

Effects of Human Unacylated Ghrelin on Insulin Sensitivity during Euglycemic-Hyperinsulinemic- Clamp in Patients with Type 2 Diabetes Mellitus.

No registrations found.

Ethical review	Positive opinion
Status	Pending
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON28343

Source

NTR

Health condition

glucose
diabetes
insulin

Sponsors and support

Primary sponsor: Erasmus Medical centre

Source(s) of monetary or material Support: none

Intervention

Outcome measures

Primary outcome

Insulin levels.

Secondary outcome

N/A

Study description

Background summary

Ghrelin has been initially characterized for its property of inducing growth hormone (GH) secretion, hence its name, GH-relin, a function mediated by GHSR1a(1;3). Since unacylated ghrelin does not bind to this receptor and has no physiological effect on GH secretion, it has long been considered as a product with no physiological role. As of today, the ghrelin system is known to exhibit numerous biological effects on the secretion of several pituitary hormones, on the gastric acid secretion and motility, on the exocrine and endocrine pancreatic function, on glucose metabolism, on appetite stimulation and on the cardio-vascular system.

Unacylated ghrelin is known to act on some of these systems, sometimes agonizing, sometimes antagonizing the effects of ghrelin. In particular, unacylated ghrelin has been shown able to prevent the hyperglycaemic effects of ghrelin, when administered concomitantly, in healthy volunteers. This initial observation was followed by several laboratory and clinical works documenting the anti-diabetogenic potential of unacylated ghrelin.

In the Erasmus MC we performed already 2 studies with UAG; one in GH deficient patients and one in morbid obese subjects without overt diabetes. Both of these studies used single bolus i.v. administrations. Accumulated in vitro, in vivo and clinical evidence suggest that unacylated ghrelin:

1. Prevents the diabetogenic effects of acylated ghrelin: this has been evidenced in healthy volunteers and in GH-deficient patients;
2. Inhibits both basal and ghrelin-induced glycogenolysis by human hepatocytes;
3. In vitro, stimulates insulin secretion from insulinoma cells and promote proliferation and inhibit apoptosis of beta cells, a very unique property;
4. Enhances portal insulin response to glucose in rats;
5. May also reduce fat deposition and triglycerides levels, as evidenced in transgenic mice overexpressing unacylated ghrelin.

Moreover, in collaboration with the University of Turin, we observed that a 16-hour continuous infusion of unacylated ghrelin in healthy volunteers increased the first-phase insulin response following meal, reduced glucose levels, and decreased FFA levels, when compared to a saline infusion. Also, preliminary data obtained by the same groups

(unpublished data; study location Turin) in diet-controlled type 2 diabetes patients suggest that the continuous infusion of UAG for 5 hours reduced fasting and post-prandial glucose as well as postprandial FFA.

In addition, the proliferative and anti-apoptotic effects documented on beta cells, apparently a very unique property, support the rationale to also develop UAG in type 1 diabetes and in the pancreas islets transplantations.

Finally, results of recent experiments by the group in Turin on circulating angiogenic cells (CAC) suggest that UAG may beneficially impact the vascular remodeling process which is known to be impaired in type 2 diabetes patients.

From literature, we know that patients with so-called neuro-endocrine tumors sometimes produce large amounts of UAG, leading to serum concentrations of more than 0.1 mcg/ml). Strikingly these patients had no specific phenotype, nor complaints that suggest a direct role of UAG in these symptoms.

Moreover, we have not observed any side-effects in any of the patients that we enrolled in previous study subjects.

Taken together, our data strongly suggest that UAG might have a:

1. Broad safety range, as ultra-high serum levels don't induce specific signs or symptoms;
2. Blood glucose lowering effect;
3. Positive effect on the first phase post-prandial insulin secretion;
4. Insulin sensitizer, potentially with insulin-sparing effect;
5. Trophic effect on the endocrine pancreas;
6. Induces weight loss by preventing fat deposition;
7. Positive effect on the lipid profile, especially on triglycerides and free fatty acids.

Study objective

Unacylated Ghrelin will improve insulin sensitivity.

Study design

No interim analyses, at the end of the study the analyses will take place.

Intervention

Infusion of placebo or UAG during a euglycemic, hyperinsulinemic clamp.

Contacts

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Eligibility criteria

Inclusion criteria

1. Female or Male subject of 18 years of age or older;
2. Documented diagnosis of type 2 diabetes as defined by American Diabetes Association;
3. Diagnosis of type 2 diabetes for at least 3 months prior to screening;
4. Metformin monotherapy for at least 3 months prior to screening is allowed;
5. Screening HbA1c between 6.5% and 8.5%;
6. Body Mass Index between 25 and 35 kg/m².

Exclusion criteria

1. History of or presence of active concomitant conditions or disease that would interfere with the protocol conduct and study assessments, as judged by the investigator;
2. History or presence of long-term type 2 diabetes complications;

3. Clinically significant abnormalities in laboratory evaluation at screening, as judged by the investigator;
4. Use of systemic corticosteroids within 60 days prior to screening;
5. If female, pregnancy or breast feeding;
6. Drug or alcohol dependence or abuse;
7. Participation in a trial of an experimental drug or device within 60 days prior to screening; 30 days for subjects that participated in the oGTT study.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Placebo

Recruitment

NL	
Recruitment status:	Pending
Start date (anticipated):	01-12-2010
Enrollment:	12
Type:	Anticipated

Ethics review

Positive opinion	
Date:	30-08-2010
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 36378

Bron: ToetsingOnline

Titel:

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL2381
NTR-old	NTR2488
CCMO	NL31349.078.10
ISRCTN	ISRCTN wordt niet meer aangevraagd.
OMON	NL-OMON36378

Study results

Summary results

N/A