.9[c]	6.7[c]	18.5 (12.7 to 24.4)	<.001	9.3 (2.7 to 15.8)	.006
Observed proportions, No. (%)[b]	NA	96 (23.4)	29 (14.4)	9 (4.3)	NA	NA	NA	NA

Table 3. Summary of Secondary Efficacy End Points At Week 56[a]

End Point	Change From Baseline to Week 56 or Percentage At Week 56			Estimate (95% CI)				
	Liraglutide				Liraglutide			
	3.0 mg (n = 411)	1.8 mg (n = 204)	Placebo (n = 211)	Estimate Type	3.0 mg vs Placebo	*P* Value	1.8 mg vs Placebo	*P* Value
Waist circumference, mean (SD), cm[b]	-6.1 (6.5)	-4.8 (5.6)	-2.7 (5.4)	Treatment difference	-3.22 (-4.20 to -2.23)	<.001	-2.06 (-3.20 to -0.92)	<.001
Body mass index, mean (SD)[b,c]	-2.2 (2.1)	-1.7 (2.1)	-0.8 (1.7)	Treatment difference	-1.50 (-1.83 to -1.18)	<.001	-0.95 (-1.33 to -0.57)	<.001
HbA_{1c}, mean (SD), % change[b]	-1.3 (0.9)	-1.1 (1.0)	-0.3 (0.9)	Treatment difference	-0.93 (-1.08 to -0.78)	<.001	-0.74 (-0.91 to -0.57)	<.001
No. of individuals achieving HbA_{1c} target, No. %[d]								
<7.0 %	278 (69.2)	130 (66.7)	56 (27.2)	Odds ratio	8.79 (5.74 to 13.44)	<.001	7.71 (4.76 to 12.51)	<.001
≤6.5 %	227 (56.5)	89 (45.6)	31 (15.0)	Odds ratio	9.61 (6.05 to 15.26)	<.001	5.98 (3.59 to 9.97)	<.001
Fasting plasma glucose, mean (SD), mg/dL[b]	-34.3 (38.5)	-26.8 (50.3)	-0.2 (37.0)	Treatment difference	-31.89 (-38.02 to-25.59)	<.001	-23.06 (-30.27 to -15.86)	<.001
PPG increment, mean (SD), mg/dL[b]	-16.2 (37.8)	-12.6 (37.8)	-5.4 (36.0)	Treatment difference	-9.91 (-15.14 to -4.68)	<.001	-7.93 (-13.87 to -1.98)	.009
C-peptide	3.3 (53.4)	2.4 (34.0)	-2.4 (28.5)	Ratio	1.04 (0.98 to 1.10)	.17	1.03 (0.97 to 1.10)	.29
Proinsulin to insulin ratio	-38.4 (64.4)	-31.6 (87.1)	-2.2 (176.0)	Ratio	0.63 (0.58 to 0.69)	<.001	0.72 (0.64 to 0.79)	<.001
HOMA-B, geometric mean (CV), %[e]	94.3 (419.0)	72.3 (55.1)	9.1 (57.0)	Ratio	1.71 (1.52 to 1.92)	<.001	1.53 (1.34 to 1.74)	<.001
HOMA-IR, geometric mean (CV), %[e]	-20.0 (76.7)	-10.5 (79.4)	-3.3 (79.5)	Ratio	0.84 (0.75 to 0.94)	.003	0.93 (0.82 to 1.07)	.32

End Point	3.0 mg (n = 411)	1.8 mg (n = 204)	Placebo (n = 211)	Estimate Type	3.0 mg vs Placebo	P Value	1.8 mg vs Placebo	P Value
Cardiovascular biomarkers[a]								
hsCRP, geometric mean (CV), %	-33.51 (141.0)	-33.34 (119.0)	-10.45 (125.0)	Ratio	0.73 (0.64 to 0.83)	<.001	0.75 (0.65 to 0.88)	<.001
Adiponectin, geometric mean (CV), %	6.6 (1848.0)	3.5 (90.3)	1.3 (35.5)	Ratio	1.06 (0.98 to 1.15)	.17	1.07 (0.97 to 1.18)	.18
Fibrinogen, geometric mean (CV), %	4.54 (32.2)	1.68 (35.8)	-3.11 (33.9)	Ratio	1.05 (1.00 to 1.09)	.046	1.04 (0.98 to 1.09)	.18
PAI-1	NA	NA	NA		0.76 (0.66 to 0.89)	<.001	0.84 (0.71 to 1.00)	.06
Lipid profile[a]								
Cholesterol, geometric mean (CV), %								
Total	-1.46 (16.9)	-2.20 (20.2)	3.80 (16.2)	Ratio	0.96 (0.94to 0.99)	.01	0.97 (0.94 to 1.00)	.06
HDL	4.70 (16.1)	4.45 (14.2)	1.93 (14.3)	Ratio	1.03 (1.00 to 1.05)	.03	1.02 (0.99 to 1.05)	.16
LDL	0.58 (38.8)	-3.07 (30.5)	5.02 (27.3)	Ratio	0.98 (0.93 to 1.03)	.36	0.95 (0.90 to 1.01)	.10
VLDL	-14.10 (43.0)	-8.14 (41.7)	0.53 (35.5)	Ratio	0.87 (0.81 to 0.93)	<.001	0.94 (0.87 to 1.01)	.09
Triglycerides, geometric mean (CV), %	-14.68 (46.9)	-9.45 (47.9)	0.41 (40.5)	Ratio	0.86 (0.80 to 0.92)	<.001	0.93 (0.86 to1.01)	.07
Free fatty acids, geometric mean (CV), %	-13.57 (157.0)	-11.66 (60.6)	-9.02 (42.6)	Ratio	0.94 (0.88 to 1.01)	.10	0.95 (0.88 to1.03)	.22

Change in net use of concomitant oral hypoglycemic agents, No. (% patients)[f]								
Decrease	54 (13.1)	17 (8.3)	12 (5.7)					
Increase	21 (5.1)	19 (9.3)	57 (27.0)	Odds ratio	5.63 (3.62 to 8.76)	<.001	3.36 (2.07 to 5.47)	<.001
No change	337 (81.8)	168 (82.4)	142 (67.3)					
IWQoL-Lite score, mean (SD)								
Physical function	15.16 (18.02)	12.50 (17.30)	8.92 (16.13)	Treatment difference	4.92 (2.12 to 7.71)	<.001	2.64 (-0.59 to 5.88)	.11
Self esteem	12.48 (19.31)	9.80 (17.67)	9.61 (18.63)	Treatment difference	1.51 (-1.37 to 4.39)	.30	0.01 (-3.32 to 3.34)	>.99
Sexual life	9.22 (23.72)	6.90 (21.70)	7.78 (21.86)	Treatment difference	-0.70 (-4.27 to 2.88)	.70	-2.03 (-6.16 to 2.11)	.34
Public distress	7.06 (16.94)	4.84 (14.06)	4.11 (12.57)	Treatment difference	1.64 (-0.61 to 3.89)	.15	0.00 (-2.60 to 2.60)	>.99
Work	8.80 (17.23)	5.48 (16.56)	5.45 (15.77)	Treatment difference	1.54 (-0.76 to 3.85)	.19	-1.06 (-3.73 to 1.61)	.44
Total score	11.68 (14.67)	9.07 (14.05)	7.58 (12.57)	Treatment difference	2.75 (0.57 to 4.93)	.01	0.78 (-1.74 to 3.31)	.54
DTSQ, mean (SD)								
Total score	4.15 (7.61)	3.89 (7.62)	2.32 (7.03)	Treatment difference	1.44 (0.40 to 2.48)	.007	1.14 (-0.07 to 2.34)	.06

International Journal of Obesity (2013), 1–9

www.nature.com/ijo

ORIGINAL ARTICLE

Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: The Scale Maintenance randomized study

TA Wadden[1], P Hollander[2], S Klein[3], K Niswender[4], V Woo[5], PM Hale[6] and L Aronne[7] on behalf of the NN8022-1923 Investigators[8]

OBJECTIVE: Liraglutide, a once-daily human glucagon-like peptide-1 analog, induced clinically meaningful weight loss in a phase 2 study in obese individuals without diabetes. The present randomized phase 3 trial assessed the efficacy of liraglutide in maintaining weight loss achieved with a low-calorie diet (LCD).

METHODS: Obese/overweight participants (⩾18 years, body mass index ⩾30 kg m^{-2} or ⩾27 kg m^{-2} with comorbidities) who lost ⩾5% of initial weight during a LCD run-in were randomly assigned to liraglutide 3.0 mg per day or placebo (subcutaneous administration) for 56 weeks. Diet and exercise counseling were provided throughout the trial. Co-primary end points were percentage weight change from randomization, the proportion of participants that maintained the initial ⩾5% weight loss, and the proportion that lost ⩾5% of randomization weight (intention-to-treat analysis). ClinicalTrials.gov identifier: NCT00781937.

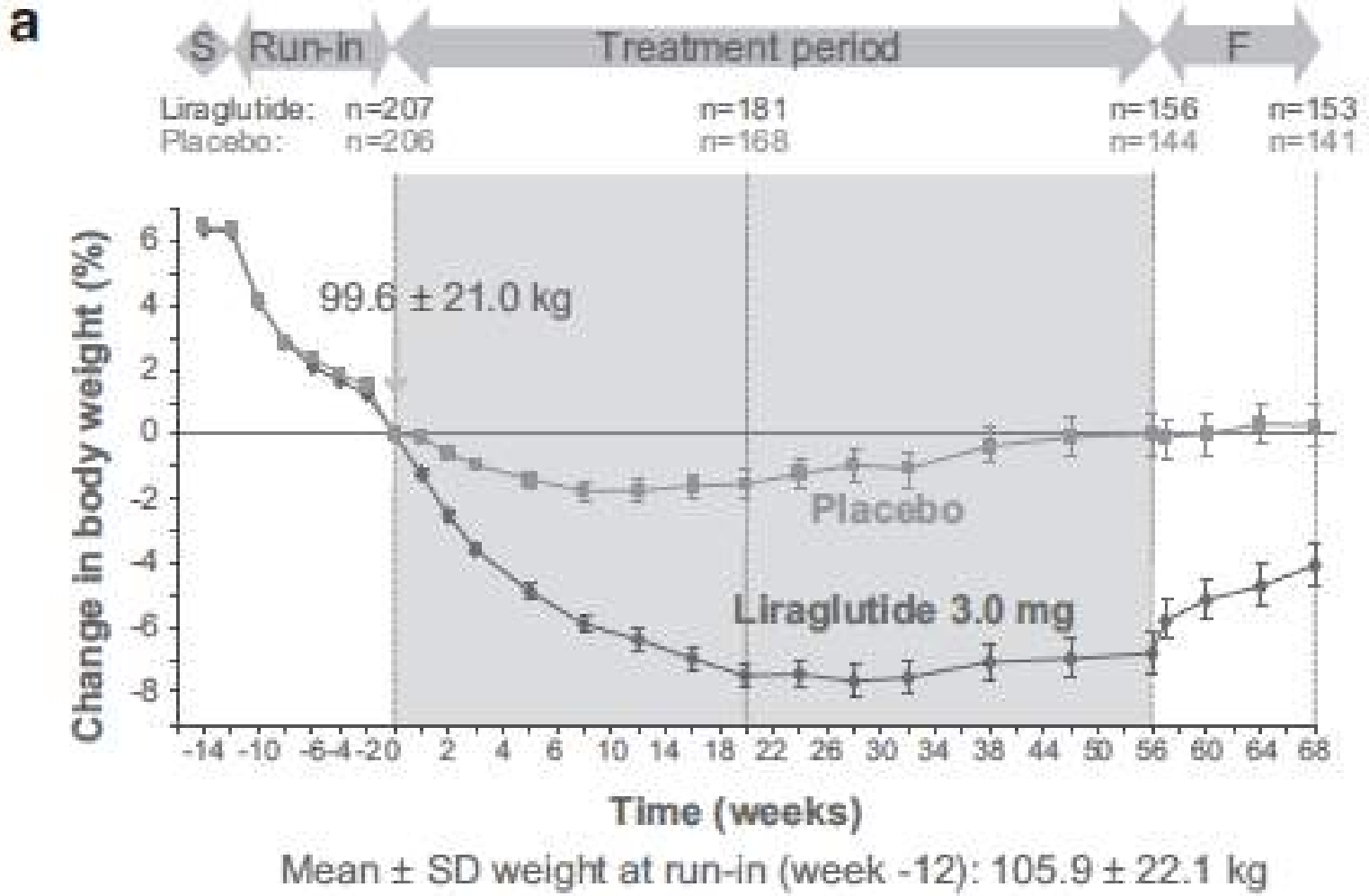

a
S
Run-in
Treatment period
F
Liraglutide: n=207 n=181 n=156 n=153
Placebo: n=206 n=168 n=144 n=141
99.6 ± 21.0 kg
Placebo
Liraglutide 3.0 mg
Change in body weight (%)
6
4
2
0
-2
-4
-6
-8
-14 -10 -6 -4 -2 0 2 4 6 10 14 18 22 26 30 34 38 44 50 56 60 64 68
Time (weeks)
Mean ± SD weight at run-in (week -12): 105.9 ± 22.1 kg

Table 3. Changes in body weight measures from randomization

	Change from randomization to week 56		*ETD or OR for liraglutide versus placebo (95% CI), P-value*
	Liraglutide 3.0 mg (n = 207)	*Placebo (n = 206)*	
Co-primary end points			
Body weight (% change)	−6.2 (7.3)	−0.2 (7.0)	ETD = −6.1 (−7.5 to −4.6), $P<0.0001$
Proportion maintaining >5% run-in weight loss	81.4%	48.9%	OR = 4.8 (3.0 to 7.7), $P<0.0001$
Proportion with >5% weight loss	50.5%	21.8%	OR = 3.9 (2.4 to 6.1), $P<0.0001$
Secondary end points			
Body weight (kg)	−6.0 (7.3)	−0.1 (6.9)	ETD = −5.9 (−7.3 to −4.4), $P<0.0001$
Proportion with >10% weight loss	26.1%	6.3%	OR = 5.3 (2.8 to 10.1), $P<0.0001$
BMI (kg m^{-2})	−2.1 (2.6)	−0.0 (2.3)	ETD = −2.1 (−2.5 to −1.6), $P<0.0001$
Waist circumference (cm)	−4.7 (7.4)	−1.2 (6.4)	ETD = −3.5 (−4.8 to −2.2), $P<0.0001$
	Change from randomization to week 68 (follow-up) for participants entering follow-up		*ETD for liraglutide versus placebo (95% CI), P-value*
	(n = 159)	*(n = 144)*	
Body weight (% change)	−4.1 (8.2)	0.3 (7.7)	−4.2 (−6.0 to −2.4), $P<0.0001$

Abbreviations: BMI, body mass index; CI, confidence intervals; ETD, estimated treatment difference; OR, odds ratio. Changes from randomization to week 56 or 68 are observed means (s.d.). ETDs are from an analysis of covariance and OR are from a logistic regression analysis, all using the full analysis set and with the last observation carried forward, except for percentage weight-loss data at week 68, which was without last observation carried forward. Body weight was measured in the fasting state.

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A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management

Xavier Pi-Sunyer, M.D., Arne Astrup, M.D., D.M.Sc., Ken Fujioka, M.D., Frank Greenway, M.D., Alfredo Halpern, M.D., Michel Krempf, M.D., Ph.D., David C.W. Lau, M.D., Ph.D., Carel W. le Roux, F.R.C.P., Ph.D., Rafael Violante Ortiz, M.D., Christine Bjørn Jensen, M.D., Ph.D., and John P.H. Wilding, D.M., for the SCALE Obesity and Prediabetes NN8022-1839 Study Group*

3731 Diyabeti Olmayan Obez Hasta
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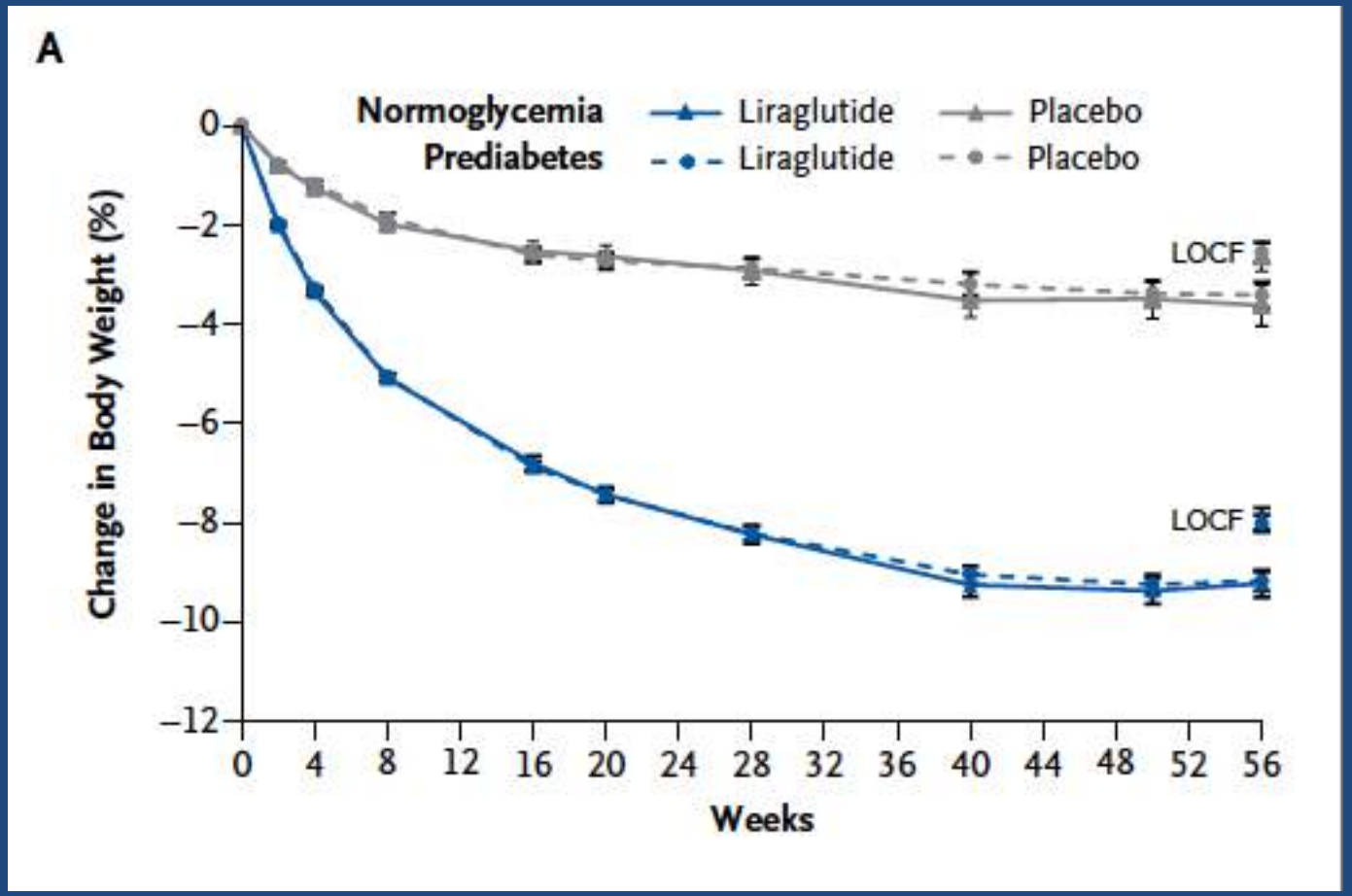
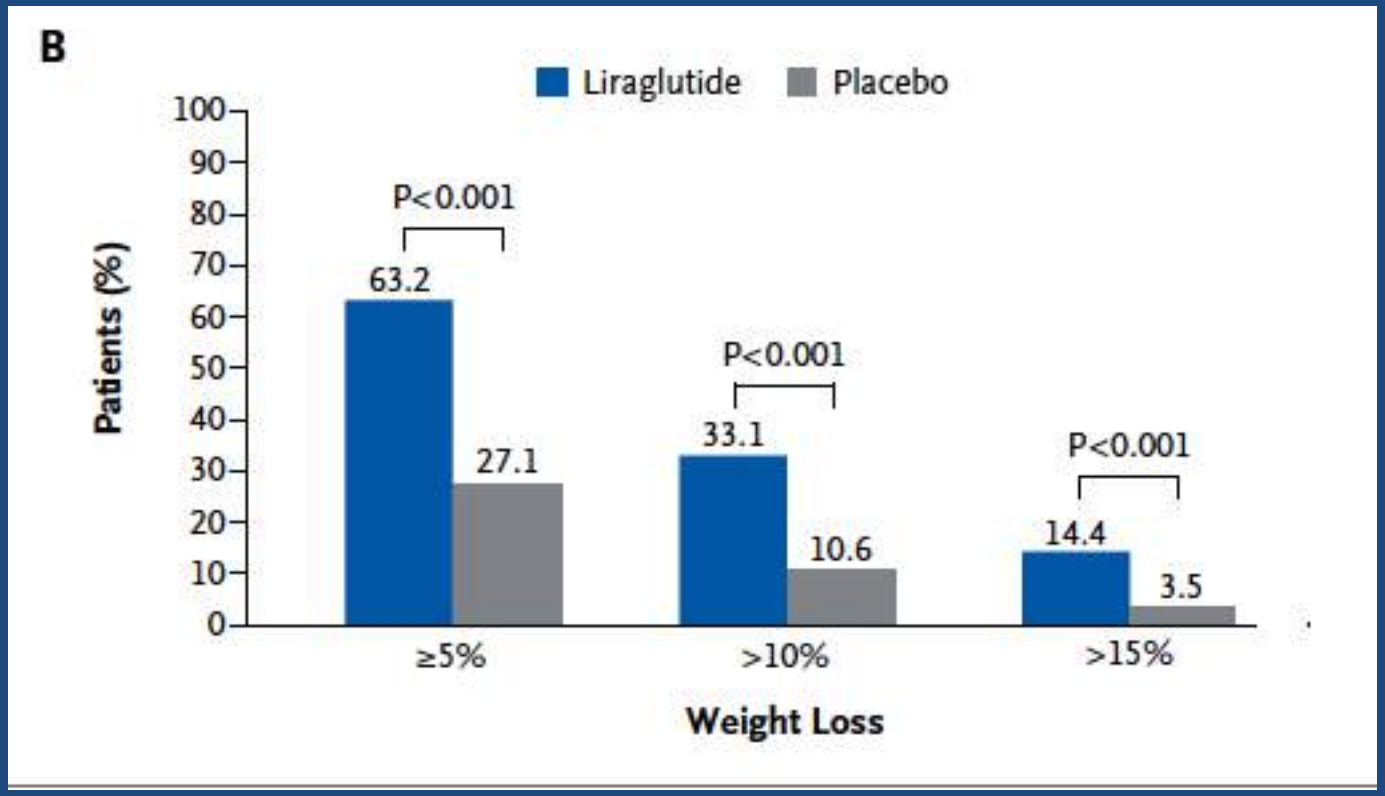
Table 1. Baseline Characteristics of the Patients.*

Characteristic	Liraglutide (N=2487)	Placebo (N=1244)
Sex — no. (%)		
Female	1957 (78.7)	971 (78.1)
Male	530 (21.3)	273 (21.9)
Age — yr	45.2±12.1	45.0±12.0
[illegible]		
Weight — kg	106.2±21.2	106.2±21.7
Body-mass index‡	38.3±6.4	38.3±6.3
Body-mass index categories — no. (%)‡		
27–29.9: overweight	66 (2.7)	44 (3.5)
30–34.9: obese class I	806 (32.4)	388 (31.2)
35–39.9: obese class II	787 (31.6)	398 (32.0)
≥40: obese class III	828 (33.3)	414 (33.3)
Waist circumference — cm	115.0±14.4	114.5±14.3
Glycated hemoglobin — %	5.6±0.4	5.6±0.4
Fasting glucose — mg/dl	95.9±10.6	95.5±9.8
Fasting insulin — μIU/ml§	16.3±79.8	16.1±89.3
Triglycerides — mg/dl	126.2±56.9	128.9±61.0
Prediabetes — no. (%)¶	1528 (61.4)	757 (60.9)
Dyslipidemia — no. (%)‖	737 (29.6)	359 (28.9)
Hypertension — no. (%)‖	850 (34.2)	446 (35.9)


A
Normoglycemia
Liraglutide
Placebo
Prediabetes
Liraglutide
Placebo
LOCF
LOCF
Change in Body Weight (%)
0
−2
−4
−6
−8
−10
−12
0
4
8
12
16
20
24
28
32
36
40
44
48
52
56
Weeks


B
Liraglutide
Placebo
Patients (%)
100
90
80
70
60
50
40
30
20
10
0
P<0.001
63.2
27.1
P<0.001
33.1
10.6
P<0.001
14.4
3.5
≥5%
>10%
>15%
Weight Loss

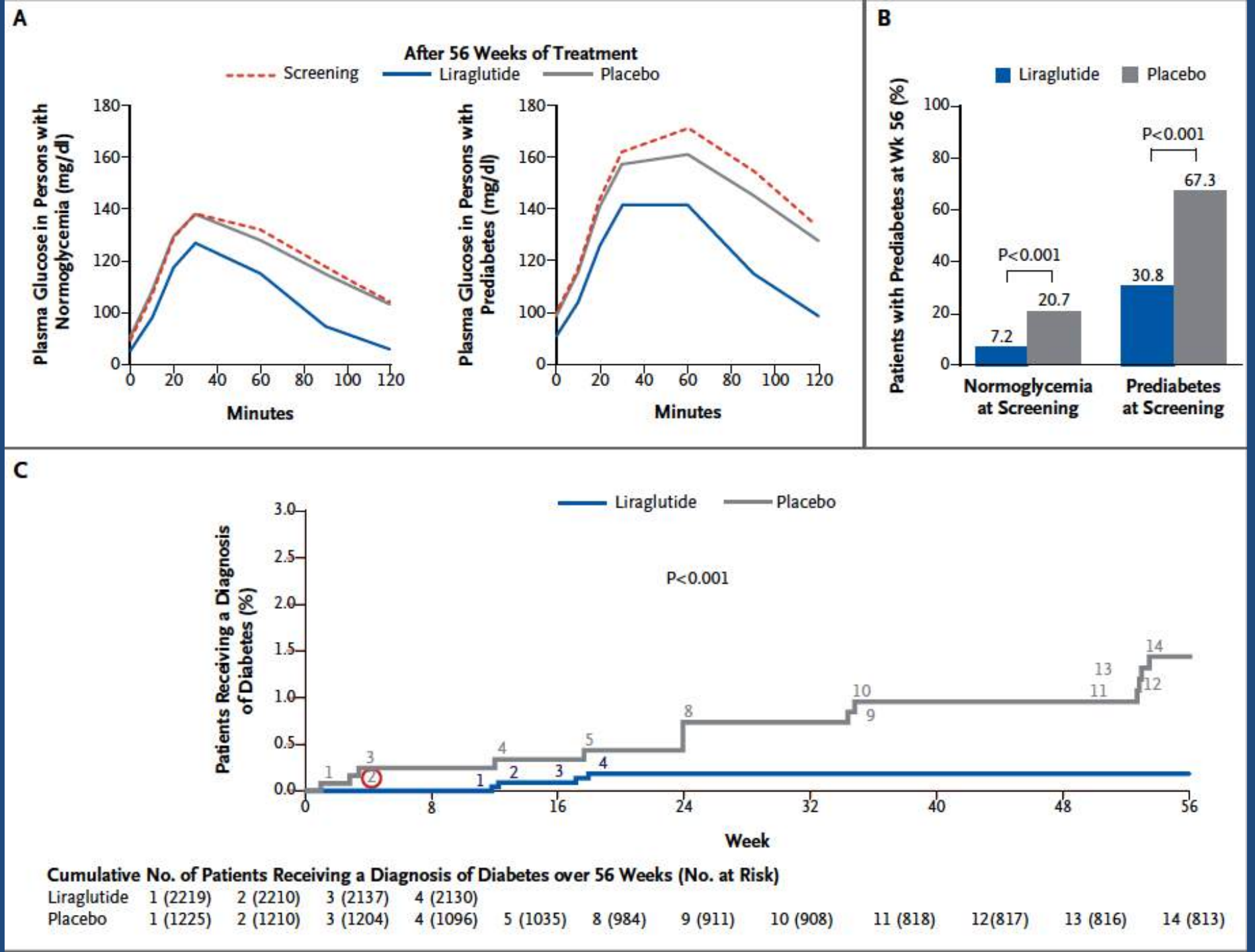

A
After 56 Weeks of Treatment
Screening
Liraglutide
Placebo
Plasma Glucose in Persons with Normoglycemia (mg/dl)
Plasma Glucose in Persons with Prediabetes (mg/dl)
Minutes
Minutes
B
Liraglutide
Placebo
Patients with Prediabetes at Wk 56 (%)
P<0.001
P<0.001
7.2
20.7
30.8
67.3
Normoglycemia at Screening
Prediabetes at Screening
C
Liraglutide
Placebo
Patients Receiving a Diagnosis of Diabetes (%)
P<0.001
Week
Cumulative No. of Patients Receiving a Diagnosis of Diabetes over 56 Weeks (No. at Risk)
Liraglutide 1 (2219) 2 (2210) 3 (2137) 4 (2130)
Placebo 1 (1225) 2 (1210) 3 (1204) 4 (1096) 5 (1035) 8 (984) 9 (911) 10 (908) 11 (818) 12(817) 13 (816) 14 (813)

Table 3. Adverse Events and Serious Adverse Events.*

Event	Liraglutide (N=2481)			Placebo (N=1242)		
	No. of Patients (%)	No. of Events	Event Rate per 100 Exposure-Years	No. of Patients (%)	No. of Events	Event Rate per 100 Exposure-Years
Adverse events in ≥5% of patients	1992 (80.3)	7191	321.8	786 (63.3)	2068	193.7
Nausea	997 (40.2)	1429	63.9	183 (14.7)	223	20.9
Diarrhea	518 (20.9)	754	33.7	115 (9.3)	142	13.3
Constipation	495 (20.0)	593	26.5	108 (8.7)	121	11.3
Vomiting	404 (16.3)	597	26.7	51 (4.1)	62	5.8
Dyspepsia	236 (9.5)	282	12.6	39 (3.1)	44	4.1
Upper abdominal pain	141 (5.7)	171	7.7	43 (3.5)	49	4.6
Abdominal pain	130 (5.2)	163	7.3	43 (3.5)	53	5.0
Nasopharyngitis	427 (17.2)	586	26.2	234 (18.8)	302	28.3
Upper respiratory tract infection	213 (8.6)	247	11.1	122 (9.8)	149	14.0
Sinusitis	128 (5.2)	141	6.3	73 (5.9)	95	8.9
Influenza	144 (5.8)	170	7.6	66 (5.3)	84	7.9
Headache	327 (13.2)	441	19.7	154 (12.4)	220	20.6
Dizziness	167 (6.7)	203	9.1	60 (4.8)	65	6.1
Decreased appetite	267 (10.8)	283	12.7	38 (3.1)	39	3.7
Back pain	171 (6.9)	210	9.4	105 (8.5)	121	11.3
Arthralgia	125 (5.0)	133	6.0	71 (5.7)	80	7.5
Fatigue	185 (7.5)	203	9.1	65 (5.2)	72	6.7
Injection-site hematoma	142 (5.7)	154	6.9	93 (7.5)	101	9.5
Serious adverse events in ≥0.2% of patients	154 (6.2)	194	8.7	62 (5.0)	75	7.0
Cholelithiasis	20 (0.8)	20	0.9	5 (0.4)	5	0.5
Cholecystitis acute	12 (0.5)	12	0.5	0	0	0.0
Osteoarthritis	6 (0.2)	7	0.3	0	0	0.0
Intervertebral disc protrusion	5 (0.2)	5	0.2	1 (0.1)	1	0.1
Pancreatitis acute†	4 (0.2)	4	0.2	0	0	0.0
Cholecystitis	4 (0.2)	4	0.2	0	0	0.0
Breast cancer	4 (0.2)	4	0.2	1 (0.1)	1	0.1
Back pain	2 (0.1)	2	<0.1	2 (0.2)	2	0.2
Uterine leiomyoma	1 (<0.1)	1	<0.1	2 (0.2)	2	0.2
Cellulitis	1 (<0.1)	1	<0.1	3 (0.2)	3	0.3
Gastroesophageal reflux disease	0	0	0.0	2 (0.2)	2	0.2
Bronchitis	0	0	0.0	2 (0.2)	2	0.2
Bladder prolapse	0	0	0.0	2 (0.2)	2	0.2
Chest pain	0	0	0.0	3 (0.2)	3	0.3

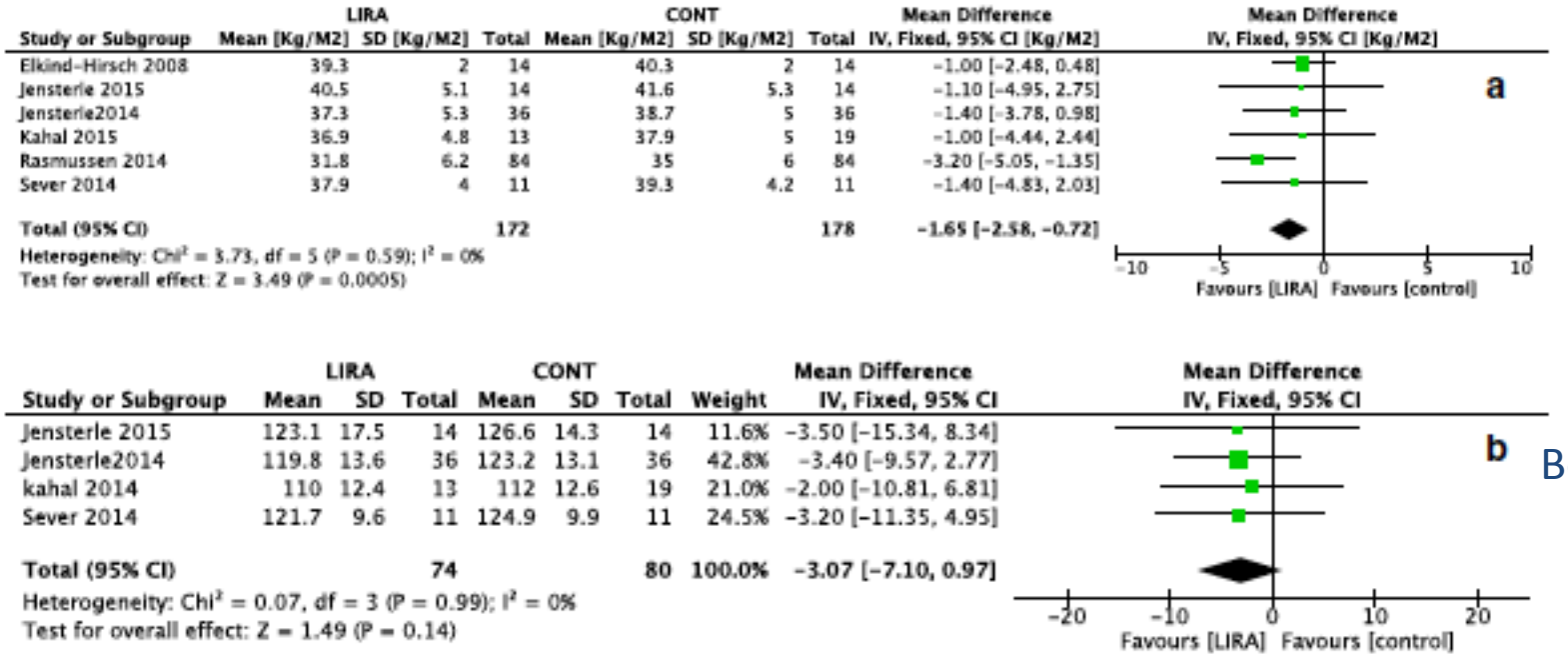
Arch Gynecol Obstet (2016) 293:509–515
DOI 10.1007/s00404-015-3976-7

REVIEW

A systematic review of GLP-1 agonists on the metabolic syndrome in women with polycystic ovaries

Mitra Niafar[1] · Leili Pourafkari[2] · Jahan Porhomayon[2] · Nader Nader[2]

BKI ve Bel Cevresi



Study or Subgroup	LIRA Mean [Kg/M2]	LIRA SD [Kg/M2]	LIRA Total	CONT Mean [Kg/M2]	CONT SD [Kg/M2]	CONT Total	Mean Difference IV, Fixed, 95% CI [Kg/M2]
Elkind-Hirsch 2008	39.3	2	14	40.3	2	14	-1.00 [-2.48, 0.48]
Jensterle 2015	40.5	5.1	14	41.6	5.3	14	-1.10 [-4.95, 2.75]
Jensterle2014	37.3	5.3	36	38.7	5	36	-1.40 [-3.78, 0.98]
Kahal 2015	36.9	4.8	13	37.9	5	19	-1.00 [-4.44, 2.44]
Rasmussen 2014	31.8	6.2	84	35	6	84	-3.20 [-5.05, -1.35]
Sever 2014	37.9	4	11	39.3	4.2	11	-1.40 [-4.83, 2.03]
Total (95% CI)			**172**			**178**	**-1.65 [-2.58, -0.72]**

Heterogeneity: Chi² = 3.73, df = 5 (P = 0.59); I² = 0%
Test for overall effect: Z = 3.49 (P = 0.0005)

Mean Difference IV, Fixed, 95% CI [Kg/M2]

-10 -5 0 5 10
Favours [LIRA] Favours [control]

a

BMI

Study or Subgroup	LIRA Mean	LIRA SD	LIRA Total	CONT Mean	CONT SD	CONT Total	Weight	Mean Difference IV, Fixed, 95% CI
Jensterle 2015	123.1	17.5	14	126.6	14.3	14	11.6%	-3.50 [-15.34, 8.34]
Jensterle2014	119.8	13.6	36	123.2	13.1	36	42.8%	-3.40 [-9.57, 2.77]
kahal 2014	110	12.4	13	112	12.6	19	21.0%	-2.00 [-10.81, 6.81]
Sever 2014	121.7	9.6	11	124.9	9.9	11	24.5%	-3.20 [-11.35, 4.95]
Total (95% CI)			**74**			**80**	**100.0%**	**-3.07 [-7.10, 0.97]**

Heterogeneity: Chi² = 0.07, df = 3 (P = 0.99); I² = 0%
Test for overall effect: Z = 1.49 (P = 0.14)

Mean Difference IV, Fixed, 95% CI

-20 -10 0 10 20
Favours [LIRA] Favours [control]

b

Bel Cevresi

Fig. 1 Forest plot for the studies that have examined body mass index (BMI) as their outcome variable is shown in the *upper panel* (**a**) and the plot for the studies that have examined waist circumference is shown in the *lower panel* (**b**)

Insulin Konsantrasyonu ve HOMA-IR

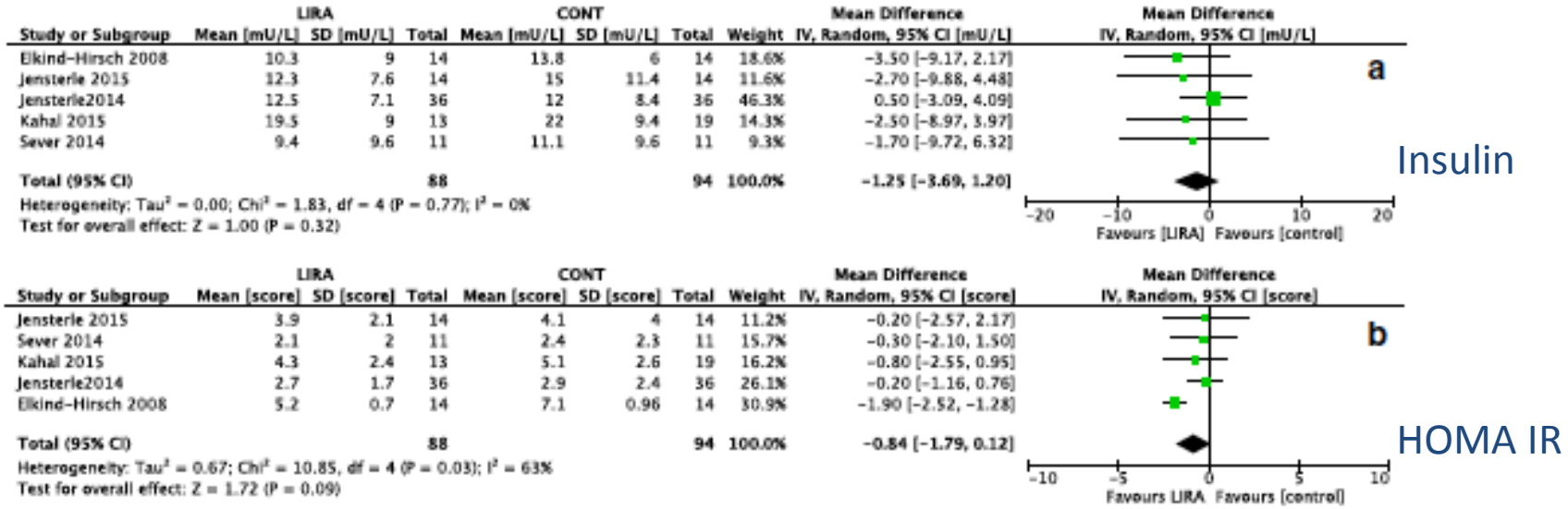
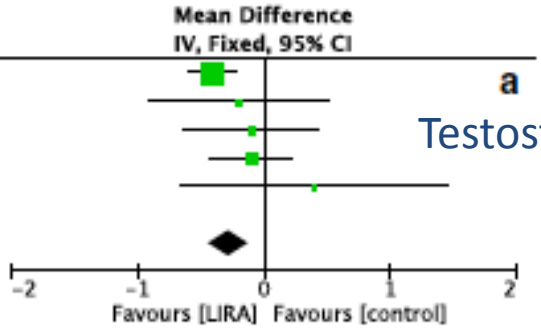


Fig. 2 Forest plot for the studies that have examined fasting serum concentrations of insulin as their outcome variable is shown in the *upper panel* (**a**) and the plot for the studies that have examined homeostatic model of insulin resistance (HOMA-IR) scores is shown in the *lower panel* (**b**)

Testesteron ve SHBG

Study or Subgroup	LIRA Mean	LIRA SD	LIRA Total	CONT Mean	CONT SD	CONT Total	Weight	Mean Difference IV, Fixed, 95% CI
Elkind-Hirsch 2008	2.2	0.26	14	2.61	0.27	14	62.2%	−0.41 [−0.61, −0.21]
Jensterle 2015	2	1.1	14	2.2	0.9	17	4.7%	−0.20 [−0.92, 0.52]
Jensterle2014	1.7	1.1	36	1.8	1.2	36	8.5%	−0.10 [−0.63, 0.43]
Kahal 2015	1.2	0.5	13	1.3	0.4	19	22.6%	−0.10 [−0.43, 0.23]
Sever 2014	2.2	1.4	11	1.8	1.1	11	2.2%	0.40 [−0.65, 1.45]
Total (95% CI)			**88**			**97**	**100.0%**	**−0.29 [−0.44, −0.13]**

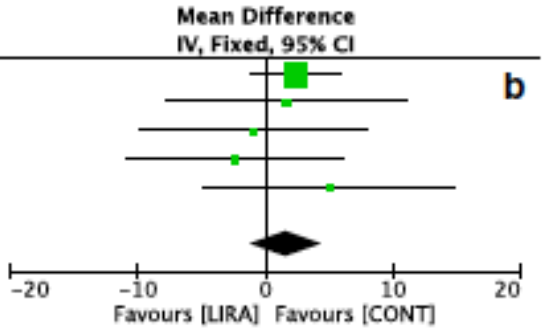
Heterogeneity: $Chi^2 = 4.94$, $df = 4$ ($P = 0.29$); $I^2 = 19\%$
Test for overall effect: $Z = 3.63$ ($P = 0.0003$)



Testosteron

Study or Subgroup	LIRA Mean	LIRA SD	LIRA Total	CONT Mean	CONT SD	CONT Total	Weight	Mean Difference IV, Fixed, 95% CI
Elkind-Hirsch 2008	19.7	6.2	14	17.4	2.4	14	63.3%	2.30 [−1.18, 5.78]
Jensterle 2015	31.6	12.4	14	30	14.5	17	8.6%	1.60 [−7.87, 11.07]
Jensterle2014	27.6	11.8	36	28.6	24.7	36	9.6%	−1.00 [−9.94, 7.94]
Kahal 2015	30.8	10	13	33.2	14.6	19	10.6%	−2.40 [−10.92, 6.12]
Sever 2014	21	12.5	11	16	11	11	7.9%	5.00 [−4.84, 14.84]
Total (95% CI)			**88**			**97**	**100.0%**	**1.64 [−1.13, 4.41]**

Heterogeneity: $Chi^2 = 1.78$, $df = 4$ ($P = 0.78$); $I^2 = 0\%$
Test for overall effect: $Z = 1.16$ ($P = 0.25$)



SHBG

Fig. 3 Forest plot for the studies that have examined serum concentrations of testosterone as their outcome variable is shown in the *upper panel* (**a**) and the plot for the studies that have examined sex hormone-binding globulin (SHBG) is shown in the *lower panel* (**b**)

Kahal *et al. BMC Endocrine Disorders* (2015) 15:14
DOI 10.1186/s12902-015-0005-6

BMC
Endocrine Disorders

RESEARCH ARTICLE Open Access

The effects of treatment with liraglutide on atherothrombotic risk in obese young women with polycystic ovary syndrome and controls

Hassan Kahal[1,2,9*], Ahmed Aburima[2], Tamas Ungvari[3], Alan S Rigby[2], Anne M Coady[4], Rebecca V Vince[5], Ramzi A Ajjan[6], Eric S Kilpatrick[7], Khalid M Naseem[2] and Stephen L Atkin[8]

Conclusions: Six months treatment with liraglutide (1.8 mg od) equally affected young obese women with PCOS and controls. In both groups, liraglutide treatment was associated with 3–4% weight loss and significant reduction in atherothrombosis markers including inflammation, endothelial function and clotting. Our data support the use of liraglutide as weight loss medication in simple obesity and suggest a potential beneficial effect on platelet function and atherothrombotic risk at 6 months of treatment.

ANDROLOGY

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ORIGINAL ARTICLE

Correspondence:
Vito A. Giagulli, Outpatient Clinic for Endocrinology and Metabolic Diseases, Conversano Hospital, ASL Bari, Via De Amicis, 70014 Conversano, Italy.
E-mail vitogiagulli@alice.it

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erectile dysfunction, glucagon-like peptide-1 agonist, hypogonadism, obesity, testosterone replacement therapy, type 2 diabetes mellitus

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Adding liraglutide to lifestyle changes, metformin and testosterone therapy boosts erectile function in diabetic obese men with overt hypogonadism

[1,2]V. A. Giagulli, [3]M. D. Carbone, [1]M. I. Ramunni, [2]B. Licchelli, [4]G. De Pergola, [5]C. Sabbà, [2]E. Guastamacchia and [2]V. Triggiani

[1]Outpatient Clinic for Endocrinology and Metabolic Diseases, Conversano Hospital, Conversano, [2]Endocrinology and Metabolic Diseases, University of Bari, Bari, [3]Institute of Clinical and Hormonal Research, Foggia, [4]Nutrition Outpatient Clinic, Clinical Oncology Unit, and [5]Rare Diseases Center, University of Bari, Bari, Italy

G1N (n = 16)	T1	T2	p1 (p)	T3	p2 (p)
Age (years)	52.7 ± 4.5	–	–	–	–
Duration of diabetes (years)	3.8 ± 0.8	–	–	–	–
Height (cm)	171.2 ± 5.7	–	–	–	–
Weight (kg)	102.7 ± 9.1	99.0 ± 7.6	<**0.01**	93.7 ± 6.3	<**0.01**
BMI (kg/m^2)	35.2 ± 2.3	34.0 ± 3.1	<**0.01**	32.6 ± 2.0	<**0.01**
WC (cm)	103.7 ± 7.0	99.1 ± 6.2	<**0.01**	92.5 ± 5.3	<**0.001**
SBP (mmHg)	155.8 ± 13.7	150.1 ± 12.0	<**0.01**	145.7 ± 9.6	<**0.001**
DBP (mmHg)	86.4 ± 4.5	85.5 ± 4.2	<0.07	82.5 ± 2.6	<**0.01**
Gly (mg/dL)	180.4 ± 24.8	155.5 ± 19.7	<**0.001**	130.3 ± 15.6	<**0.001**
HbA1c (%)	9.1 ± 0.4	8.3 ± 0.3	<**0.001**	7.3 ± 0.3	<**0.001**
TC (mg/dL)	226.6 ± 20.8	216.8 ± 16.8	<**0.01**	206.9 ± 10.8	<**0.01**
TG (mg/dL)	202.8 ± 28.6	190.1 ± 27.3	<**0.001**	175.4 ± 19.4	<**0.001**
HDL (mg/dL)	38.6 ± 2.8	39.0 ± 2.6	<0.61	39.6 ± 3.0	<0.07
LDL (mg/dL)	147.3 ± 21.3	133.6 ± 15.4	<**0.001**	125.5 ± 10.7	<**0.001**
T (ng/dL)	285.8 ± 25.0	466.1 ± 63.6	<**0.001**	481.7 ± 57.3	<**0.001**
SHBG (nmol/L)	36.0 ± 3.2	37.1 ± 2.8	<**0.05**	39.1 ± 2.2	<**0.01**
FT (ng/dL)	5.4 ± 0.6	8.7 ± 1.6	<**0.001**	9.0 ± 1.3	<0.13
BioT (ng/dL)	124.6 ± 13.4	204.0 ± 37.1	<**0.001**	211.1 ± 30.0	<0.14
IIEF (score)	12.2 ± 2.2	14.6 ± 1.7	<**0.05**	19.9 ± 2.0	<**0.001**

Table 2 Clinical characteristics, metabolic and hormonal parameters of the subgroup of poor responders among the post-pubertal onset hypogonadal men (G1N; n = 16) at the observational starting time point (T1), after Met plus TU for 12 months (T2) and after the addition of L (1.2 µg/day) for further 12 months (T3)

T1 Baslangic
T2 Met + Testesteron 1000mg/12hafta
T3 +Liraglutide 1.2mg/gun

G2 N (n = 10)	T1	T2	p1 (p)	T3	p2 (p)
Age (years)	50.0 ± 4.7	–	–	–	–
Duration of diabetes (years)	3.2 ± 0.8	–	–	–	–
Height (cm)	172.9 ± 2.5	–	–	–	–
Weight (kg)	105.3 ± 9.8	102.5 ± 7.1	**<0.05**	98.0 ± 8.3	**<0.01**
BMI (kg/m^2)	34.8 ± 2.6	33.5 ± 2.0	**<0.05**	32.5 ± 2.3	**<0.05**
WC (cm)	106.8 ± 11.0	104.5 ± 9.9	**<0.05**	99.2 ± 9.8	**<0.001**
SBP (mmHg)	151.5 ± 8.8	147.5 ± 8.3	**<0.05**	142.0 ± 8.6	**<0.01**
DBP (mmHg)	89.5 ± 4.4	87.7 ± 2.6	<0.06	85.9 ± 4.1	**<0.05**
Gly (mg/dL)	211.4 ± 25.7	169.9 ± 15.3	**<0.01**	133.9 ± 12.8	**<0.01**
HbA1c (%)	8.8 ± 0.8	8.2 ± 0.3	**<0.04**	7.4 ± 0.6	**<0.01**
TC (mg/dL)	189.9 ± 12.4	176.5 ± 25.7	**<0.01**	175.8 ± 19.0	<0.15
TG (mg/dL)	319.1 ± 152.7	270.3 ± 104.9	**<0.01**	226.0 ± 48.7	**<0.001**
HDL (mg/dL)	35.7 ± 3.7	37.1 ± 3.0	<0.34	37.9 ± 3.5	<0.12
LDL (mg/dL)	105.6 ± 12.4	94.3 ± 19.5	**<0.05**	92.4 ± 18.9	**<0.05**
T (ng/dL)	304.8 ± 30.4	395.5 ± 40.0	**<0.01**	420.0 ± 27.5	**<0.01**
SHBG (nmol/L)	37.1 ± 2.6	38.4 ± 2.0	**<0.02**	40.8 ± 1.5	**<0.02**
FT (ng/dL)	5.6 ± 0.7	7.2 ± 0.8	**<0.01**	7.6 ± 0.6	<0.16
BioT (ng/dL)	132.8 ± 16.2	170.7 ± 18.0	**<0.01**	178.4 ± 13.6	<0.18
IIEF (score)	14.2 ± 1.8	16.5 ± 1.6	**<0.01**	19.9 ± 1.1	**<0.001**

Table 5 Clinical characteristics and metabolic and hormonal parameters of the poor responders among patients belonging to the prepubertal onset hypogonadal group (G2N; n = 10) at T1, after 1 year of Met and TU therapy (T2) and after the addition of L (1.2 μg/day) for further 12 months (T3)

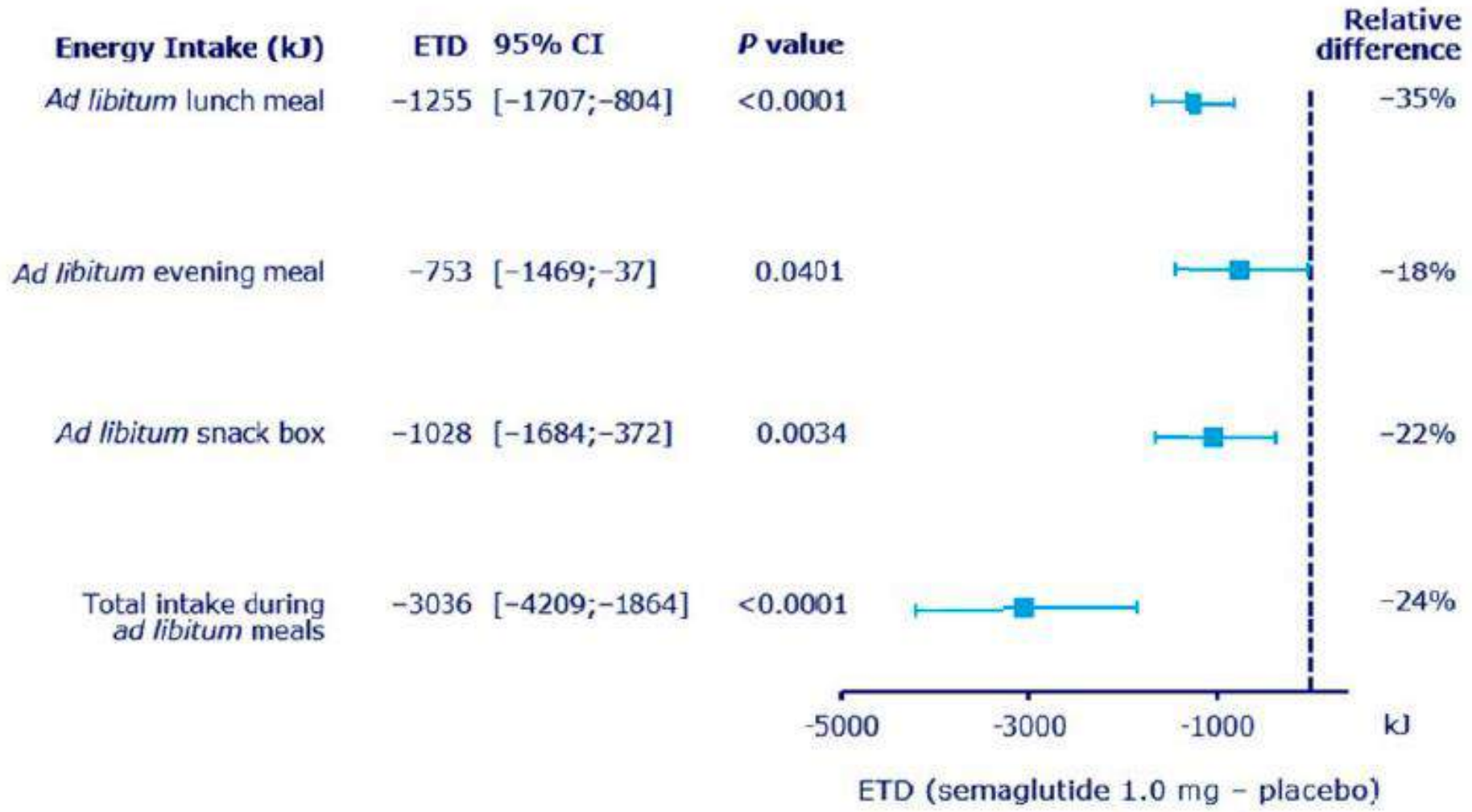
Effects of once-weekly semaglutide on appetite, energy intake, control of eating, food preference and body weight in subjects with obesity

John Blundell1, Graham Finlayson1, Mads Buhl Axelsen2, Anne Flint2,
Catherine Gibbons1, Trine Kvist2, Julie Hjerpsted2

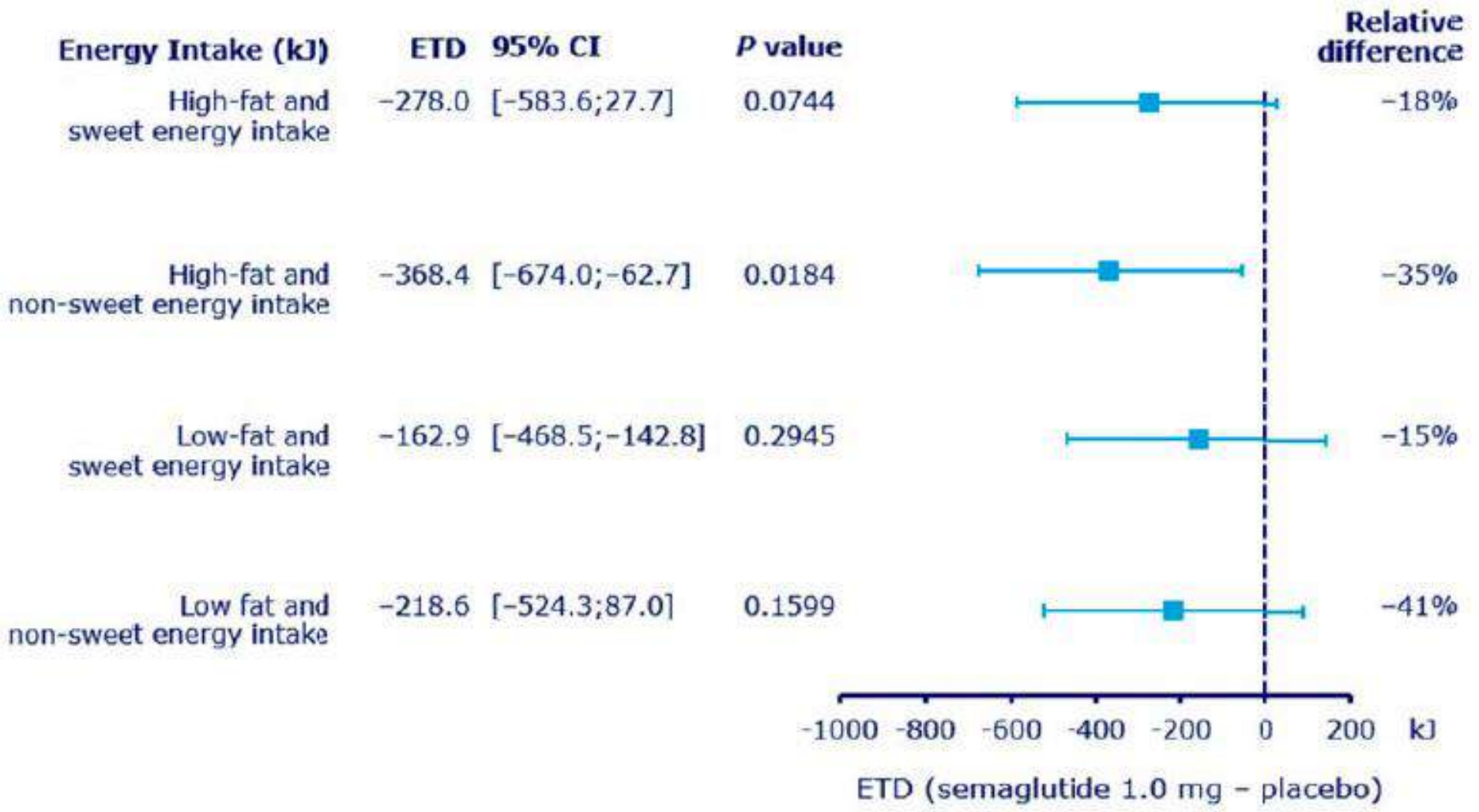
AIMTo investigate the mechanism of action for body weight loss with semaglutide. **Materials and Methods:** This randomised, double-blind,placebo-controlled, two-period crossover trial investigated the effects of 12 weeks treatment with once-weekly subcutaneous semaglutide, dose escalated to 1.0 mg, in 30 subjects with obesity. Ad libitum energy intake,ratings of appetite, thirst, nausea and well-being, control of eating, foodpreference, resting metabolic rate, body weight and body composition were assessed.

Figure 1. *Energy intake during (a) ad libitum meals* and *(b) ad libitum* snack box, by food group

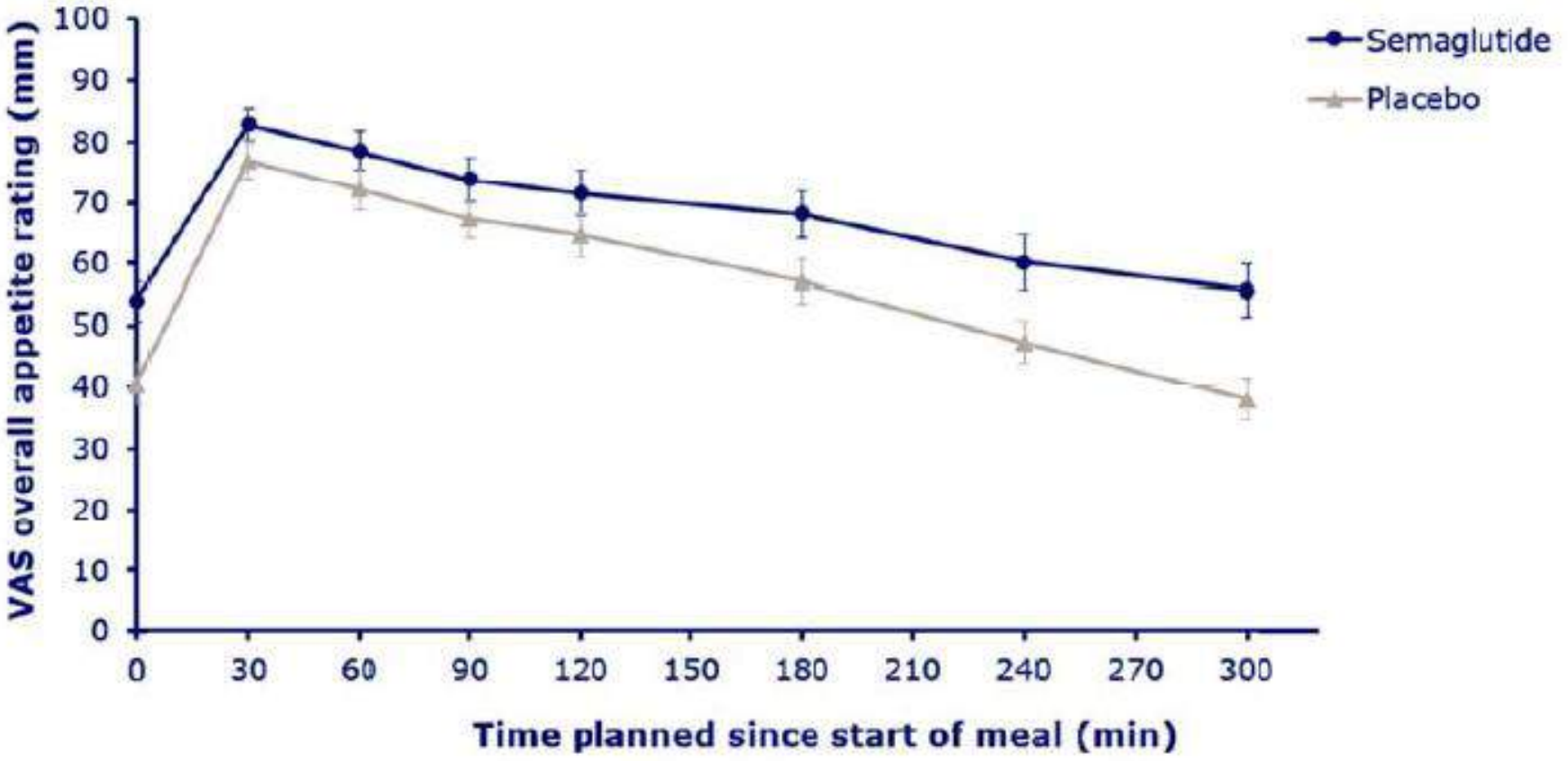
(a)



b

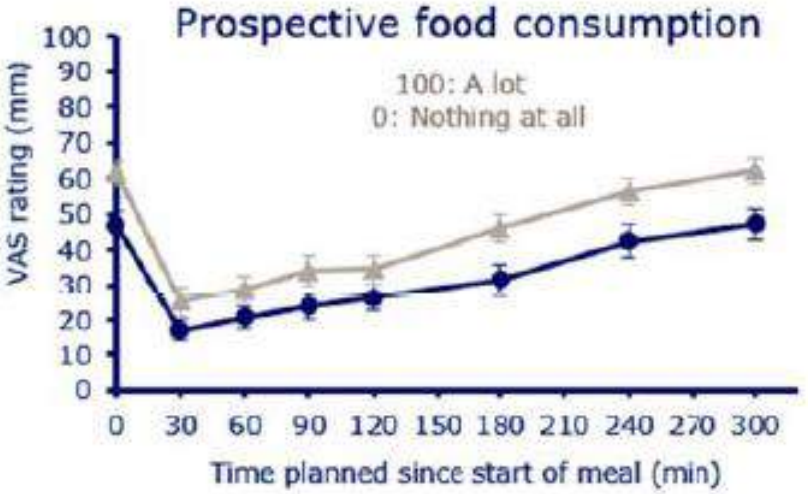

Energy Intake (kJ)
ETD
95% CI
P value
Relative difference
High-fat and sweet energy intake
−278.0
[−583.6;27.7]
0.0744
−18%
High-fat and non-sweet energy intake
−368.4
[−674.0;−62.7]
0.0184
−35%
Low-fat and sweet energy intake
−162.9
[−468.5;−142.8]
0.2945
−15%
Low fat and non-sweet energy intake
−218.6
[−524.3;87.0]
0.1599
−41%
-1000 -800 -600 -400 -200 0 200 kJ
ETD (semaglutide 1.0 mg − placebo)

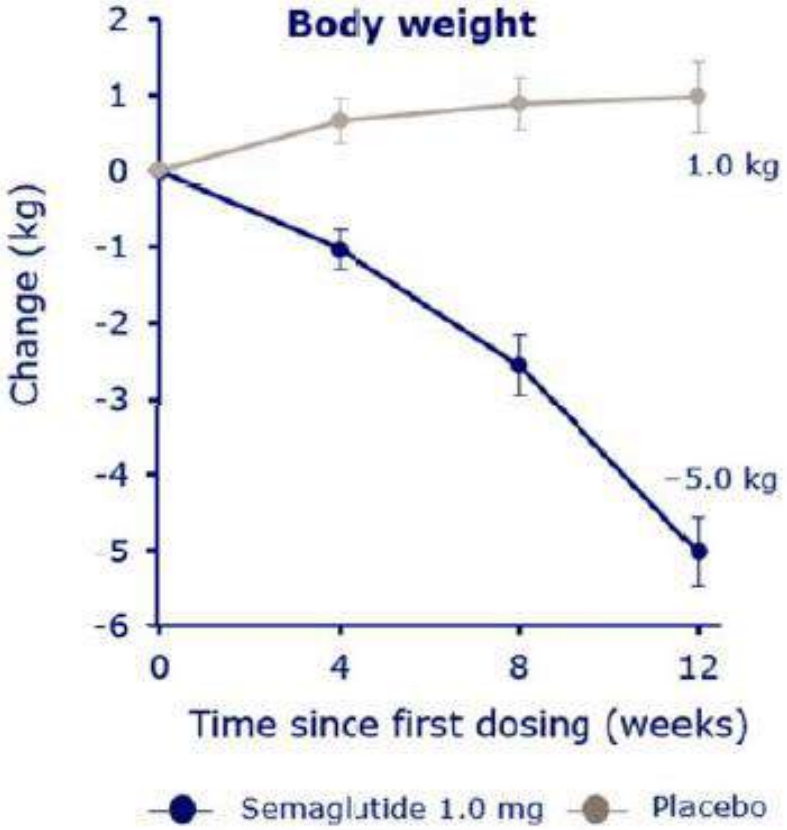
Overall appettite suppression score after a standardised breakfast

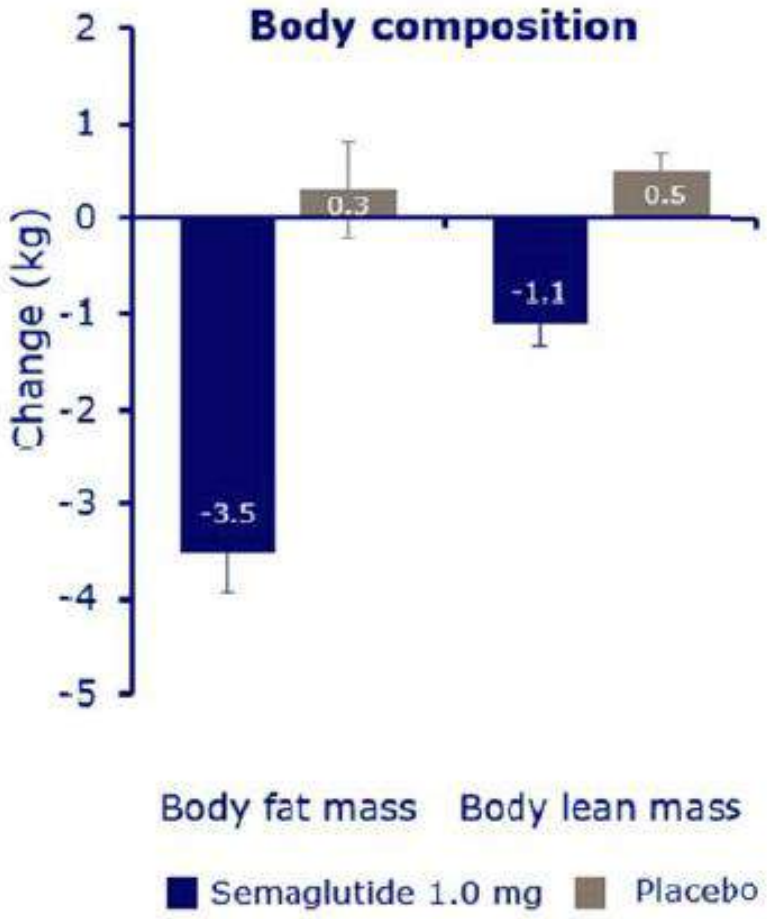


Visual Analogue Scale (VAS) ratings of Appetite during a standardised breakfast

(b)




Body weight
Change (kg)
2
1
0
-1
-2
-3
-4
5
-6
1.0 kg
−5.0 kg
0
4
8
12
Time since first dosing (weeks)
Semaglutide 1.0 mg
Placebo


Body composition
Change (kg)
2
1
0
-1
-2
-3
-4
-5
0.3
0.5
-1.1
-3.5
Body fat mass
Body lean mass
Semaglutide 1.0 mg
Placebo

Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial

Bo Ahrén, Luis Masmiquel, Harish Kumar, Mehmet Sargin, Julie Denving Karsbøl, Sanja Hald Jacobsen, Francis Chow

www.thelancet.com/diabetes-endocrinology
Published online April 3, 2017
http://dx.doi.org/10.1016/S2213-8587(17)30092-X

18 ulke ve 128 Merkez

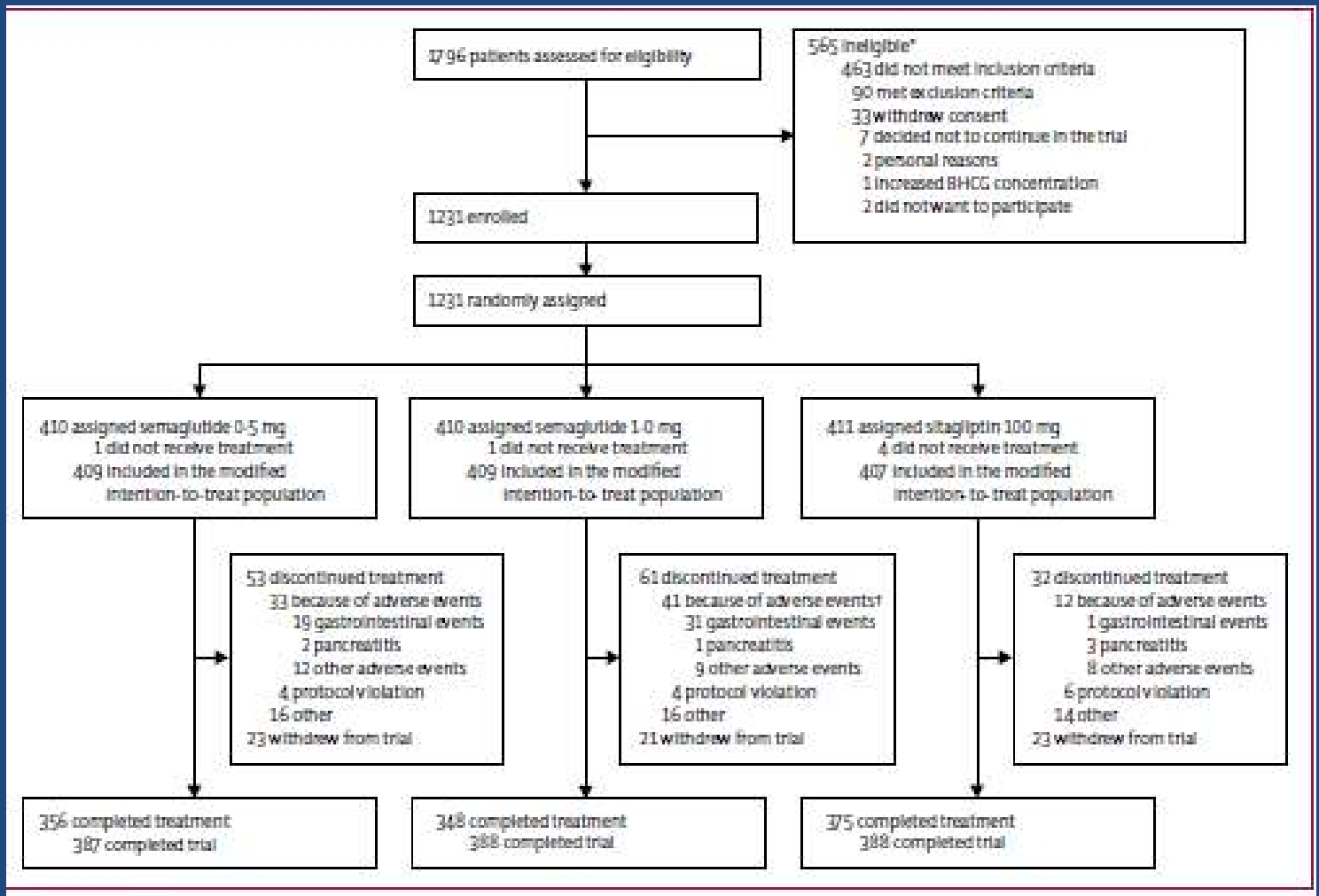


Figure 1: Trial profile

Trial completers calculated as all subjects with a follow-up visit. BHCG=β-human chorionic gonadotropin. * Participants could have been ineligible for more than one reason. † Note that this number (n=41) differs from the corresponding number in table 3 (n=39). For one participant, the primary reason for premature treatment discontinuation was due to an adverse event, but the action to the drug was recorded as "drug interrupted" rather than "drug withdrawn". Hence, this participant was recorded as having an adverse event, but this adverse event did not lead to premature treatment discontinuation. In an additional participant, the adverse event that led to premature treatment discontinuation was reported outside the on-treatment period (day -5) and thus is not included in the on-treatment adverse event summary tables.

Semaglutide – Beden Agirligina etkisi

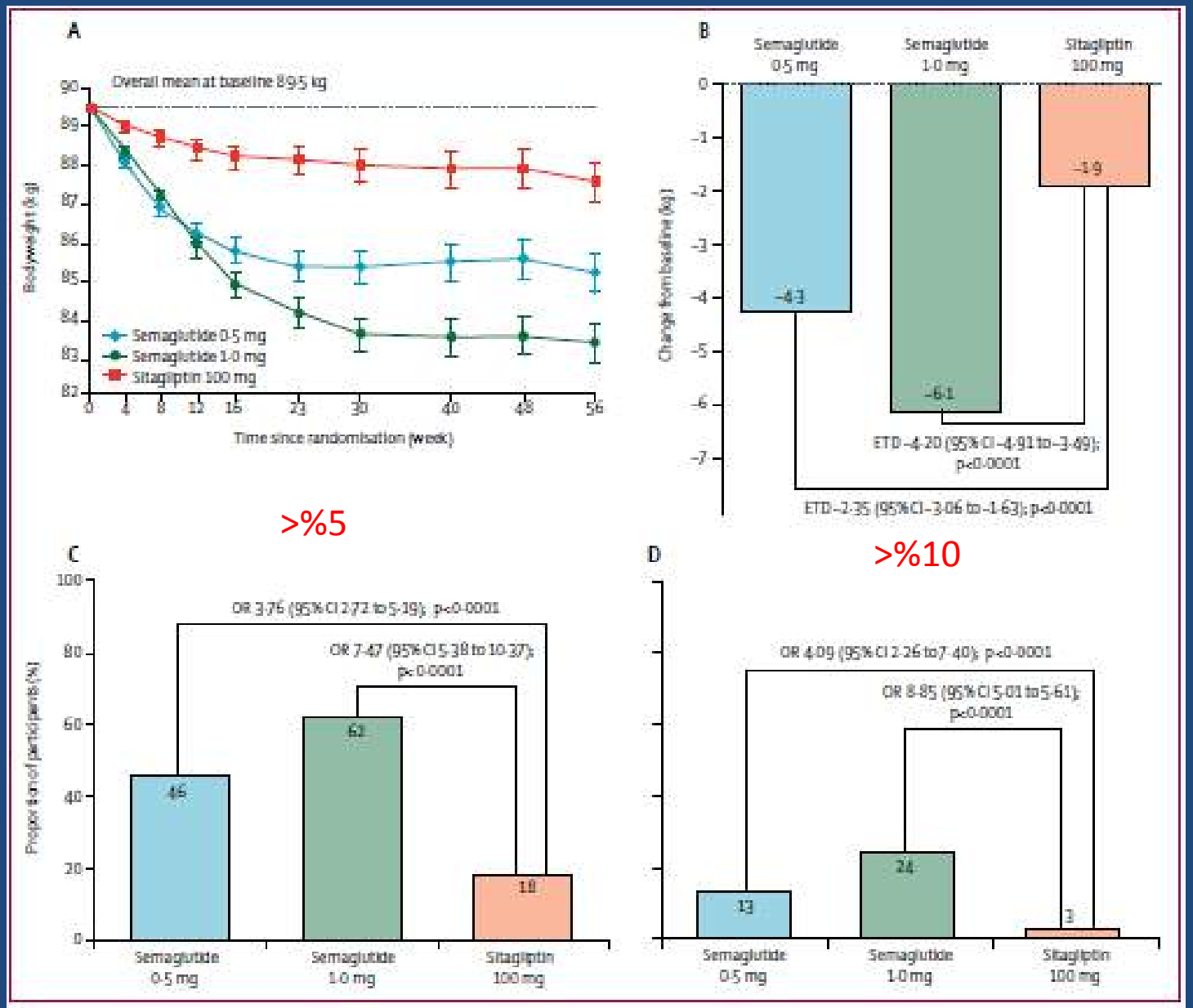
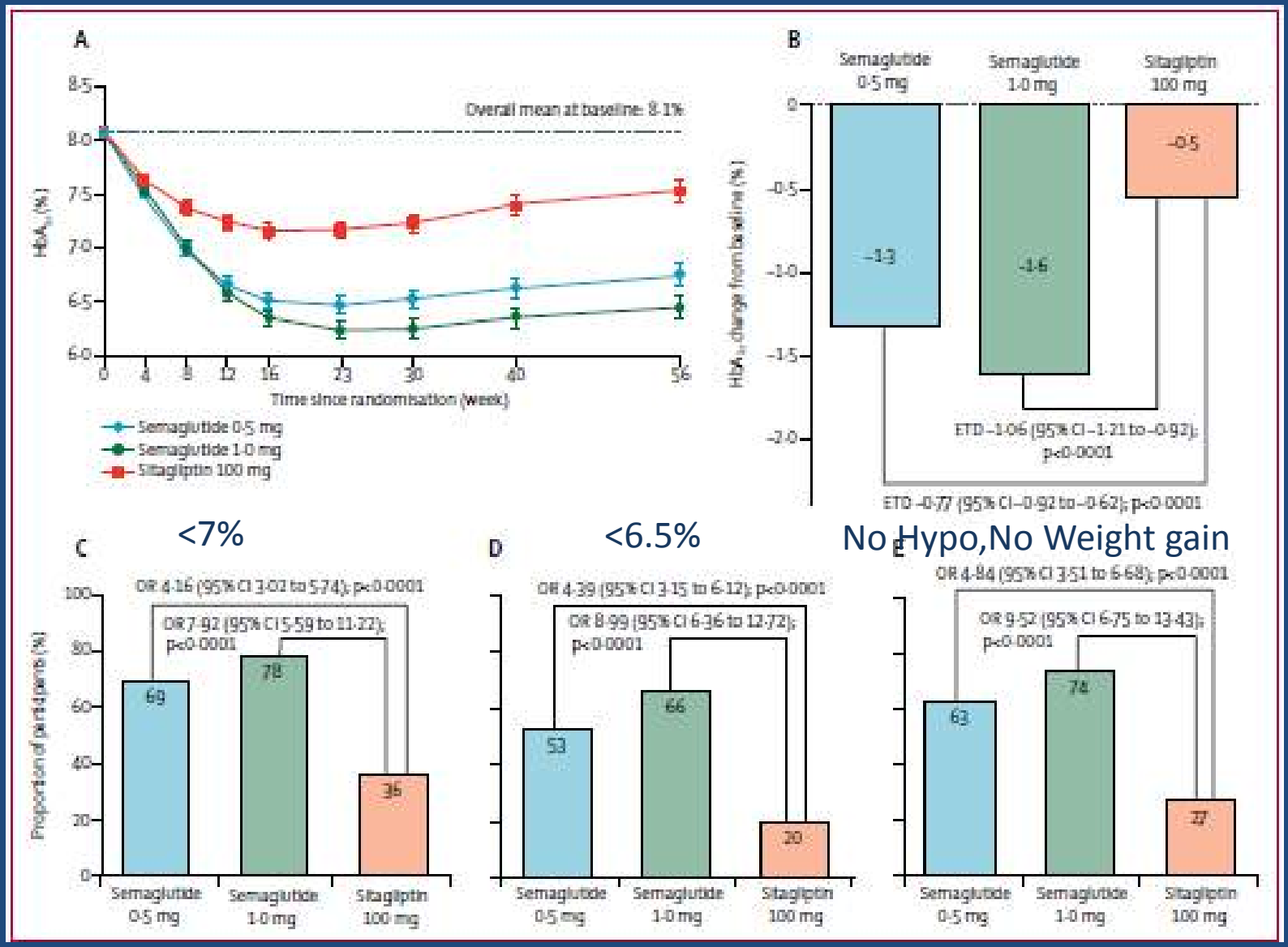


Figure 3: Bodyweight outcomes of semaglutide 0·5 mg and 1·0 mg once weekly, compared with sitagliptin 100 mg

Semaglutide-Glukoz metabolizmasina etkisi



SGLT 2 Inhibitorleri ve Kilo Kontrolu

SGLT2 inhibitorleri hastalarda glukoz kaybindan dolayi kilo kaybina da neden olurlar (Cefalu and Riddle, 2015; Clar et al., 2012; Whaley etal., 2012).

Dapagliflozin, canagliflozin ve empagliflozin de benzer etkilere sahiptirler.(Bolinder et al., 2012; Blonde et al., 2016; McGill, 2014).

Dual-energy X-ray absorptiometry ile yapilan calismalar bu kilo kaybinin sivi kaybindan veya yag disi doku kaybindan degil yag kitlesinin kaybindan oldugunu gostermistir. (Bolinder et al., 2014).

Ancak kilo kaybinin anlamsiz miktarda oldugunu ve hatta kilo alimini bildiren celiskili bildirimlerde vardir. (Anon, 2014d; Okauchi et al., 2016; Jackson et al.,2014).

Buna neden olan ise bir olasilik glukozuri ile ortaya cikan enerji kaybinin kompansasyonu icin gida aliminda artis olabilir (Napolitano et al., 2014).

Canagliflozin ile Faz IV klinik calisma yapilmaktadir. : NCT02360774. Tip 2 DM li Obez hastalarda beden agirligi ve metabolizmaya etkisini arastiran bu calisma Agustos 2017 de sonuclanacaktir

Empagliflozinin kardiyovaskuler riski yuksek Tip 2 DM li hastalarda kardiyovaskuler olaylari ve mortaliteyi azalttigi gosterilmistir. (Zinman et al., 2015).

Dapagliflozin ile yapilan calismada benzeri sonuclarin alinmasi Dziuba et al., 2014.

Tofogliflozin, luseogliflozin, and remogliflozin etabonate non-alkolik steatohepatitisi duzelttigi gosterilmistir (Nakano et al., 2015, Suzuki et al., 2014; Qiang et al., 2015).

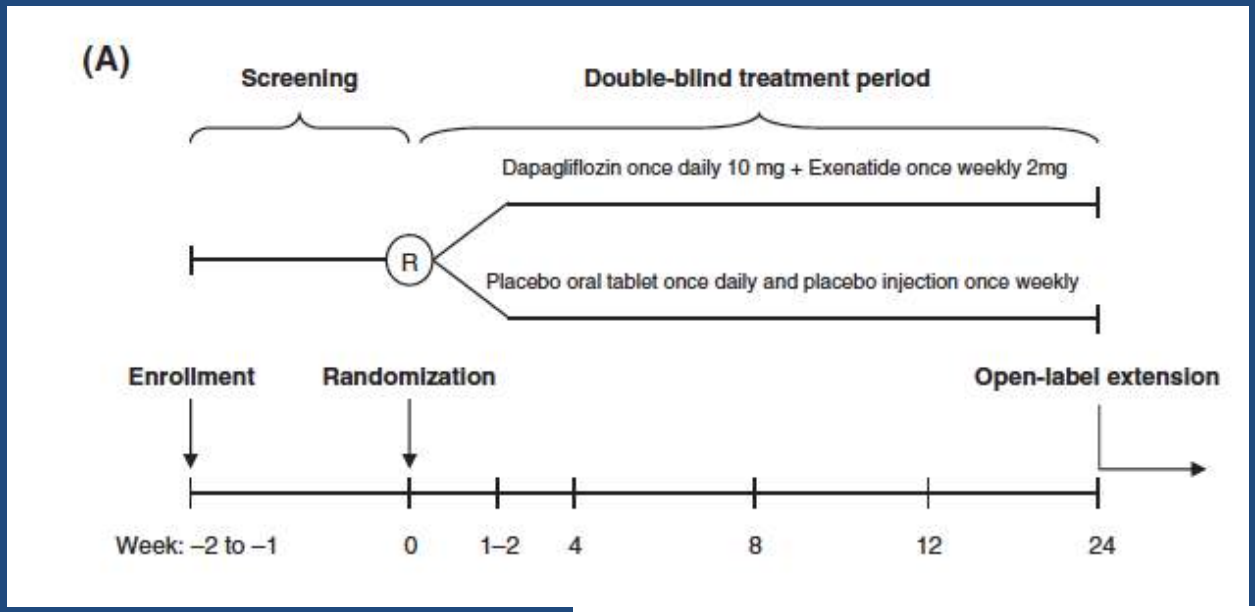
Sonuc,

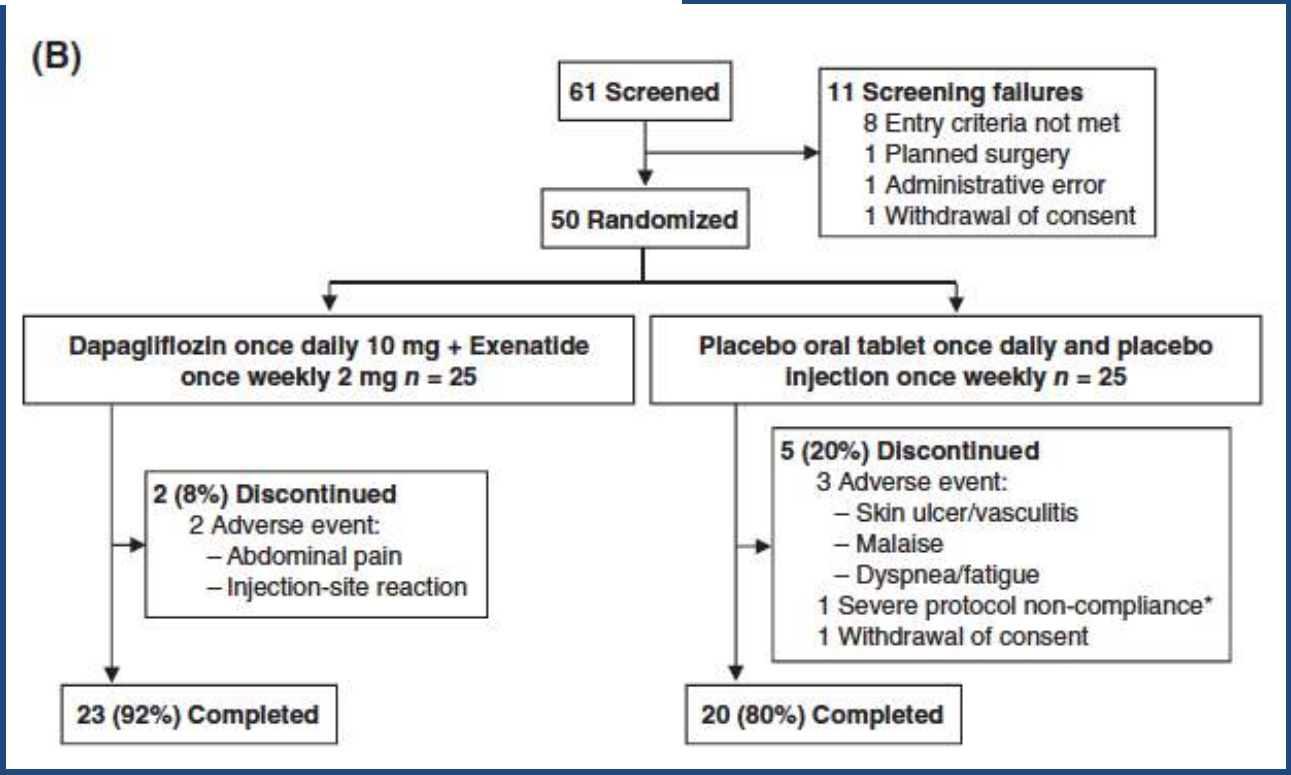
SGLT2 inhibitorleri have sadece tip 2 diabetes mellitus tedavisinde etkili bir ajan olarak kullanilabilmelerinin yanisira obezite, kardiyovaskuler hastaliklar, hepatosteatoz gibi haslaliklarin tedavisinde de kullanilabilme potansiyeli tasimaktadirlar.

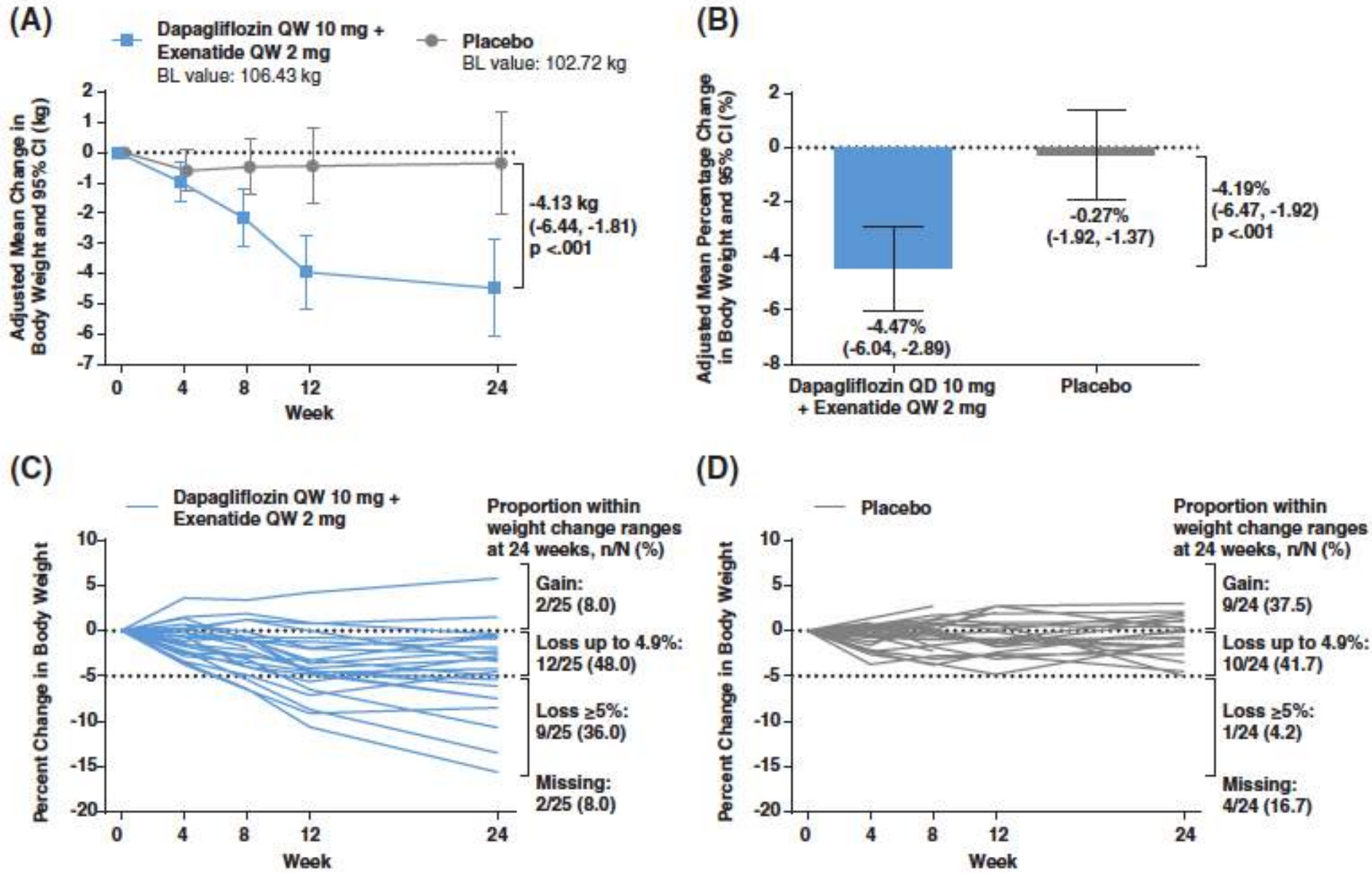
Dapagliflozin once-daily and exenatide once-weekly dual therapy: A 24-week randomized, placebo-controlled, phase II study examining effects on body weight and prediabetes in obese adults without diabetes

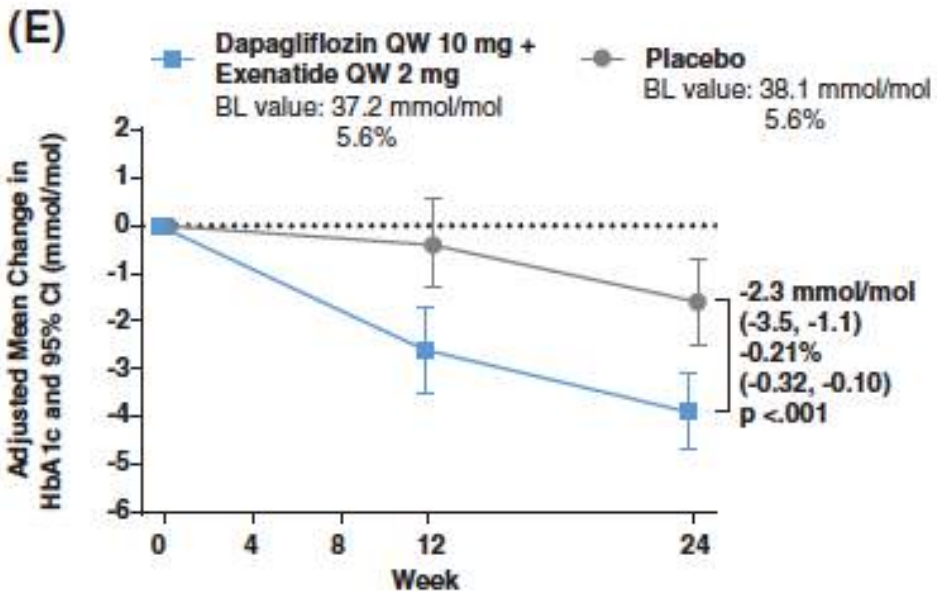
Per Lundkvist MD[1] | C. David Sjöström MD, PhD[2] | Sam Amini MD[1] | Maria J. Pereira PhD[1] | Eva Johnsson MD, PhD[2] | Jan W. Eriksson MD, PhD[1]

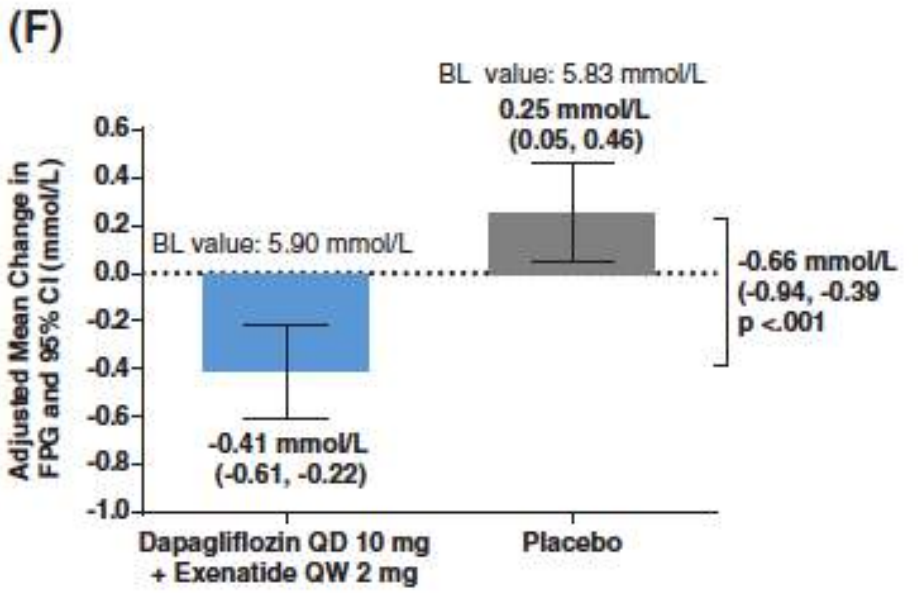
Diabetes Obes Metab 2017; **19(1)**:49–60

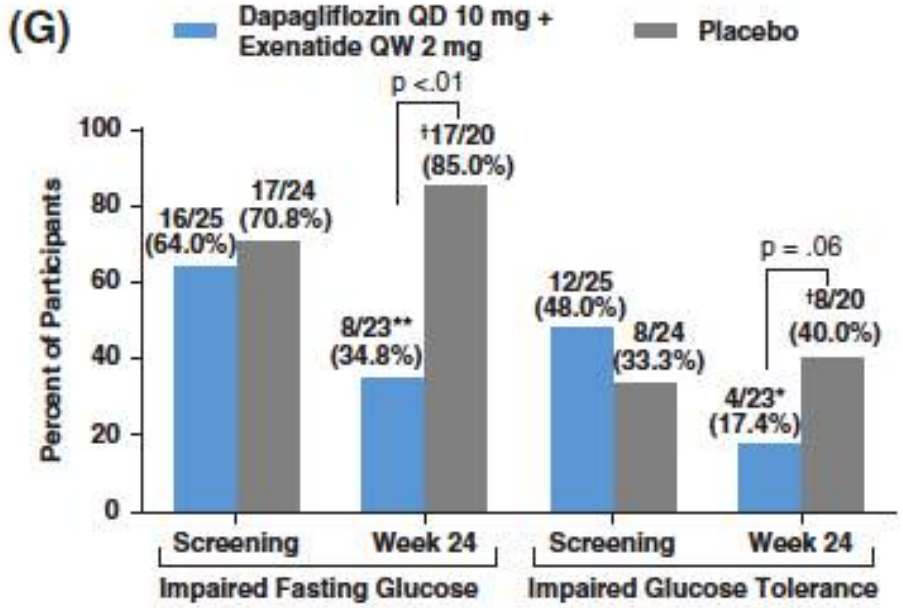

(A)
Screening
Double-blind treatment period
Dapagliflozin once daily 10 mg + Exenatide once weekly 2mg
R
Placebo oral tablet once daily and placebo injection once weekly
Enrollment
Randomization
Open-label extension
Week: –2 to –1
0
1–2
4
8
12
24

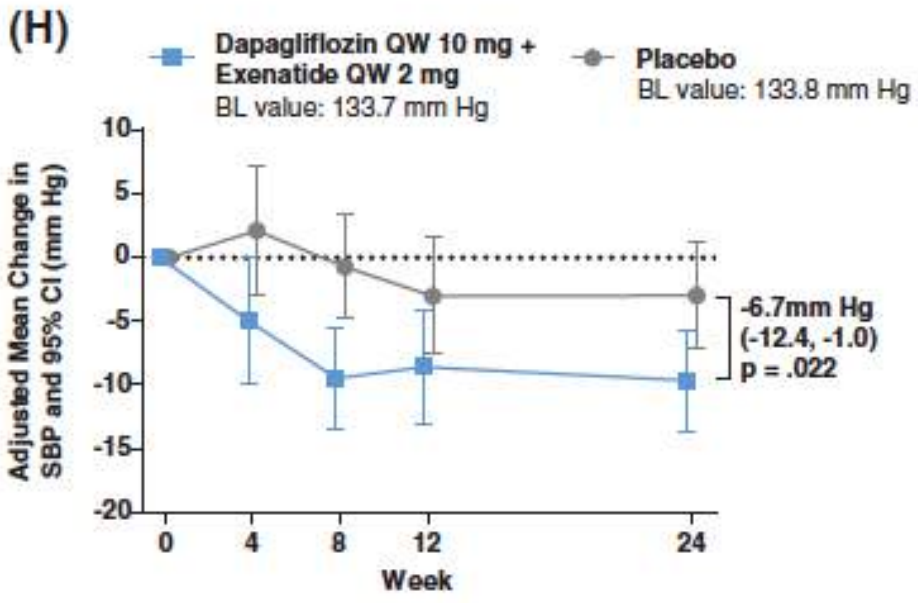

(B)
61 Screened
11 Screening failures
8 Entry criteria not met
1 Planned surgery
1 Administrative error
1 Withdrawal of consent
50 Randomized
Dapagliflozin once daily 10 mg + Exenatide once weekly 2 mg n = 25
Placebo oral tablet once daily and placebo injection once weekly n = 25
2 (8%) Discontinued
2 Adverse event:
– Abdominal pain
– Injection-site reaction
5 (20%) Discontinued
3 Adverse event:
– Skin ulcer/vasculitis
– Malaise
– Dyspnea/fatigue
1 Severe protocol non-compliance*
1 Withdrawal of consent
23 (92%) Completed
20 (80%) Completed


(A)
Dapagliflozin QW 10 mg + Exenatide QW 2 mg
BL value: 106.43 kg
Placebo
BL value: 102.72 kg
Adjusted Mean Change in Body Weight and 95% CI (kg)
2
1
0
-1
-2
-3
-4
-5
-6
-7
0
4
8
12
24
Week
-4.13 kg
(-6.44, -1.81)
p <.001
(B)
Adjusted Mean Percentage Change in Body Weight and 95% CI (%)
2
0
-2
-4
-6
-8
-4.47%
(-6.04, -2.89)
-0.27%
(-1.92, -1.37)
-4.19%
(-6.47, -1.92)
p <.001
Dapagliflozin QD 10 mg + Exenatide QW 2 mg
Placebo
(C)
Dapagliflozin QW 10 mg + Exenatide QW 2 mg
Percent Change in Body Weight
10
5
0
-5
-10
-15
-20
0
4
8
12
24
Week
Proportion within weight change ranges at 24 weeks, n/N (%)
Gain:
2/25 (8.0)
Loss up to 4.9%:
12/25 (48.0)
Loss ≥5%:
9/25 (36.0)
Missing:
2/25 (8.0)
(D)
Placebo
Percent Change in Body Weight
10
5
0
-5
-10
-15
-20
0
4
8
12
24
Week
Proportion within weight change ranges at 24 weeks, n/N (%)
Gain:
9/24 (37.5)
Loss up to 4.9%:
10/24 (41.7)
Loss ≥5%:
1/24 (4.2)
Missing:
4/24 (16.7)


(E)
Dapagliflozin QW 10 mg + Exenatide QW 2 mg
BL value: 37.2 mmol/mol 5.6%
Placebo
BL value: 38.1 mmol/mol 5.6%
Adjusted Mean Change in HbA1c and 95% CI (mmol/mol)
2
1
0
-1
-2
-3
-4
-5
-6
0
4
8
12
24
Week
-2.3 mmol/mol (-3.5, -1.1)
-0.21% (-0.32, -0.10)
p <.001


(F)
BL value: 5.83 mmol/L
0.25 mmol/L (0.05, 0.46)
BL value: 5.90 mmol/L
Adjusted Mean Change in FPG and 95% CI (mmol/L)
0.6
0.4
0.2
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
-0.41 mmol/L (-0.61, -0.22)
-0.66 mmol/L (-0.94, -0.39)
p <.001
Dapagliflozin QD 10 mg + Exenatide QW 2 mg
Placebo


(G)
Dapagliflozin QD 10 mg + Exenatide QW 2 mg
Placebo
p <.01
p = .06
Percent of Participants
100
80
60
40
20
0
16/25 (64.0%)
17/24 (70.8%)
8/23** (34.8%)
†17/20 (85.0%)
12/25 (48.0%)
8/24 (33.3%)
4/23* (17.4%)
†8/20 (40.0%)
Screening
Week 24
Screening
Week 24
Impaired Fasting Glucose
Impaired Glucose Tolerance


(H)
Dapagliflozin QW 10 mg + Exenatide QW 2 mg
BL value: 133.7 mm Hg
Placebo
BL value: 133.8 mm Hg
Adjusted Mean Change in SBP and 95% CI (mm Hg)
10
5
0
-5
-10
-15
-20
0
4
8
12
24
Week
-6.7mm Hg (-12.4, -1.0)
p = .022

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ORIGINAL ARTICLE

Combination therapy with GLP-1 analogues and SGLT-2 inhibitors in the management of diabesity: the real world experience

Herpreet Deol[1] · Leoni Lekkakou[1] · Ananth K. Viswanath[1] · Joseph M. Pappachan[1]

Table 1 Baseline demographic parameters before commencement of combination therapy with glucagon-like peptide-1 (GLP-1) agonists and sodium-glucose co-transporter type-2 (SGLT-2) inhibitors

Parameters	Sub-type	Mean ± SD/frequency
Age (years)	–	57.4 ± 7.8
BMI kg/m^2	–	38.4 ± 6.3
Weight in kg	–	107.2 ± 17.8
Years of diabetes	–	13.1 ± 7.2
HbA1c (%)	–	8.8 ± 1.47
Systolic BP mmHg	–	134 ± 16
Diastolic BP mmHg	–	77 ± 10
Renal function	eGFR (ml/min)	80 ± 13
	Creatinine (μmol/L)	78 ± 16
Diabetes medications	***Insulin***	62.2 % (n23)
	Mean dose	89 units ± 51
	Metformin	78.4 % (n29)
	GLP-1 agonist	
	Exenatide	8.1 % (n3)
	Liraglutide	78.4 % (n29)
	Lixisenatide	13.5 % (n5)
	SGLT-2 inhibitor	
	Dapagliflozin	97.3 % (n36)
	Canagliflozin	2.7 % (n1)
Duration of treatment with combination regimen (days)		139 ± 32.6

HbA1c glycated haemoglobin, *BMI* body mass index, *eGFR* estimated glomerular filtration rate

Table 2 Univariate analysis showing study outcomes at 3–6 months in patients on combination therapy with glucagon-like peptide-1 (GLP-1) agonists and sodium-glucose co-transporter type-2 (SGLT-2) inhibitors

Variables	Mean difference	95 % confidence interval	'*P*' value
Weight	3.07	1.781–4.359	0.000
HbA1c	1.05	0.69–1.41	0.000
BMI	1.13	0.674–1.58	0.000
Systolic blood pressure	1.162	–6.09–8.42	0.747
Creatinine	–1.28	–6.14—3.62	0.561
eGFR	–2.584	–2.314—6.982	0.314
Total insulin dose reduction	6.81	0.62–13.00	0.032

HbA1c glycated haemoglobin, *BMI* body mass index, *eGFR* estimated glomerular filtration rate

Mesaj

Eslik eden DM olsun veya olmasin Obezite cok onemli bir kronik hastaliktir

Tedavisinde yanliz yasam tarzi degisikliginde israr edilmesi dogru bir yaklasim degildir

Biyolojik / Farmakolojik tedavi hep gundemde Tutulmalidir ve hastalar ikna edilmelidir.