Ghrelin for patients with anorexia/cachexia related to advanced cancer: a randomised, placebo-controlled, double-blind, cross-over Phase I/II Study

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Background: Cachexia

To palliate cachexia a multidimensional approach is needed, including pharmacologcial treatments

Italic: „neg“
Red: Combos

Pharmacological treatmens cachexia

Progestins (Megestrol acetate, MPA)
Corticosteroids
(Prokinetic agents (domperidone, metoclopramide))

Cannabinoids, synthetic Cannabinoids
Ω-3-fatty acids (Eicosapentaneoic acid [EPA])
Thalidomide
Anti-TNF (infliximab, enbrel); anti-IL6, etc.
Anti-oxidants, COX-II inhibitors
Ghrelin, GH-secretagogues small molecules
Anabolics (clenbuterol, **oxandrolone**, ***fluoxymester***.)
Condit. Essent. nutrients (BCAA, Arg., Glutamine, Zinc,…)
ATP / ACE-Inhibitors / Allopurinol /B2-mimetics
Melatonin / Carnitine
Erythropoietin
Interleukin – 15, gene-therapy (IGF-1)

„established“

„experimental“

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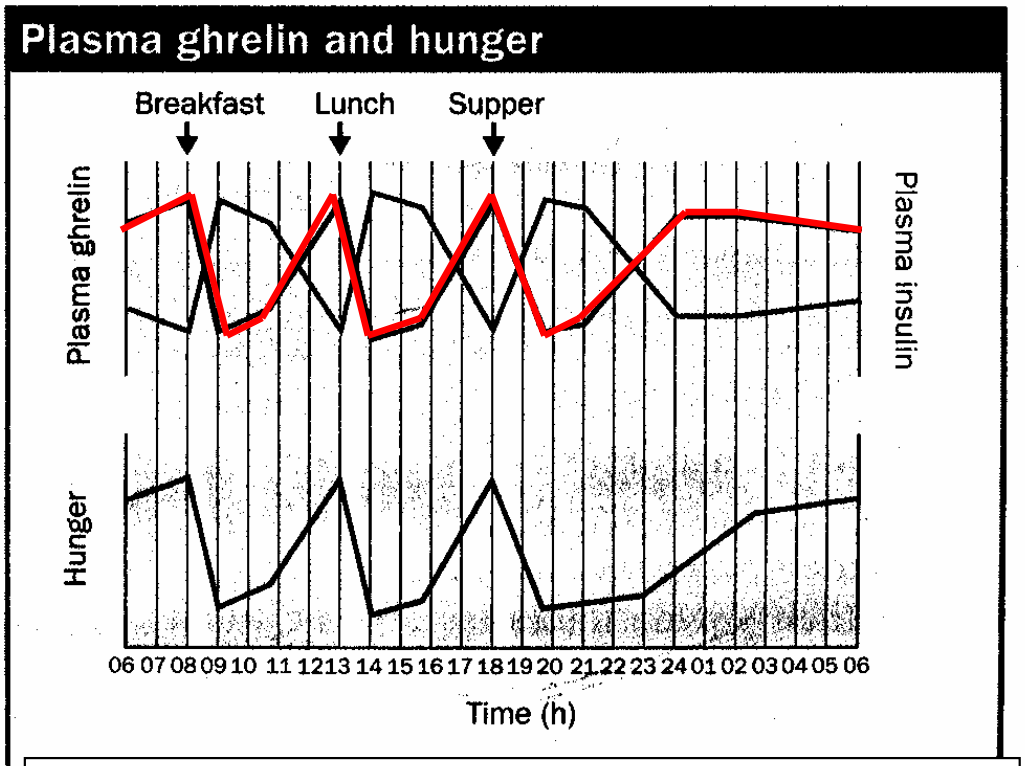
Background: Ghrelin

Stimulatory effects on appetite, gastrointestinal motility, energy metabolism, potential anti-inflammatory



Empty stomach → increase → hunger

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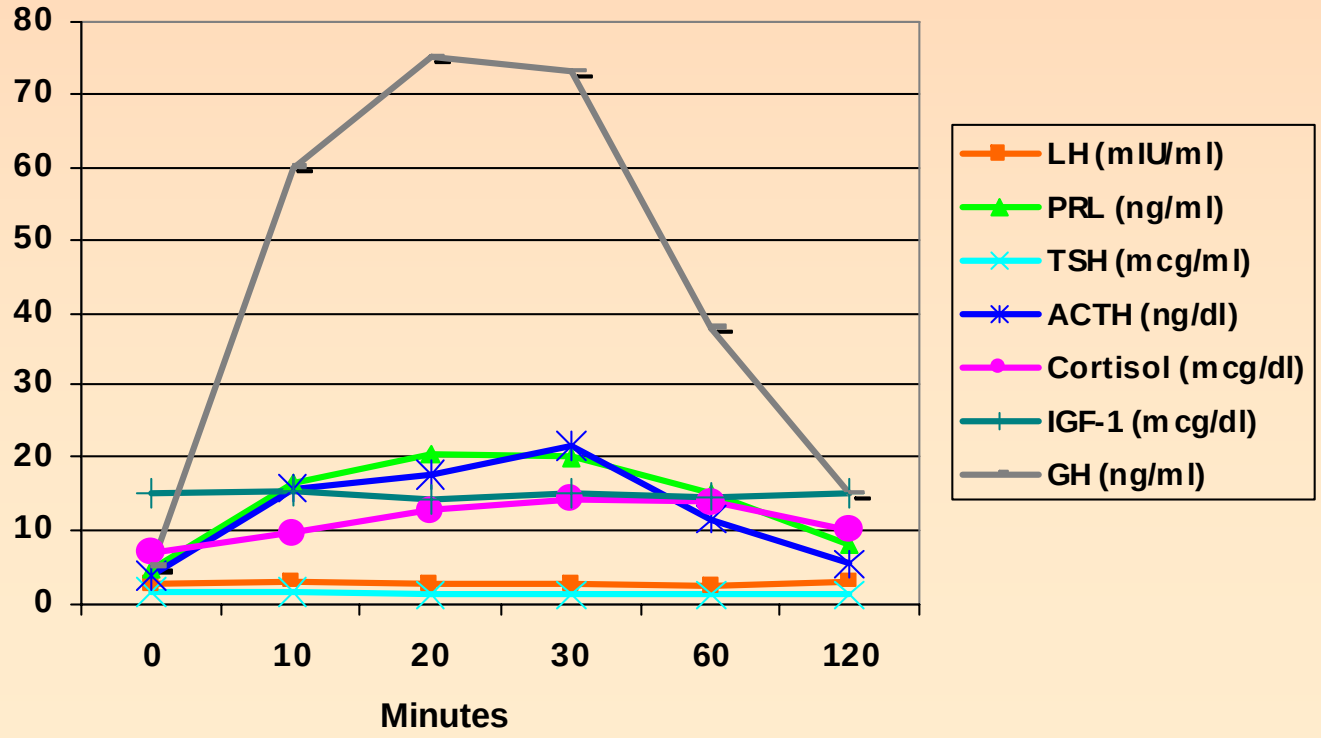
Background: Ghrelin

Very short half-life (minutes)

Stimulates
- Ghrelin receptors
- GH-receptors

Hormonal responses to intravenous administration of 10 μg/kg ghrelin, Adapted from Nagaya et al 2001



Study	Study Population	N	Dose	Main Results	Adverse Events
Takaya et al 2000	Healthy subjects	6	0.2 µg/kg i.v. (n=4) 1 µg/kg i.v. (n=4) 5 µg/kg i.v. (n=4)	Dose-dependent increases in GH, ACTH and cortisol, and PRL levels, no change in LH, FSH, or TSH levels.	Warm sensation and/or bowel movements (n=2)
Peino et al 2000	Healthy subjects	12	0.25-6.6 µg/kg i.v.	Dose-dependent increase in GH and PRL-levels	Sweating (n=2)
Arvat et al 2000	Healthy subjects	4	1 µg/kg i.v.	Marked increase in GH-levels	Hunger (n=3)
Nagaya et al 2001	Patients with chronic heart failure	6	0.1 µg/kg/min i.v. for 60 min	9 mmHg decrease in MAP, 25% increase in CI, 30% increase in stroke volume index	Sensation of warmth and sleepiness (n=2)
Wren et al 2001	Healthy subjects	9	5 pmol/kg/min i.v. for 270 min	28% increase in energy intake and 16-46% increase in appetite score	N.A.
Broglio et al 2001	Healthy subjects	11	1 µg/kg i.v.	Decrease in insulin, increase in glucose levels	Hunger (n=6)
Hataya et al 2001	Healthy subjects	8	0.08 µg/kg i.v. 0.2 µg/kg i.v. 1 µg/kg i.v. 5 µg/kg i.v (n=4)	Synergistic effect of ghrelin and GHRH (1µg/kg) on GH-release	Bowel movements (n=3)
Nagaya et al 2001	Healthy subjects	6	10 µg/kg i.v.	16% increase in CI, 22% increase in stroke volume index , 12 mmHg decrease in MAP, with no effect on heart rate	Warm feeling and sleepiness (n=4)
Arvat et al 2001	Healthy subjects	7	1 µg/kg i.v.	GH-response to ghrelin stronger than response to hexarelin 1 µg/kg and to GHRH 1 µg/kg	Hunger (n=3)
Di Vito et al 2002	Healthy subjects	7	1 µg/kg i.v.	GH-releasing effect of ghrelin reduced by somatostatin.	Hunger (n=5)
Micic et al 2002	Healthy subjects	6	1 µg/kg i.v.	Greater GH-response than GHRH (1 µg/kg) administration	None
Enomoto et al 2003	Healthy subjects	6	1 µg/kg s.c. (n=6) 5 µg/kg s.c. (n=6) 10 µg/kg s.c. (n=6)	Dose-dependent increase in GH-levels, no effect on ACTH, cortisol, IGF-1, or catecholamine levels. Minor increase in LVEF, no impact on MAP or heart rate	Warm sensation and hunger (n=3)
Tassone et al 2003	Obese subjects (n=9) Normal subjects (n=7)	16	1 µg/kg i.v.	GH-response to ghrelin reduced by 55% in obese subjects. PRL, ACTH and cortisol responses similar in obese and normal weight subjects	Facial flushing (n=9) Hunger (n=11)
Broglio et al 2003	Healthy subjects	7	1 µg/kg i.v.	Increase in GH, PRL, cortisol, and glucose levels, decrease in insulin levels. Endocrine activities of ghrelin not significantly affected by cholinergic enhancement or blockade	Hunger (n=4)
Broglio et al 2003	Healthy subjects	7	1 µg/kg i.v.	Blunting of arginine induced insulin increase, no effect on glucose induced insulin increase.	Hunger (n=4)
Broglio et al 2003	Healthy subjects	7	1 µg/kg i.v.	Increase in GH, PRL, ACTH and F-levels. Decrease in insulin levels preceded by increase in glucose levels,	N.A.
Popovic et al 2003	Patients with hypothalamo-pituitary disconnection	9	1 µg/kg i.v.	GH-response to ghrelin, to GHRH and to ghrelin + GHRH markedly reduced in patients with hypothalamopituitary disconnection	N.A.
Broglio et al 2003	Healthy subjects	34	1 µg/kg i.v.	GH-releasing effect of ghrelin found to be independent of gender but to decease with age.	Facial flushing (n=6) Hunger (n=12)
Arosio et al 2003	Healthy subjects	8	3.3 µg/kg i.v.	Increase in GH, SS, PP and glucose levels, decrease in insulin levels.	N.A.
Weikel et al 2003	Healthy subjects	7	50 µg x 4 i.v. during 3 hours	Increase in slow-wave sleep.	None
Broglio et al 2004	Healthy subjects	6	1 µg/kg i.v.	Non-acylated ghrelin antagonises the effects of acylated ghrelin on insulin and glucose.	Hunger (n=3)
Broglio et al 2004	Patients with anorexia nervosa (n=9)	16	1 µg/kg i.v.	GH-response to ghrelin reduced by 57% in patients with anorexia nervosa. Similar PRL, ACTH and cortisol responses in patients with	Facial flushing (n=7) Hunger (n=11)

Clinical experience

Mostly healthy „subjects“

Intravenous Bolus or max 270 min

Doses „low“ 1 mcg/kg

Effect: GH, appetite, energy intake

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Ghrelin – Regulation in patients with advanced cancer

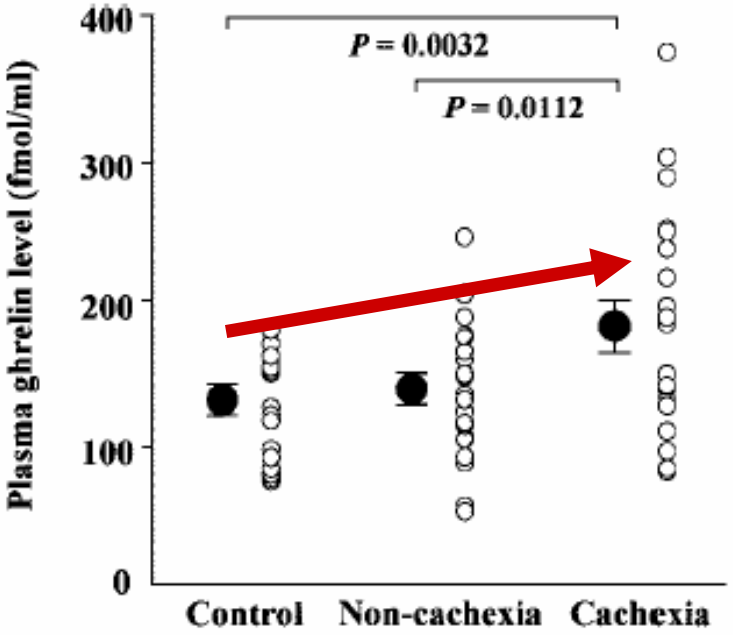

Fig. 1 Plasma ghrelin level in control subjects (*Control*), noncachectic patients with lung cancer (*Non-cachexia*), and cachectic patients with lung cancer (*Cachexia*).

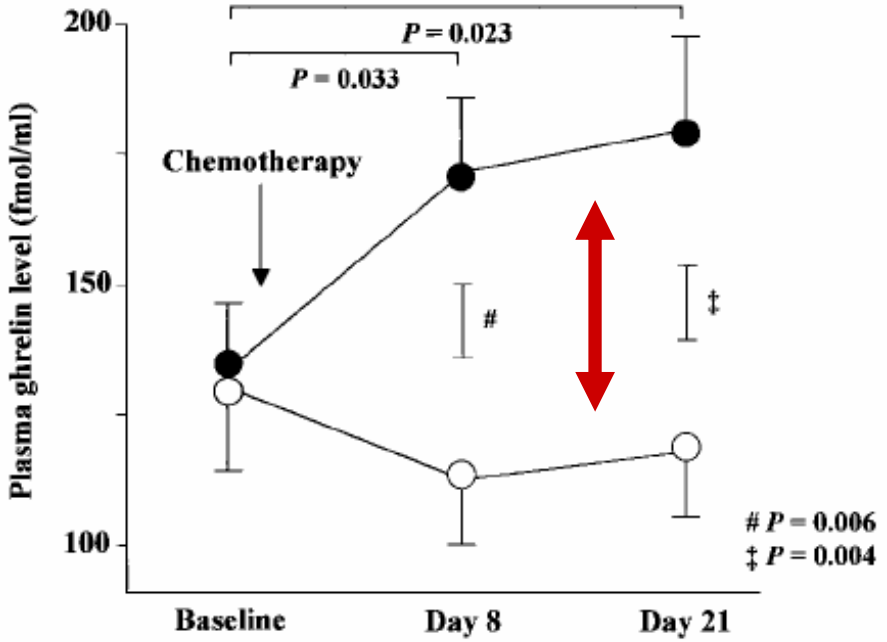

Fig. 3 Change in plasma ghrelin level in lung cancer patients with decreased food intake (●) and those without decreased food intake (○) after chemotherapy. *Baseline*, before chemotherapy.

More cachexia → Ghrelin ↑

Oral intake ↓ → Ghrelin ↑

Shimizu J et al. Clin Cancer Res 2003;9:774

Cachexia → Ghrelin ↑, but only in 2/3 of patients

Wolf I et al. Cancer 2006;106:966

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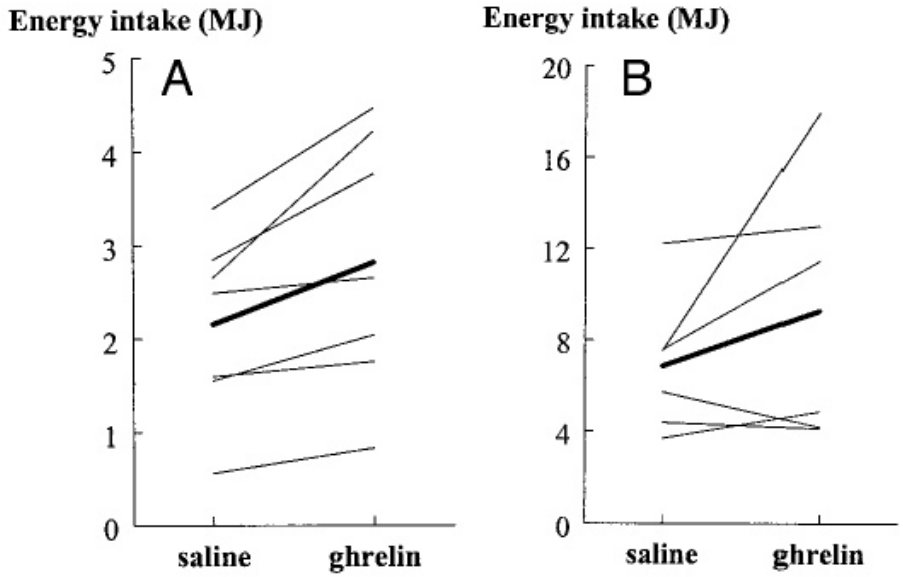
Clinical experience in advanced cancer patients

One trial: Neary NM et al., JCEM 2004;89:2832

TABLE 1. Patient details

Patient no.	Age (yr)	Sex	Precancer weight (kg)	Current weight (kg)	Current BMI (kg/m^2)	Cancer	On chemotherapy?
1	52	F	58	44.3	17.3	Malignant melanoma	No
2	63	F	64	57.5	21.4	Breast	Yes
3	66	F	67	52.7	21.1	Breast	No
4	55	F	58	54.8	25.7	Breast	No
5	54	F	65	64.6	24.3	Breast	No
6	49	M	80	59	19.0	Colon	No
7	41	F	86	83.8	29.3	Breast	Yes

BMI, Body mass index; F, female; M, male.



Hypothesis generating

Breast cancer patients few cachexia

Ghrelin - trial

Aim

to assess safety, tolerability, and preliminary efficacy of i.v. ghrelin in pts with advanced, incurable cancer

Trial design

Inclusion criteria: „real life“

Double – blind (placebo) RCT, double cross-over (Baseline – Day 1 – *Day 4* – Day 8 – *Day 11* – End d17/18)

Short trial: 3 weeks

Monitor Pharmacokinetics of Ghrelin

Patients assessed and treated for secondary anorexia before inclusion (constipation!)

Ghrelin - trial

Drug

From a protein-synthesizing Laboratory

GMP-quality

Wren et al. 2001

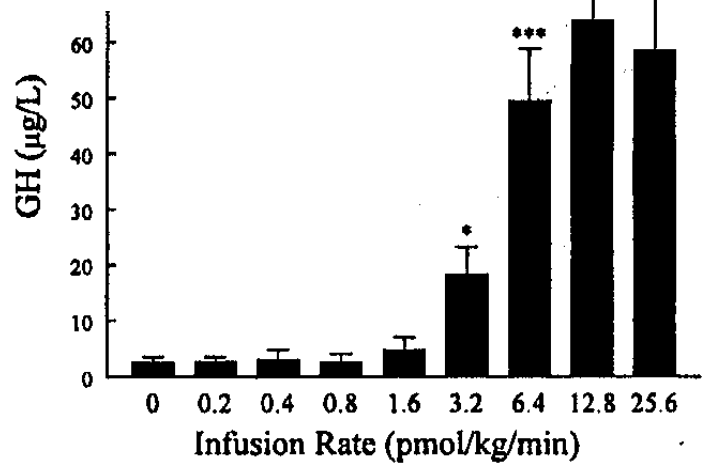


Figure 2. Average GH response to increasing rates of ghrelin infusion, doubling every 20 min from 0.2 to 25.6 pmol/kg/min. * p<0.05, ***p<0.001.

Dose: 2 x maximal GH-stimulation of prior trial

Low dose:
10 pmol/kg/min x 60 min

High dose:
After 10 patients dose x 4:
40pmol

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Ghrelin – trial: endpoints

Toxicity/Tolerability	**CTC-toxicity criteria, subjective rating post-infusion Day 8 and end-of-study: preference of treatment**
Safety	**CTC-criteria, tumor measurements, labs**
Nutritional Intake	**Lunch in the hospital: Fotographs, measure before/after**
Subjective acute effects	**VAS of appetite, hunger, anxiety, early satiety, nausea, fatigue and nutritional intake**
Subjective preference	**At day 8 and EOS: which treatment do you prefer?**
Symptoms & QoL	**EORTC-QlQ-C30, adapted FAACT, NCCTG-instrument**
Weight & Body comp.	**Baseline and end-of-study (3-4weeks)**
Autonomic dysfunction	**Holter-EKG 20 minutes, BL/EOS, then during treatments**
Hormones	**GH, active Ghrelin, total Ghrelin, IGF-1, Insulin, Leptin**

Ghrelin – trial: Patients

Age (years)	Low dose group (n=10)	High dose group (n=11)
Mean	64	68
Min, Max	45, 76	45, 80
Gender		
Male	9	9
Weight (kg)		
Mean	64	56
Min, Max	54, 95	44, 77
Body Mass Index (kg/m^2)		
Mean	21.4	21.1
Min, Max	15.7, 30.0	17.3, 30.4
Diagnosis [n (%)]		
Pancreatic cancer	2(20)	3(27)
Mesothelioma	2(20)	0(0)
Prostate cancer	1(10)	2(18)
Colorectal cancer	3(30)	1(9)
Stomach/esophageal cancer	0(0)	2(18)
NSCLC	1(10)	2(18)
Urogenital cancer	1(10)	0(0)
Cholangiocarcinoma	0(0)	1(9)
Prior Chemotherapy (Number of regimens)		
0	2(20)	3(27)
1	1(10)	4(36)
2	4(40)	2(18)
3	2(20)	2(18)
5	1(10)	0(0)
Prior Radiotherapy	3(30)	5(45)
Prior Hormonal Therapy	1(10)	2(18)
Prior Major GI-surgery [n(%)]		2(18)
Gastrectomy	0(0)	1(9)
Whipple procedure	0(0)	1(9)

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Ghrelin – trial: Preliminary results

Drug-related adverse events (placebo or ghrelin) included increased bowel activity in many patients, sweating, and sporadic nausea/vomiting, dyspnea, chest pain, diarrhea and constipation.

The development of tumour was as expected in the population.

Final results of are expected by Saturday June 3rd

Ghrelin – trial: Conclusion

Ghrelin as given here is well tolerated and safe in pts with far advanced cancer.

Data analysis will reveal whether ghrelin has a potential to palliate eating-related suffering in the palliative care context.

Next steps

1) **Dose finding (minimal dose for maximal nutritional intake)**
2) **Subgroups of patients may respond better?**
3) **Daily application, subcutaneous**

Thank you

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my family

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