Cancer Cachexia: Organ-specific Protein Synthesis 2

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Primary Objectives:1. To compare protein synthesis rate of the tumour and normal pancreas between cachectic and non-cachectic patients with pancreatic cancer.Secondary Objective(s):1. To compare protein synthesis rate of liver, intestinal, adipose...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Malignant and unspecified neoplasms gastrointestinal NEC
Study type	Observational invasive

Summary

ID

NL-OMON43238

Source
ToetsingOnline

Brief title
CCOPS2

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC
- Gastrointestinal neoplasms malignant and unspecified

Synonym
Cancer cachexia, pancreatic cancer

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Cancer cachexia, Pancreatic cancer, Protein metabolism, Tracer

Outcome measures

Primary outcome

The primary outcome parameter in this study is tumour and pancreas specific protein synthesis, expressed as fractional synthetic rate (FSR) [%/day]. This parameter is calculated from:

• Plasma and tissue free alanine concentration

• Plasma enrichment of alanine

• Tissue protein bound enrichment of alanine

• Alanine enrichment of the tissue free amino acid pool

The FSR can be calculated using the following formula: FSR = ((tissue enrichment biopsy - calculated baseline tissue enrichment)/(saliva enrichment*time of study))*100%. Baseline plasma albumin enrichment will be used to calculate baseline tissue enrichment

Secondary outcome

Tissues/protein-specific FSR will be calculated from:

o Albumin

o Leukocytes

o Vastus lateralis muscle

o Rectus abdominis muscle

o Liver

o Gallbladder

o Small intestine

o Subcutaneous fat

o Visceral fat

Plasma protein FSR using an unbiased quadrupole time-of-flight mass

spectrometry approach.

Regional tumour protein incorporation will be assessed using matrix assisted

laser desorption/ionisation mass spectrometry imaging.

Study description

Background summary

Pancreatic cancer is a serious disease with high mortality. It is the eighth leading cause of cancer deaths in men and the ninth in women with respectively 138,100 and 127,900 annual deaths worldwide. In the Netherlands, it is the tenth most common form of cancer in men (1024 annual new patients) and eighth in women (1052 annual new patients) with a general 1- and 5-year survival of 18% and 4% respectively. Cancer cachexia is a major problem in patients with pancreatic cancer and greatly decreases survival and quality of life. It is responsible for more than 80% of pancreatic cancer related deaths. Cancer cachexia is a complex syndrome characterized by weight loss and muscle wasting due to a negative energy and muscle protein balance caused by anorexia and catabolic drivers such as systemic inflammation. It is defined as weight loss of >= 5% or weight loss of >= 2% and a body mass index (BMI) of <= 19 or sarcopenia (muscle wasting) in cancer patients.

Many theories have been proposed for the cause of weight loss and profound muscle wasting in cachexia. Muscle protein metabolism is a dynamic process characterized by the balance between the synthesis and breakdown of muscle proteins. A disturbance of this equilibrium can lead to the loss of muscle mass in cachexia. Some theories involve increased catabolic drivers whereas others focus on anabolic resistance. Though both theories may be true, they have never been properly proven in humans. The availability of amino acids labelled with stable isotopes creates the possibility to *trace* them at different points in their metabolism using mass spectrometry. However, previous studies provide conflicting data on protein metabolism in cachexia. Some show that there is increased (muscle) protein breakdown whereas other studies in humans and animals show that this is not the case and that there is in fact a slight decrease in muscle protein synthesis.

Next to protein metabolism in muscle, protein metabolism in visceral organs (e.g. liver, small intestine) might be an important factor in cachexia. A recent bovine study showed that protein synthesis in several visceral organs is in fact much higher than protein synthesis in muscle. Because of its visibility and accessibility, muscle protein has been the main interest of most studies. However, organ protein turnover is much higher than muscle protein turnover and therefore possibly more affected by the negative protein balance in cachexia. Common symptoms in cancer cachexia such as nausea, anorexia and insulin resistance indicate multiple organ dysfunction. Also, tumour protein metabolism has never been studied properly. An extremely high tumour protein turnover would indicate that tumour protein consumption would strongly contribute to the negative balance in cachexia. Some studies on tumour metabolism found a higher protein synthesis rate in colonic and various gastrointestinal malignancies but used the *flooding dose* tracer technique which has limitations compared with the *constant infusion* tracer technique. In our recent study (METC 13-3-068), we assessed the protein synthesis rates in multiple organs during surgery in cachectic patients with pancreatic cancer. Our first analyses indicate high turnover rates as expected. However, because we only included cachectic patients and due to the relatively short time of tracer infusion (around 6 hours), we will not be able to properly show a relation of the cachectic status of a patient with tumour-specific and organ-specific protein synthesis rates.

Tracer techniques have been improved over the last few years and studies using deuterium labelled water (2H2O) have been grown in popularity. Using 2H2O to endogenously label the patient*s protein pool is an elegant method since it allows for longer study duration (days rather than hours) and there is less burden for the patient since and intensive tracer infusion day is no longer necessary. Also, a recent study indicates that fractional synthetic rates (FSRs) of plasma markers of muscle tissue (e.g. creatine kinase M) correlate very well with muscle tissue FSR. Thought this has not been explored yet, plasma protein coming from organs such as the liver or gut might be used to assess organ FSR, which could be used to replace biopsies in many future studies.

In the study proposed here, we will compare tissue protein synthesis of cachectic with non cachectic patients with pancreatic cancer by assessing fractional synthetic rates using deuterium labelled water in a two week period. In addition, we will explore the correlation of plasma protein FSRs with tissue protein FSRs.

Study objective

Primary Objectives:
1. To compare protein synthesis rate of the tumour and normal pancreas between cachectic and non-cachectic patients with pancreatic cancer.
Secondary Objective(s):
1. To compare protein synthesis rate of liver, intestinal, adipose tissue,

muscle tissue, and leukocytes between cachectic and non-cachectic patients with pancreatic cancer and non-oncologic controls.
2. To assess the correlations between organ-specific plasma protein FSRs and organ FSRs.
3. To assess regional tumour protein synthesis using mass spectrometry imaging

Study design

This study will be a cross-sectional study that will be conducted at Maastricht University Medical Centre (MUMC, Maastricht, Netherlands).
In this study, protein turnover and protein incorporation into various organs and tissues of patients with pancreatic cancer undergoing surgery will be analysed by oral ingestion of 2H2O. In addition, non-oncologic patients undergoing a cholecystectomy will be included into this study. After having signed for informed consent, first data collection will take place. The following patient characteristics will be collected from the patient*s medical record:
• Age
• Sex
• American Association of Anesthesiologists (ASA) classification
• BMI
• Weight loss in the past six months
• Nutritional Status
• Abdominal computed tomography scan (CT-scan)
• Intoxication (smoking, alcohol, drugs)
• Systemic steroid or non-steroidal anti-inflammatory drug (NSAID) use in the last four weeks
• World Health Organisation (WHO) performance status
• Presence of diabetes mellitus
• Presence of cardiac comorbidity
• Presence of pulmonary comorbidity
• Neoadjuvant therapy

The total study period will last two weeks. Fourteen days prior to surgery (day 0), the patient will come to the hospital or will be visited at home by the investigator for sampling of 20ml of venous blood by venepuncture and a saliva sample (using a swab). The patient will receive seven portions of 2H2O. The patient will be instructed to 1) take a saliva swab daily and 2) ingest 60ml of 2H2O daily. After a week (day 7), the patient will meet the investigator. This can either be at the hospital or at the patient*s home, which will be decided by the patient*s preference. During this visit 1) an additional blood sample of 20ml will be drawn through standard venipuncture, 2) the empty water bottles will be collected by the investigator, 3) the patient will receive 7 new 2H2O bottles for the next week, 4) the saliva swabs will be collected, 5) the patient will receive a movement meter and a nutritional diary. The patient should keep the movement meter strapped on during the remaining study period and to keep a nutritional diary to track every meal, snack, and/or drink that

is consumed during this week. All in all this visit will not take longer than one hour. The patient will than continue with saliva swabs and ingestion of 60ml 2H2O daily, until the day of surgery. The day before surgery (day 13), patients will be admitted to the hospital, as part of standard preoperative care. The investigator will visit the patient at the ward in the evening and will collect the patient*s saliva swabs, movement meter, nutritional diary, and empty water bottles. Next morning, the investigator will take a blood sample (20ml), through the intravenous catheter that has been placed as part of preoperative care. After one hour of surgery there will be adequate exposure of the abdominal organs. A muscle biopsy from the rectus abdominis and vastus lateralis muscle will be collected as well as a biopsy of the liver, small intestine, subcutaneous fat and visceral fat. After the surgeon has performed a cholecystectomy (which is part of the standard surgical procedure), a single surgical biopsy will be taken from the gallbladder. When the tumour and adjacent pancreatic tissue has been removed, a biopsy of the pancreas and pancreatic tumour will be taken. For non-oncologic patients all biopsies will be taken directly after start of surgery. The gall bladder biopsy will be taken after removal of the gallbladder. No pancreas, tumour, or intestinal biopsies will be taken in non-oncologic patients. In total, patients will have to make either two additional visit to the hospital or the investigator will visit the patient two times at home (1 hour per visit). Patient*s discomfort is reduced to the minimum since all biopsies are taken under general anaesthesia. Only two additional venipunctures will be performed. After diagnoses by the pathologist (usually one week after surgery), tissue that would be otherwise discarded will be collected and stored for future analysis.

Study burden and risks

There are some small risks involved in participating in this study. A venipuncture has a small risk of a small local hematoma. The same counts for the muscle biopsy. The incision made for obtaining the muscle biopsy will be done by an experienced physician and will heal completely. Within our research group we have extensive experience with taking muscle biopsies. During the follow up several days after taking the biopsy, no complications have been reported. Saliva swabs are collected by the patients themselves with a cotton swab and do not form any kind of risk or discomfort. The biopsies of the small intestine, subcutaneous fat, visceral fat, pancreas and tumour will be taken from parts that will be resected during the surgery, thus preventing the risk for permanent complications. Potential peroperative bleeding of the tissue will be electrocoagulated by the surgeon. The liver biopsy is associated with a small chance of bleeding. This can be stopped by electrocoagulation during surgery. There are no possible complications for the gallbladder biopsy since this is taken after the gallbladder has been removed from the patient*s body. All abdominal biopsies will be taken by skilled hepatobiliarypancreatic surgeons.
The labelled 2H2O tracers applied in this experiment are not radioactive and are completely safe. The production of the tracers for oral administration will

occur in a sterile environment according to GMP guidelines.
Time investment of patients is low since only two extra one-hour visits are required, which can also be scheduled at the patient*s home. Other sample collection will take place during surgery when the patient is asleep. The number of biopsies and blood samples has been reduced to the minimum for minimal patient discomfort. All biopsies are taken while under general anaesthesia.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Cachectic patients with pancreatic cancer (n=11)
- Age >= 18
- Planned pancreaticoduodenectomy for suspected adenocarcinoma of the pancreas head

(histological evidence not necessary)
- Weight loss > 5% in the last six months or BMI < 20 and weight loss > 2% or sarcopenia (L3-skeletal muscle index of <55 cm2/m2 for men or <39 cm2/m2 for women) and weight loss > 2%
- Treated with pancreatic enzyme replacement therapy;Non-cachectic patients with pancreatic cancer (n=11)
- Age >= 18
- Planned pancreaticoduodenectomy for suspected adenocarcinoma of the pancreas head (histological evidence not necessary)
- Weight loss <= 5% in the last six months or BMI >= 20 and weight loss <= 2% or no sarcopenia (L3-skeletal muscle index of >=55 cm2/m2 for men or >=39 cm2/m2 for women) and weight loss <= 2%
- Treated with pancreatic enzyme replacement therapy;Non-oncologic control patients (n=11)
-Age >= 18
-No history of cancer
-Weight loss <= 1% in the last six months
-Planned cholecystectomy for symptomatic cholecystolithiasis

Exclusion criteria

-Active acute pancreatitis
-Chronic pancreatitis
-Previous pancreatic surgery
-Inflammatory bowel disease (e.g. Crohn*s disease)
-Use of systemic steroids in the past four weeks
-Use of anti-inflammatory biological (e.g. TNF-α blockers) in the past four weeks
-Abdominal surgery in the past four weeks
-Insulin dependent diabetes mellitus
-Chronic obstructive pulmonary disease GOLD III and IV
-Hearth failure
-Total parenteral nutrition at day of surgery
-Wheelchair bound
-Pregnancy
-Neoadjuvant chemotherapy or radiotherapy

Study design

Design

Study type:	Observational invasive
Intervention model:	Other

Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	33
Type:	Anticipated

Ethics review

Approved WMO Date:	10-08-2016
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

No registrations found.

In other registers

Register	ID
CCMO	NL57600.068.16