Institutionen för klinisk vetenskap, intervention och teknik (CLINTEC), Enheten för kirurgi

ADIPOSE AND MUSCLE TISSUE METABOLISM IN CANCER CACHEXIA

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i föreläsningssal M63, Karolinska Universitetssjukhuset, Huddinge

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ABSTRACT

Background: Loss of adipose and muscle tissue mass is a key feature of cancer cachexia. Weight loss, glucose intolerance, and insulin resistance are seen in patients with pancreatic ductal adenocarcinoma (PDAC). The mechanism behind the loss of adipose tissue is unknown but has been attributed to increased adipocyte lipolysis, systemic inflammation, apoptosis or reduced lipogenesis. The volume of adipose and muscle tissue in cancer cachexia can be determined by computed tomography (CT).

Aims: The aim of this research was to: 1) Investigate the action of insulin on glucose metabolism and the content of energy metabolites in the muscle tissue of patients with PDAC. 2) Determine whether alterations in fat cell numbers, lipolysis and lipogenesis could account for some of the functional changes observed in adipose tissue in cancer cachexia. 3) Investigate if inflammation is involved in the loss of adipose tissue in cancer cachexia. 4) CT determined tissue volume, could give information about the distribution of wasting of muscle and adipose tissue in patients with recently diagnosed cancer cachexia.

Material and Methods: Muscle biopsies from patients with PDAC and three control groups were assessed for glycogen, adenosine triphosphate and phosphocreatine content. Also measured were glucose incorporation into glycogen, glucose transport in human muscle and rat muscle cell conditioned by PDAC cells. In cancer cachexia patients (CC) and two cancer control patient groups, weight stable (WS,) and gastric obstruction (GO), blood, subcutaneous adipocytes and differentiated preadipocytes were investigated for: 1) Expression of genes regulating inflammation and measurement of systemic and local secretion of inflammation markers (interleukin 6 (IL-6)). 2) In vivo lipolytic activity, lipolysis, lipogenesis and expression of genes regulating lipolysis. 3) Measurements of number and volume of adipocytes. The volume of muscle and adipose tissue was measured with CT and body composition.

Results: Patients in the CC group lost 10% of their habitual weight, patients in GO group lost 17% and patients in WS group lost 3%. Glucose transport, muscle glycogen, and adenosine triphosphate contents were decreased in patients with PDAC compared with control patients, and insulin stimulation did not significantly increase glucose incorporation into glycogen in vitro in patients with PDAC. Media conditioned with PDAC cells did not affect glucose transport in rat muscle cell. Circulating levels of IL-6 and in vivo lipolytic activity were increased in patients in the CC group compared to control patients. In patients in the CC group, there was increased lipolytic effect of catecholamines and natriuretic peptide, and the expression levels of Hormone Sensitive Lipase (HSL) mRNA and protein were increased compared to those in the control patients. The antilipolytic effect of insulin in mature adipocytes and the stimulated lipolytic effect in differentiated preadipocytes were unaltered in cancer cachexia. Patients in the GO group had no change in adipocyte lipolysis. There were no differences in mRNA expression of IL-6 or secretion in adipose tissue and lipogenesis. Adipocytes were decreased in size but their numbers were normal in patients in the CC group compared with those in the WS control group. Adipose tissue was reduced in patients in the CC and GO groups, both according to CT and body composition. CT showed that patients in the CC group displayed a selective decrease in visceral adipose tissue.

Conclusion: Wasting of adipose tissue is a prominent part of the cancer cachexia syndrome and commences before the wasting of muscle tissue. The insulin resistance for active glucose transport in the skeletal muscle of pancreatic cancer patients is not directly related to factors from pancreatic cancer. It is lipolysis, not inflammation, increased apoptosis or decreased lipogenesis, which is involved in the loss of adipose tissue in patients with cancer cachexia. There is increased expression and activity of HSL, which gives rise to an increased rate of lipolysis in patients with cancer cachexia. Although cancer patients with gastrointestinal obstruction, at the time of diagnosis, have lost almost twice the amount of body weight compared to patients with cancer cachexia, the latter group displays more loss of visceral adipose tissue.

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