Ghrelin levels in cirrhosis and hepatocellular carcinoma

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List of Abbreviations

- AGRP — Agouti-related protein.
- AN — Anorexia nervosa.
- BAT — Brown adipose tissue.
- BCAAS — Branched-chain amino acids.
- CHF — Congestive heart failure.
- CNS — Central nervous system.
- COPD — Chronic obstructive pulmonary disease.
- COX-2 — Cyclooxygenase-2.
- CRF — Chronic renal failure.
- CRP — C-reactive protein.
- CST — Cortistatin.
- CT — Calcitonin.
- EPA — Eicosapentaenoic acid.
- ESRD — End stage renal disease.
- GABA — γ-aminobutyric acid.
- GHD — GH deficiency.
- GHRH — Growth hormone releasing hormone.
- GHRP — GH-releasing peptide.
- GHS — GH secretagogue(s).
- GHS-R 1a — GHS receptor type 1a

- GLP Glucagon-like peptide.
- HCC Hepatocellular carcinoma.
- HDL High-density lipoprotein.
- HMTC Human medullary thyroid carcinoma.
- IGF-1 Insulin-like growth factor 1.
- IL Interleukin.
- INF Interferon.
- LMF Lipid mobilizing factor.
- LPL Lipoprotein lipase.
- LPS Lipopolysaccharide.
- LV Left ventricular.
- MAFbx Muscle Atrophy F-box.
- MuRF1 Muscle RING Finger 1
- NAFLD Nonalcoholic fatty liver disease.
- NASH Nonalcoholic steatohepatitis.
- NFκß Nuclear factor kappa ß.
- NPY Neuropeptide Y.
- NSAIDs Non-steroidal anti-inflammatory drugs.
- PIF Proteolysis inducing factor.
- POMC Proopiomelanocortin.
- POMC/CART Proopiomelanocortin and amphetamine regulated transcript.
- PRL prolactin
- PWS Prader-Willi syndrome.

- REE Resting energy expenditure.
- RMR Resting metabolic rate.
- SAP Serum amyloid protein.
- SS Somatostatin.
- Th1 T helper 1.
- TNF Tumor necrosis factor.
- UCP Uncoupling protein.
- ZAG Zinc α2 glycoprotein.

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Introduction:

Ghrelin is a recently identified enteric hormone composed of 28 amino-acid, it is predominantly produced by the stomach, and substantially lower amounts were detected in the bowel, pancreas, testis, pituitary, lung and hypothalamus **(Tena-sempere et al., 2002)**. Ghrelin is an orexigenic hormone, involved in food intake, circulating ghrelin levels rise shortly before expected food intake and fall shortly after every meal **(Cummings et al., 2001)**.

Ghrelin levels are significantly elevated in cachexia associated with heart failure. Similarly in cancer cachexia, ghrelin levels increase in subjects with cachexia and further increase occurs with decreased food intake with chemotherapy **(Shimizu et al., 2003)**.

Anorexia is a problem of paramount importance in patients with advanced liver cirrhosis contributing to malnutrition **(Marchesini et al., 2004)**. Malnutrition is a common problem in liver cirrhosis and hepatocellular carcinoma that may deteriorate the clinical condition with resultant poor prognosis **(Ataseven et al., 2006)**. Because of its orexigenic properties ghrelin hormone may be involved in regulating food intake to compensate for malnutrition **(Wren et al., 2001)**.

In vitro-experiments demonstrate that ghrelin as well as some synthetic analogues are able to modulate the proliferation of several human cell lines. In fact, ghrelin stimulates the cell proliferation of human hepatoma cells that express growth hormone secretagogue receptor-1a (GHSR-1a) **(Jeffery et al., 2002)**.

Aim of the study:

Assessment of ghrelin role in the development of appetite disorders in patients with post-hepatitic liver cirrhosis, and in the development of cachexia associated with hepatocellular carcinoma.

Ghrelin

Ghrelin is a 28- amino acid residue peptide predominantly produced by the stomach (Fig.1). Lower amounts were detected in bowel, pancreas, kidneys, the immune system, placenta, testes, pituitary, lung, and hypothalamus **(Tena-Sempere et al., 2002)**. Ghrelin displays a strong growth hormone-releasing activity which is mediated by the activation of the GH secretagogue receptor type 1a (GHS-R 1a), before the discovery of ghrelin this orphan receptor was known to be specific for the family of synthetic, peptidyl and non- peptidyl GHS **(Kojima et al., 1999)**.

The discovery of ghrelin is an example of reverse pharmacology in which the discovery of the natural ligand ghrelin was started by the synthesis of analogs which led to the discovery of natural receptor and ended by the discovery of the natural ligand (ghrelin**) (Van Der lely et al., 2004)**. Synthetic growth hormone secretagogues (GHS) are a family of ligands, including peptidyl and non peptidyl molecules **(Ghigo et al., 2001).** The first synthesized molecules were non natural peptides [Growth hormone-releasing peptides; GHRPs] designed by Bowers and Momany in the late 1970s **(Bowers, 1998)**. They were