Ghrelin, the endogenous ligand for the growth hormone secretagogue receptor, was discovered in 1999 by Kojima et al. (Kojima *et al*. 1999). Ghrelin is composed of 28 amino acids, with a unique octanoyl modification of hydroxygroup on serine at the 3rd position. This peptide modification is entirely unique to the organism and is essential for the function of this peptide (Bednarek *et al*. 2000). Ghrelin is predominantly produced by cells in the oxyntic mucosa of the stomach (Date *et al*. 2000). According to the widespread distribution of the peptide and its receptor ghrelin has multiple biological effects. Ghrelin is a strong stimulator of the growth hormone secretion in the somatotroph cells of hypophysis (Takaya *et al*. 2000, Peino *et al*. 2000), plays an important role in signaling hypothalamic centers regulating feeding and caloric state (ghrelin leads to an increase of the food intake and a decrease of the energy expenditure) (Nakazoto *et al*. 2001). Its orexigenic effects are independent of growth hormone stimulation and appear to be mediated at least in part through activation of NPY/agouti gene-related protein neurons in the hypothalamic arcuate nucleus.

The aim of our study is to demonstrate the change of active and total ghrelin in malnourished patient and during systemic inflammatory response and their relationship with gender, age, parameters of body composition, nutritional parameters, insulin, leptin and GH/IGF-I axis.

In our study we reported gender differences in plasma total ghrelin levels with higher levels in women. We did not confirm these findings in the plasma active ghrelin. Active and total ghrelin does not affected by ageing.

HDL cholesterol is positively associated with plasma total ghrelin levels. Recent study demonstrated that ghrelin binds to HDL particles. These findings support the possible role of HDL particles as circulating transporters of ghrelin. It's possible that some of enzymes, which are part of HDL particle is responsible for octanoyl modification of hydroxygroup on serine at the 3rd position.

Total ghrelin levels correlated negatively with fasting insulin levels, insulin resistance estimated by HOMA and positively with the insulin sensitivity estimated by QUICKI. In our study we showed no correlation between fasting plasma ghrelin and percent body fat or leptin concentration. On the other hand, fasting plasma total ghrelin significantly negatively correlated with BMI and waist - hip ratio. Our data suggest, that total ghrelin levels best reflect the body weight rather the subcutaneous fat mass. The inverse correlation of total plasma ghrelin with waist - hip ratio support the hypothesis that ghrelin is associated with



central adiposity. These findings support hypothesis that ghrelin may play a role in the etiology of insulin resistance and metabolic syndrom. On the other hand, total plasma ghrelin levels are down regulated in the hyperinsulinemic states.

Ghrelin is a potent stimulator of GH secretion, especially the active ghrelin, which represent a small proportion of total ghrelin levels. In our study, we have not proved a linear relation between the GH level and total or active ghrelin. This finding does not support the unique role of gastric ghrelin on regulation of GH secretion in hypophysis. Ghrelin is important link between actual energy state and production of GH in somatotroph cells. Ghrelin is one of several cooperative factors – pituitary, hypothalamic and peripheral, involving in regulation of GH synthesis and secretion.

Total ghrelin plasma levels are decreased in human obesity and increase in patients with anorexia nervosa (Rosicka *et al. 2003, Kršek et al, 2003*). Circulating ghrelin concentration returns to the base level after normalization of weight. Active ghrelin does not change, but in obese group, we documented relative elevation of active ghrelin.

We propose hypothesis that the change of total plasma ghrelin concentrations observed in obese and malnourished patients represent a physiological adaptation to long-term positive or negative energy balance. The down regulation of ghrelin in obese subject may be

consequence of elevated insulin and higher insulin resistance associated with visceral fat accumulation, and not consequence of total body (mainly subcutaneous) fat accumulation (associated with elevated leptin concentration.

In contrast to patients with anorexia nervosa, total plasma ghrelin levels are surprisingly decreased in malnourished patients with short bowel syndrome characterised by a significant reduction of gut length. We can speculate that the decrease in ghrelin plasma levels is caused by a significant reduction of endocrine cells producing ghrelin in gastrointestinal tract. The fall of plasma levels of orexigennic peptide ghrelin may be contribute partly to decrease appetite in these patients.

According to recent findings ghrelin shows itself as a new inflammatory mediator during both infectious and non-infectious inflammatory reaction. Ghrelin has some features of inflammatory cytokines: low molecular weight, production by different cell types, pluripotent effect, and interaction with other members of cytokine network. During postoperative intraabdominal

sepsis, total ghrelin plasma levels are elevated and positively correlate with both inflammatory cytokines (TNF-alfa, IL-6) and main APP member (CRP). It supports experimental finding that TNF-alfa and IL-6 can be important regulatory factors of ghrelin



synthesis and secretion. This hormonal reaction is not specific to sepsis – the significant increase of total ghrelin occurs during an uncomplicated postoperative response, although to a lesser extent than was shown in sepsis. With regard to its cardiovascular, metabolic and central nervous effects, ghrelin belong to a compensatory antinflammatory response syndrome. It contra-regulates potentially autoaggressive influence of proinflammatory cytokines.