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Effect of liraglutide on estimates of lipolysis and lipid oxidation in obese patients with stable coronary artery disease and newly diagnosed type 2 diabetes: A randomized trial.

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Abstract

Elevated levels of non-esterified fatty acids (NEFA) play a role in insulin resistance, impaired beta-cell function and is a denominator of the abnormal atherogenic lipid profile characterizing obese type 2 diabetes (T2DM) patients. We hypothesized that the GLP-1 receptor agonist liraglutide in combination with metformin would reduce lipolysis. In a randomized, double-blind, placebo-controlled, cross-over trial 41 T2DM patients with coronary artery disease were randomized and treated with liraglutide-metformin vs. placebo-metformin in 12 + 12-week periods with ≥2-weeks wash-out before and between the intervention periods. NEFA kinetics were estimated by the Boston *NEFA minimal model* from plasma NEFA and glucose levels measured during a standard 180 minutes frequently sampled intravenous glucose tolerance test. Liraglutide-metformin reduced estimate of lipolysis. Furthermore, placebo-metformin increased estimates of lipid oxidation; while, liraglutide abolished this effect. We conclude that liraglutide exerts a clinically relevant reduction in estimates of lipolysis and lipid oxidation, partially explained by improved insulin secretion during an intravenous glucose tolerance test.

Introduction

Obesity, insulin resistance (IR) and type 2 diabetes mellitus (T2DM), are risk factors for cardiovascular morbidity and mortality. Non-esterified fatty acids (NEFA) are important oxidative fuels but elevated levels (lipotoxicity) plays a role in the development of IR in obesity and T2DM, however, it is suggested that other pathophysiologic pathways may explain the relationship between NEFA and IR in obesity.[1] Elevated plasma NEFA level is also a major cause of impaired beta-cell function, increased gluconeogenesis and, in addition by increasing VLDL secretion from the liver induces hypertriglyceridemia and facilitates appearance of small dense low-density lipoproteins as well as endothelial dysfunction, all factors contributing to arteriosclerosis[2]. IR accelerates lipolysis increasing NEFA concentrations, whereas acute reduction of NEFA concentration in plasma lowers plasma glucose and improves insulin sensitivity in patients with T2DM[3]. High levels of NEFA are associated independently to increase risk for cardiovascular disease and adverse outcome in patients with coronary artery disease (CAD)[4].

The incretin glucagon-like peptide-1 (GLP-1) is a powerful insulin-releasing hormone and its effect is glucose dependent and exerted by a G-protein coupled receptor. Metformin enhances the secretion of GLP-1. The GLP-1 receptor agonist (GLP-1-RA) liraglutide reduces NEFA plasma levels, primarily by increasing insulin secretion[5]. However, elevated levels of NEFA contributes to impaired beta-cell responsiveness to GLP-1 and improvements in lipid control increase the efficacy of incretin-based therapy[6]. Furthermore, the mechanism by which liraglutide improves cardiovascular morbidity and mortality in T2DM patients is yet debated. We hypothesized that liraglutide may impact on lipolysis and lipid oxidation in these patients. To

obtain an estimate of the effect of liraglutide on these parameters we applied the Boston Minimal Model for NEFA metabolism on the insulin modified frequently sampled intravenous glucose tolerance (im-FSIGT).[7]

Materials and methods

The study was an investigator-initiated, double-blind, randomized, placebo-controlled, cross-over trial. Patients included had stable CAD and newly diagnosed (< 2 years) T2DM and with body mass index (BMI) ≥25 kg/m^2. The intervention was liraglutide + metformin vs. placebo + metformin. Details on time course and intervention are presented in Supplementary Appendix, figure 1. In the beginning and end of each 12-week treatment period each treatment effect was evaluated by an im-FSIGT using a standardized protocol according to the *Minimal Model* approach (MINMOD Millenium used for calculations)[8]. A NEFA *minimal model* was applied on NEFA and glucose[7] (for further details on this: Supplementary appendix figure 2). For assay specifications see supplementary appendix, table 1.

Statistical analysis was performed with SAS 9.4 (SAS Institute Inc., Cary, North Carolina, USA). The area under curve (AUC) was calculated using the trapezoidal rule. Data are reported as mean (SD) or median (IQR). Student's paired t-test/Wilcoxon's Signed Rank were used when data were normally/non-normally distributed. Two-sided $p<0.05$ was considered statistically significant. Power calculation was based on an >70% improvement in disposition index (DI) and would require 22 patients in paired analyses provide a statistical power of 80%[8]. Post-hoc power analysis is provided in the supplementary appendix.

The study was approved by the Regional Committee on Biomedical Research Ethics of the Capital Region of Denmark and informed consent was obtained from all participants. The protocol was registered at Clinicaltrials.gov with ID: NCT01595789.

Results

The main result of the study was that liraglutide reduced indices of lipolysis and lipid oxidation during an im-FSIGT.

NEFA: Fasting NEFA was reduced in both treatment arms but more so with liraglutide (difference: -9.4 (3.9) µmol/L, $p < 0.0001$). Both placebo-metformin and liraglutide-metformin reduced $NEFA_{AUC}$ with no difference between treatments ($p = 0.75$). However, $NEFA_{nadir}$ was lower and reached earlier with liraglutide treatment with a significantly difference between treatments of -24.3 (0.9) µmol/L, $p < 0.0001$ (table 1 and figure 1).

Lipolysis: The rate of provision of NEFA to the plasma pool, S_{FFA}, was non-significantly reduced by placebo-metformin ($p = 0.054$) whereas, liraglutide-metformin significantly reduced the rate from 36.6 (10.4) to 25.9 (14.4) µmol/L/min, $p < 0.001$ (Table 1), however non-significant between treatment periods. Baseline net rate of lipolysis, LIP_0, was not altered by liraglutide treatment, however the $AUC_{lipolysis}$ was increased by placebo but reduced by liraglutide, resulting in at difference between treatments of -774 (31) µmol/L/min ($p < 0.0001$) (Table 1 and Supplementary appendix figure 3).

Lipid oxidation: The rate at which NEFAs left the plasma pool, K_{FFA}, was reduced by liraglutide by -2.16 (1.34) %/min, $p < 0.0001$ compared to placebo. Liraglutide exerted a reduction of baseline net rate of lipidoxidation, OX_0, of -8.2 (5.1) µmol/L/min, $p < 000.1$ compared to placebo (table 1). $AUC_{lipid\ oxidation}$ was increased by placebo but reduced by liraglutide resulting in a difference between treatments of -850 (31) µmol/L/min, $p < 0.0001$ (Table 1 and Supplementary appendix figure 3).

We have previously reported how liraglutide reduced hyperglycemia and increased insulin response to glucose and doubling DI with no effect on insulin sensitivity (*MINMOD Millennium* analysis) despite an expected net body weight loss of 2.7 kg[8] (Table 1).

The NEFA minimal model also derives additional glucometabolic parameters, thus compared to placebo; R_0, the initial concentration of glucose in remote compartments, was significantly reduced by liraglutide by -1.966 (1.525) mmol/L, p < 0001; the threshold, f_s, in plasma glucose above which plasma glucose enters remote compartments was increased by liraglutide by 1.63 (1.34) mmol/L, p < 0.0001; the delay, T (minutes), of glucose entry into the remote compartment was reduced by liraglutide by -5.0 (3.44) min, p < 0.0001; the rate of movement of plasma glucose into the remote compartment and the clearance from there, k_c, was increased by 2.09 (2.06) %/min, p = 0.0001 with liraglutide.

Explanatory variables and carry-over effect: Baseline NEFA did not correlate to weight (R^2=0.01; p=0.96), BMI (R^2=0.01; p= 0.7) or HOMA-IR (R^2=0.03; p=0.28) and the variance of weight loss was not associated with baseline weight, BMI, sequence of treatment and differences in treatment duration (R^2=0.06; p=0.8)[8]. Liraglutide induced a weight loss of 2.7 (-6.7 to -0.6) kg, p < 0.001[8] and the presence of a possible carry-over effect was estimated using sum values by the t-test,[8] but no such effect was found with respect to weight loss (p = 0.45), measures of insulin sensitivity (p = 0.21) nor beta-cell function (p = 0.88)[8].

Discussion

It was shown that liraglutide-metformin compared to placebo-metformin during an im-FSIGT reduced estimates of lipolysis and lipid oxidation in patients with CAD and newly diagnosed T2DM. This is the first study, to the best of our knowledge, which evaluated the effect of liraglutide on lipid oxidation and lipolysis by minimal model analysis in humans.

Metformin plus liraglutide reduced NEFA to a larger extend than metformin alone, which is in accordance with the findings of Kim et al.[5], however, they evaluated the effect of a liraglutide assisted weight loss combined with an energy-restricted diet. Therefore, we suggest that our setup is more able to reveal the effect of liraglutide treatment in at real-word setting, because only very few patients will be on a long-term energy-restricted diet in real-life. We found the estimate of lipolysis (S_{ffa}) was not affected by metformin but nevertheless suppressed during liraglutide therapy, though not significantly when corrected for placebo. Liraglutide is a powerful insulin secretagogues[8] and $NEFA_{nadir}$ was significantly lower with liraglutide treatment and was attained earlier (table 1). Both lipolysis and lipid oxidation during the 180 minutes test were reduced by liraglutide-metformin treatment but increased by placebo-metformin (supplementary appendix figure 3). Metformin treatment has been shown to induce lipoprotein lipase activity in muscles[9] and prevents NEFA-induced extrahepatic IR but not NEFA-induced hepatic IR[14].

Based on our present results we speculate that the effects of liraglutide on lipid metabolism could in some instances be counteracted by metformin (i.e. metformin increasing indices of lipid oxidation opposing the effect of liraglutide), but with regards to other metabolic pathways e.g. glucose metabolism the effect of metformin and liraglutide could be additive. Although weight loss and improvement in IR may mediate a decrease in NEFA, liraglutide-induced modest weight loss did not reduce NEFA[5] in the study by Kim and coworkers or improved insulin sensitivity in the present patients as previous reported[8]. Increasing plasma NEFA by infusion to diabetic levels may cause hepatic IR and inhibition of insulin secretion in normoglycemic subjects[2]. In T2DM the suppression of NEFA by insulin is diminished because of IR and also increased NEFA levels impair insulin secretion[11] and aggravates IR . Reductions in NEFA excursions by liraglutide assessed by meal tests has previously been reported[5].

To our knowledge there has been no previous reports on the effect of liraglutide on the additional glucometabolic indexes provided by the Boston NEFA minimal model. This model employs two compartments, plasma and tissue (remote compartment); liraglutide strongly decreases tissue level of glucose and increases its clearance from plasma and tissue levels. Additionally, the delay of entry of glucose to tissue level is reduced by liraglutide, it is suggested that this delay is associated to the transcapillary transport and rate determining step for insulin action[7]. Our results, suggests that by reducing this delay, liraglutide, significantly improves insulin action in tissues and thereby glucose clearance from plasma and tissue, which is in accordance with previously published data[8].

GLP-1, metformin and insulin are regulators of intestinal lipoprotein secretion[12], however, it is unclear to what extent GLP-1 exerts a direct action on adipose tissue[1] or the effect on NEFA metabolism is explained by the increased insulin secretion per se. Nevertheless, the changes in NEFA concentrations observed after liraglutide treatment are not likely to be due to weight loss or an associated improvement in IR[5]. Additionally, the intestinal lipoprotein metabolism is dysregulated in insulin resistant states and T2DM[13], however the present study design would tend to abolish intestinal NEFA production/uptake in the subjects as they were fasting >10 hours before the im-FSIGT. Despite a moderate weight loss (<5 kg), there were no carry-over effect between treatment periods in respect to weight loss or insulin sensitivity[8].

The effects on lipolysis and lipid oxidation observed may also reflect a change from NEFA to glucose utilization as liraglutide treatment reduces glucose levels indicating an increased glucose clearance suggesting a shift from lipid to glucose oxidation. This interpretation is consistent with our findings with a significant all-over reduction in lipolysis and lipid oxidation during liraglutide treatment. This may also indicate that liraglutide therapy is able to induce or improve metabolic flexibility[15].

Our data adds to the knowledge of the effect of liraglutide on glucose and lipid metabolism, and may add to the explanation of the improved long-term outcome in patients with CAD and T2DM since reducing NEFA levels also improves cardiac function[16]. However, the present experimental setting may not directly translate into a clinical setting and further research is warranted.

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	Placebo		p	Liraglutide		p	Difference	p
	before	after		before	after			
$NEFA_0$ (µmol/L)	369.5 (1.8)	324.4 (1.4)	<0.0001	394.1 (1.8)	339.6 (2.7)	<0.0001	-9.4 (3.9)	<0.0001
$NEFA_{AUC}$ (µmol/L/^{180}min)	43857 (212)	36290 (178)	<0.001	42869 (204)	35874 (187)	<0.0002	572 (392)	0.75
R_0 (mmol/L)	1.921 (0.593)	1.103 (0.595)	<0.001	3.641 (0.628)	0.857 (1.108)	<0.0001	-1.966 (1.525)	<0.0001
k_c (%/min)	3.69 (1.52)	2.32 (0.21)	<0.001	4.36 (1.21)	5.07 (0.64)	0.03	2.09 (2.06)	0.0001
S_{ffa} (µmol/L/min)	33.9 (6.8)	29.3 (7.0)	0.05	36.6 (10.4)	25.9 (5.4)	<0.001	-6.1 (15.2)	0.1
K_{ffa} (%/min)	4.37 (0.82)	6.76 (0.52)	<0.0001	5.02 (0.87)	5.25 (0.32)	0.2	-2.16 (1.34)	<0.0001
fs (mmol/L)	3.73 (0.645)	4.69 (0.639)	<0.0001	2.09 (0.451)	4.68 (0.882)	<0.0001	1.63 (1.344)	<0.0001
T (min)	3.52 (0.58)	6.99 (3.34)	0.0001	7.93 (0.32)	6.39 (0.50)	<0.0001	-5.0 (3.44)	<0.0001
LIP_0 (µmol/L/min)	17.1 (3.5)	20.2 (1.6)	0.002	15.6 (3.4)	16.7 (1.9)	0.2	-2.0 (5.5)	0.1
LIP_{180} (µmol/L/min)	14.3 (2.5)	18.6 (1.4)	<0.0001	14.5 (2.4)	17.2 (1.4)	0.0002	-1.5 (4.0)	0.1
$Lipolysis_{AUC}$ (µmol/L/^{180}min)	1856 (20)	2382 (10)	<0.0001	2059 (20)	1812 (9)	<0.0001	-774 (31)	<0.0001
OX_0 (µmol/L/min)	16.2 (3.0)	21.9 (1.7)	<0.0001	19.8 (3.4)	17.4 (1.5)	<0.01	-8.2 (5.1)	<0.0001
OX_{180} (µmol/L/min)	12.9 (2.4)	17.2 (1.3)	<0.0001	13.6 (2.4)	15.2 (1.4)	<0.02	-2.7 (3.9)	<0.01
Lipid $oxidation_{AUC}$ (µmol/L/^{180}min)	1931 (19)	2453 (10)	<0.0001	2182 (20)	1854 (9)	<0.0001	-850 (31)	<0.0001
$NEFA_{nadir}$ (µmol/L)	190.3 (0.5)	149.8 (0.4)	<0.0001	187.5 (0.5)	122.7 (0.4)	<0.0001	-24.3 (0.9)	<0.0001
T_{min} (minutes)	76 (0.04)	74 (0.04)	<0.0001	74 (0.04)	68 (0.04)	<0.0001	-4 (0.08)	<0.0001

	Baseline	Liraglutide	Placebo	Difference	n	p
Age (years)*	62.3 (7.6)					
Males (n(%))*	31 (8079.5%)					
Weight (kg)*	96.9 (17.1)	-4.5 (-6.3;-1.4)	-0.7 (-2.4;1.0)	-2.7(-6.7;-0.6)	30	0.0004
BMI (kg/m^2)*	31.6 (4.8)	-1.4 (1.2)	-0.3 (0.8)	-1.1 (1.4)	30	0.0002
Fasting Glucose (mmol/L)*	6.9 (6.1;7.4)	-1.0 (-1.42;-0.53)	-0.73 (-1.18;-0.23)	-0.35 (-0.87;0.13)	30	0.025
HbA1c (mmol/mol)*	47 (6)	-4.3 (4.23)	-1.06 (4.93)	-3.3 (6.5)	30	0.0096
HOMA-IR*	4.9 (3.0;7.5)	-1.29 (-2.68;0.29)	-0.7 (-1.82;0.05)	-0.18 (-2.58;1.12)	30	0.24
AIRg (mU x L^{-1} x min)*	101 (45;247)	497 (343;626)	80 (8;146)	402 (243;601)	30	<0.0001

DI*	807 (1840)	902(593)	302(1115)	766(824)	30	<0.0001
SI ($(mU/L)^{-1}$ x min^{-1})*	2.28 (1.16;3.45)	-0.07(-0.98;0.9)	0.1 (-1.38;0.56)	-0.37 (-1.84;1.68)	30	0.96
$AUC_{Glucose}$ ($mmol/L/^{180}min$)*	1567 (176)	-346 (196)	-105 (208)	-241 (141)	30	0.001
$AUC_{Insulin}$ ($pmol/L/^{180}min$)*	51612 (20701)	22600 (33848)	-1065 (28537)	23666 (33211)	30	0.001

Table 1.

Table 1 Legend:

NEFA model parameters and indices. Values are mean (SD). P-values without prefix "<" are exact values. $NEFA_0$) initial concentration of NEFA in plasma, R_0) initial concentration of glucose in remote compartments. k_c) rate constant describing the movement of plasma glucose into the remote compartment and the clearance of glucose from the remote compartment. S_{FFA}) rate of provision of NEFA to the plasma pool; an estimate of lipolysis. K_{FFA}) rate constant describing the rate at which NEFAs leave the plasma pool; an estimate of lipid oxidation. f_s) a threshold in plasma glucose concentration above which elevated levels of plasma glucose result after a delay of Ƭ (min), in entry of plasma into a remote compartment. LIP) the rate of lipolysis and OX) net rate of oxidation of NEFA at time 0 and 180 min. T_{min}) the time in minutes to $NEFA_{nadir}$ is reached. $Lipolysis_{AUC}$ and Lipid $oxidation_{AUC}$ are changes in AUC during the 180 minutes (see Supplementary Appendix figure 3).[7] *) excerpts of data published previously in *Diabetes, Obesity and Metabolism (2017)*[8] and AIR_g , DI and SI from *MinMod Millenium* analysis.[8]

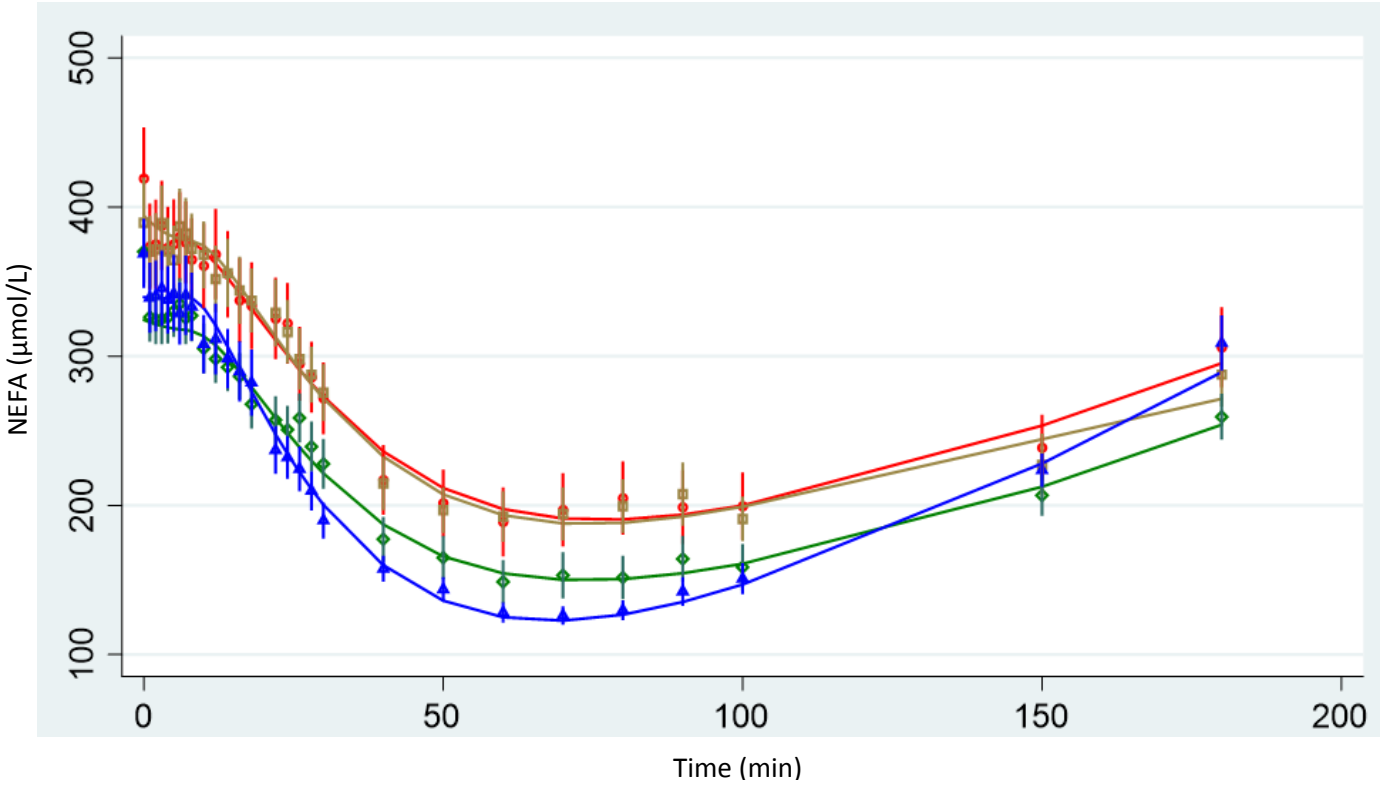

Figure 1) Time course of plasma NEFA. Dots are measured values (means) and lines are fitted values. Error bars denotes SEM. Red; start of placebo period, Green; end of placebo period (AUC, $p < 0.001$). Brown; start of liraglutide period, Blue; end of liraglutide period (AUC, $p < 0.0002$). Difference between placebo and liraglutide (AUC, $p = 0.75$). X-axis; minutes. Y-axis NEFA µmol/L. Detailed data are presented in Table 1.

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