education

FROM THE JOURNALS Edited highlights of weekly research reviews

Anticoagulants in people with acute ischaemic stroke and atrial fibrillation

Trials of direct oral anticoagulants for atrial fibrillation have excluded patients with acute ischaemic stroke because of concerns over the risk of haemorrhagic transformation of the acute infarct. Whether it's safe to start anticoagulation within the first few days in the approximately 20% of people with acute ischaemic stroke who are found to have atrial fibrillation had, until now, been unclear.

The OPTIMAS trial randomised 3648 patients to either early anticoagulation (≤4 days from onset of stroke symptoms) or late anticoagulation (7-14 days) with any direct oral anticoagulant (DOAC). The authors conclude that early DOAC initiation is non-inferior to delayed DOAC initiation for the composite outcome of recurrent ischaemic stroke, intracranial haemorrhage, unclassifiable stroke, or systemic embolism at 90 days. The primary outcome occurred in 3.3% of participants in each arm of the study.

Lancet doi:10.1016/S0140-6736(24)02197-4

Obesity profiling

"The relationship between elevated BMI and other morbidities is highly heterogeneous, underscoring the inability of this simple measure to adequately characterize the pathophysiological complexities of obesity." With all the talk of GLP-1 agonists to treat the obesity epidemic, this quote from a study seems timely. The investigators used data from four cohort studies to identify five risk profiles in people with elevated body mass index (BMI) in which cardiovascular and other disease risk varies from a more typical "concordant" risk profile. With this approach, we may soon be able to use biomarkers such as alanine transaminase, lipids, and waist-to-hip ratio to more accurately predict when someone within an elevated BMI category may be at higher—or lower—risk of disease.

Nat Med doi:10.1038/s41591-024-03299-7

tDCS for depression

Transcranial direct current stimulation (tDCS) applies a weak electric current to the brain via a flexible cap or band worn over the forehead. Studies in which tDCS was delivered on a daily basis for several weeks in a clinic setting have found improvements in symptoms of major depressive symptoms compared with sham treatments. A new study explored the effect of home based tDCS in people with major depressive symptoms recruited via the device's website, email lists, and social media. It found that people allocated to receive a 10 week course of tDCS, given five days a week under teleconferencing supervision, had lower depression scores than those receiving a sham treatment. Symptoms were measured using the 17-point Hamilton Depression Rating Scale (HDRS) score. The mean improvement in HDRS in the tDCS arm was 9.41 compared with 7.14 in those who received the sham treatment. However, skin redness and trouble concentrating were reported at higher rates in the tDCS group.

Nat Med doi:10.1038/s41591-024-03305-y

Deep learning on AI-assisted colonoscopy

We're used to thinking of colonoscopy as the gold standard for detection of bowel cancer. A systematic review and meta-analysis compared bowel cancer detection in AI-assisted colonoscopy with standard colonoscopy to see if adding some real time deep learning algorithms improves the diagnostic accuracy of colonoscopy. After analysing data from 44 randomised control trials, they found there was no difference between the average number of advanced colonic neoplasms per colonoscopy (1512 of 9296 versus 1392 of 9121, incident rate difference 0.01 (95% CI −0.01 to 0.02)), but the advanced colonic neoplasm detection rate was higher in the AI-assisted colonoscopy group (1260 of 9899 versus 1119 of 9746, relative risk 1.16 (1.02 to 1.32)).

Ann Intern Med doi:10.7326/ANNALS-24-00981

You got mail

It's so rare these days to get any letters through the post that I don't seem to know what to do: eventually—if I've not found a reason to put it in the bin unopened—I might find a pile of clutter to put it on to come back to later in the day, or week, or year. It's little surprise to me, therefore, that a deprescribing intervention that involved mailing prescribers tapering guides and deprescribing algorithms had no effect on prescribing in people with Alzheimer's disease (AD). The trial, of over 12 000 people with AD or AD related dementia, had three arms: mailing information about high risk medications (including antipsychotics, sedative-hypnotics, and strong anticholinergics) to the patient and their prescriber; mailing the information to the prescriber only; and usual care. There were no differences in prescribing of the targeted high risk medications between the groups after six months.

JAMA Intern Med doi:10.1001/jamainternmed.2024.5632

Tom Nolan, clinical editor, *The BMJ*, London; sessional GP, Surrey

Cite this as: *BMJ* 2024;387:q2378

Irritable bowel syndrome: low dose amitriptyline improves symptoms

The study

Amitriptyline at low dose and titrated for irritable bowel syndrome as second line treatment in primary care (ATLANTIS): a randomised, double blind, placebo controlled, phase 3 trial

Ford AC, Wright-Hughes A, Alderson SL, et al

Lancet 2023;402:1773-85

CPD READING

0.5 HOURS

NIHR | National Institute for Health and Care Research

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To read the full NIHR Alert, go to: https://shorturl.at/MJkG7

Why was the study needed?

People with irritable bowel syndrome (IBS) are usually managed in primary care. First line treatments include dietary changes and medicines (for constipation, diarrhoea, and abdominal spasms) but they are not always effective. In guidelines from the National Institute for Health and Care Excellence (NICE), a next potential step is to consider a low dose of an antidepressant medicine, such as amitriptyline. Before this study, limited research evidence had been available on amitriptyline for IBS, and GPs did not prescribe it often.

The ATLANTIS research trial compared low dose amitriptyline with placebo in people with IBS whose symptoms had not improved with first line treatments.

What did the study do?

Conducted between 2019 and 2022, the ATLANTIS study recruited people with IBS from 55 general practices in England. Most had moderate to severe symptoms of IBS. Participants were aged 49 on average; most (68%) were female.

In this randomised controlled trial, half the participants (232) took low dose amitriptyline (10 mg per tablet) and the other participants (231) took an identical placebo tablet for six months. They all received an information leaflet to help them manage their dose (starting at one tablet each evening and increasing to two or three tablets depending on their symptoms and side effects). Participants continued to receive usual care for IBS from their GP (such as dietary advice). Some 338 participants completed six months of treatment: 173 (75%) in the amitriptyline group and 165 (71%) in the placebo group.

To compare the groups, the researchers used the IBS severity scoring system (IBS-SSS). A score of 75-174 indicates mild symptoms; 175-299 moderate symptoms; and 300+ severe symptoms.

What did it find?

The primary outcome of the study at six months showed:

- People in the amitriptyline group reported greater improvements in IBS symptoms (their average IBS-SSS score improved by 99 points compared with 69 points for people in the placebo group).
- Secondary outcomes showed that people in the amitriptyline group:
- Were more likely to report relief of their IBS symptoms (61% participants) compared with those taking placebo (45%)
- Were more likely to find their treatment acceptable (58% participants) compared with those taking placebo (47%)
- Had similar anxiety, depression, and work and social adjustment scores (ability to work and take part in other activities) to people in the placebo group
- Were less likely to discontinue treatment during the trial (20% participants) compared with the placebo group (26%).

People in the amitriptyline group experienced more dry mouth and drowsiness side effects but less insomnia than the placebo group. Few serious adverse events occurred in either group (two in the amitriptyline group; three in the placebo group).

At three months, similar numbers in each group said they were still taking the pills as prescribed. By six months, more were still taking amitriptyline (74%) than placebo (68%).

Why is this important?

The researchers say this is the largest trial of a tricyclic antidepressant in IBS to date. The findings suggest that low dose amitriptyline reduces the severity of IBS symptoms and is safe and well tolerated.

The results will inform shared decision making and provide information to GPs and people with IBS on trying low dose amitriptyline if first line options have not been effective.

The researchers have developed guidance to help people with IBS manage their amitriptyline dose.

What's next?

The researchers hope their findings will inform the next update on NICE guidelines for treatment of IBS.

Competing interests: *The BMJ* has judged that there are no disqualifying financial ties to commercial companies. Further details of other interests, disclaimers, and permissions can be found on bmj.com

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Insulin therapy

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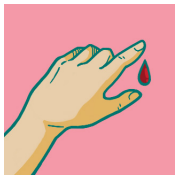
This article is part of a series that offers practical actions clinicians can take to support reaching net zero.
Browse all the articles at https://sandpit.bmj.com/graphics/2023/tangibleActions-v8/.
To pitch your idea for an article go to https://bit.ly/46Etl9i

CPD READING
0.5 HOURS



More than 500 million people live with diabetes, and around 783 million are expected to have the condition by 2045.[1] Of this population, 5% to 15% have type 1 diabetes (T1D).[2] Insulin therapy is necessary for people with T1D and for many living with type 2 diabetes (T2D) or other types of the condition (such as gestational diabetes). Waste from diabetes care includes disposables associated with insulin use, testing strips, lancets, needles, and continuous glucose monitoring (CGM) sensors. Many of these items are single use and wrapped in mixed plastics that are often difficult to recycle. Insulin therapy and glucose monitoring generate significant amounts of plastic waste, around 90% of which is packaging.[3]

Why change is needed

England's diabetes audit data from 2021 show that 21.8% of people with T1D, and 50.1% of people with T2D achieved a glycated haemoglobin of 53 mmol/mol (7.0%) or lower, suggesting that many people live with suboptimal glycaemic control.[6] This is despite the fact that, during the same period, more than 7.7 million prescriptions for insulin were written in England, suggesting that despite insulin therapy, glycaemic control is frequently suboptimal.[7] A life cycle analysis in the US and Sri Lanka suggests that one year of insulin use in a person with T2D results in the production of 34.8 kg of carbon dioxide equivalent (CO_2e); equivalent to driving 1250 km in a standard petrol car.[8] In the UK, around 23 million medical pens (most of which are for insulin) are incinerated or sent to landfill each year.[9]

In people with T1D, use of continuous subcutaneous insulin infusion (CSII) and CGM sensors is likely to expand with the use of closed loop technology (semi-automated linked CGM and CSII). This is anticipated to become the preferred method of managing T1D because of its benefits for patients, including improved glucose control, reduced hypoglycaemia, and improved quality of life.[10] CSII sets need changing every three days, and as a result generate considerable amounts of plastic waste, both in manufacture and packaging (fig 1). Recycling diabetes technology is complicated by the fact that many devices have electronic components such as glucose sensing built within a plastic coating. Many of these devices should be disposed of as per battery disposal.

Evidence for the solution

Optimising diabetes care

Improving glycaemic control in people living with diabetes reduces the risk of micro and macrovascular complications and will in turn reduce the carbon footprint of healthcare interventions that these complications would require, such as dialysis.[11] In some people with T2D, alternatives to insulin, such as very low calorie total dietary replacement to induce remission, may be feasible.[12] Where clinically indicated, therapeutic alternatives to insulin, such as newer oral agents (for example, sodium glucose transporter-2 inhibitors; SGLT-2i), may generate less waste or carbon dioxide, although this has not yet been formally tested.

Proper waste disposal

The US-based Diabetes Technology Society "Green Diabetes Initiative" has published a strategy for minimisation, collection, separation, and disposal of diabetes device waste, emphasising the waste hierarchy five "Rs": reducing, reusing, recycling, redesigning, and re-educating.[13] They advocate the principles of a circular economy which addresses the preservation of resources through continuous recirculation.

WHAT YOU NEED TO KNOW

- Insulin prescribing is carbon intensive and leads to considerable plastic waste
- Over the past decade, a broader range of medications has been made available to manage type 2 diabetes
- If insulin prescribing is required, consider reusable pen devices

Fig 1 | Waste generated from one insulin pump reservoir and sensor change

PATIENT PERSPECTIVE

I have had type 1 diabetes for almost 20 years. I get through around two pens per week, so guess I have disposed of more than 2000 pens in my lifetime. I am very concerned about the effect on the environment, especially for my children. My consultant spoke to me about using a reusable pen, but I have some problems with arthritis, so I found it difficult to use. I now send all of my empty pens to the "Pencycle" scheme, and will continue to do so. I am concerned that my glucose sensor device is just put in the bin at the end of two weeks' use. I wish the company would find a way to reuse them.

What you can do

Optimise care, incorporating shared decision making

- Review insulin use, doses, administration, timing, treatment concordance, storage.
- Deprescribe, where clinically appropriate.
  - Stop medication that is ineffective or reduce medication if the person is overtreated. Avoid routinely recommending self-monitoring of blood glucose levels in people at low risk of hypoglycaemia.[14]
- Suggest lifestyle interventions.
  - Discuss diet and physical activity recommendations. Consider whether the patient would benefit from structured education. Consider interventions to induce remission, eg, a very low calorie diet.[11]

In those with type 2 diabetes who are not already taking insulin and require further intervention to meet their agreed HbA1c target, consider alternatives where clinically appropriate

- Ensure the patient's non-pharmacological management has been optimised.
- Review their current therapy, ensuring regular concordance and timing.
  - Consider whether the person is taking their treatment as prescribed. Are adverse effects such as gastrointestinal problems limiting concordance?
- Consider additional treatments, such as SGLT2i to improve glucose control, and reduce cardiovascular and renal risk when clinically appropriate.[14 15]
- If insulin is the best option for the patient, consider suggesting a reusable pen. Insulin is available in multiple dose disposable pen devices or in refillable pens. The latter produce considerably less plastic waste and carbon: 12 kg CO_2e/year versus 7 kg,[16 17] although more time is required to educate the patient on using the device, and a degree of manual dexterity is needed to use the pens.
  - Reusable pen devices are available for most types of insulin, and can last up to three years. A recent analysis of data from the NHS suggested that around 72.5% of insulin prescribing was for disposable pens.[18] This study suggested that replacing disposable insulin pens with reusable ones could reduce insulin pen-associated plastic waste by 84-95% and its carbon footprint by over 260 tonnes CO_2e, as well as potential prescribing savings around £0.75 million per annum. Diabetes UK endorses the use of reusable pens to reduce plastic waste.[19]
- If a disposable pen is the best option for the patient, consider a pen recycling scheme.
  - Several recycling schemes have been set up to manage plastic waste. Pencycle collects insulin (and GLP-1) pens for recycling (fig 2, see bmj.com).[9] A further scheme, which collects Tyvek films that cover trays carrying insulin pumps, sends these back to the manufacturer.[20] The uptake and overall carbon impact of these schemes have yet to be evaluated, but manufacturers of Tyvek have data that suggest their recycling scheme reduced CO_2e of 100 000 tonnes, equivalent to removing 22 000 cars from the road.[21] Some companies have extended the requirement for changing infusion sets to seven days, resulting in significant reduction in plastic waste and reduction in costs of prescribing by $1324-$1677 per year.[22]

Ensure that prescribed insulin does not go to waste

Guide people with T1D (and perhaps people with T2D treated with bolus insulin) on how to dose insulin according to carbohydrate counting, so as not to over or underdose, leading to hypo or hyperglycaemia. Offer advice on how they can best manage their insulin supplies. Educate the person and their carers as to appropriate storage of insulin to prevent denaturation. For example, insulin not currently in use should be stored in the refrigerator, and the use of personal cool bags when travelling is recommended to ensure the insulin does not freeze or overheat. This is not only a sustainability consideration but also a patient safety issue as insulin that has been stored incorrectly may not have the expected effect on blood glucose.

Competing interests: None declared.

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Find the full version with references at doi: 10.1136/bmj-2024-079425

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

We spoke to a person with T1D about their concerns regarding plastic waste, and included their response in the article (Patient perspective). Many of our patients have responded positively to encouragement to use pen recycling schemes or to convert to using reusable pens.
We also consulted PBR, a person living with T2D who has enthusiastically started recycling his disposable pens, and supplied the image in fig 2 (bmj.com).

EDUCATION INTO PRACTICE

- How many of your patients use reusable pen devices?
- What educational activities could you consider within your practice to encourage the use of reusable pens and pen recycling schemes?

Cancer cachexia

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CPD READING
0.5 HOURS

Cancer cachexia is a complex syndrome characterised by tissue loss (fat, cardiac muscle, and skeletal muscle), decreased appetite (anorexia), fatigue, and reduced activity in patients with cancer (fig 1).[1] It cannot be fully reversed with nutritional support alone and is caused by inflammation and metabolic dysfunction driven by the interaction between tumour and patient. Consequences may include reduced efficacy of cancer treatment, poorer quality of life, and reduced survival.[2] This article provides an update on cancer cachexia for healthcare professionals drawing on contemporary research and guidelines developed by the European Society for Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO).

Muscle wasting is a key feature and is a result of increased catabolic activity

WHAT IS CONTROVERSIAL ABOUT CANCER CACHEXIA?

The definition of cancer cachexia remains controversial. The role of inflammation is recognised as a key component; however, some argue that loss of skeletal muscle should be the defining feature. The first international consensus definition was published in 2011, and work is under way to update this. Lack of a clear consensus definition undermines the design of clinical trials.

WHAT YOU NEED TO KNOW

- Cancer cachexia is defined as cancer related malnutrition in the presence of systemic inflammation
- The prevalence of cancer cachexia varies among different cancer types, with pancreatic, hepatobiliary, and oesophagogastric cancer having notably high rates
- Assess the patient for cancer cachexia in all healthcare interactions to allow for early intervention
- Treatment requires a multi-modal approach aimed at increasing food intake, reducing muscle wasting, and improving function, alongside psychosocial support

How common is it?

Rates of cancer cachexia vary across different cancer populations (fig 2), with both tumour site and tumour stage key determinants of prevalence. Cachexia is less common in patients with breast, prostate, and skin cancers.[3-6] Cancers most strongly associated with the syndrome include pancreatic, hepatobiliary, and oesophagogastric. Up to 80% of patients with these cancers are affected.[7]

Patients with cancer of the upper gastrointestinal tract often have locally invasive or metastatic disease at presentation, and, as cachexia is more common in advanced cancer, this may contribute to the observed high prevalence. However, cachexia is not confined to patients with end stage disease; it also affects patients with potentially curable malignancies. Approximately 40% of patients with pancreatic cancer[8] and 35% of those with oesophagogastric cancer[9] develop cachexia before their surgery. Therefore, all health professionals caring for patients with cancer, in any setting, should understand the syndrome and its consequences.

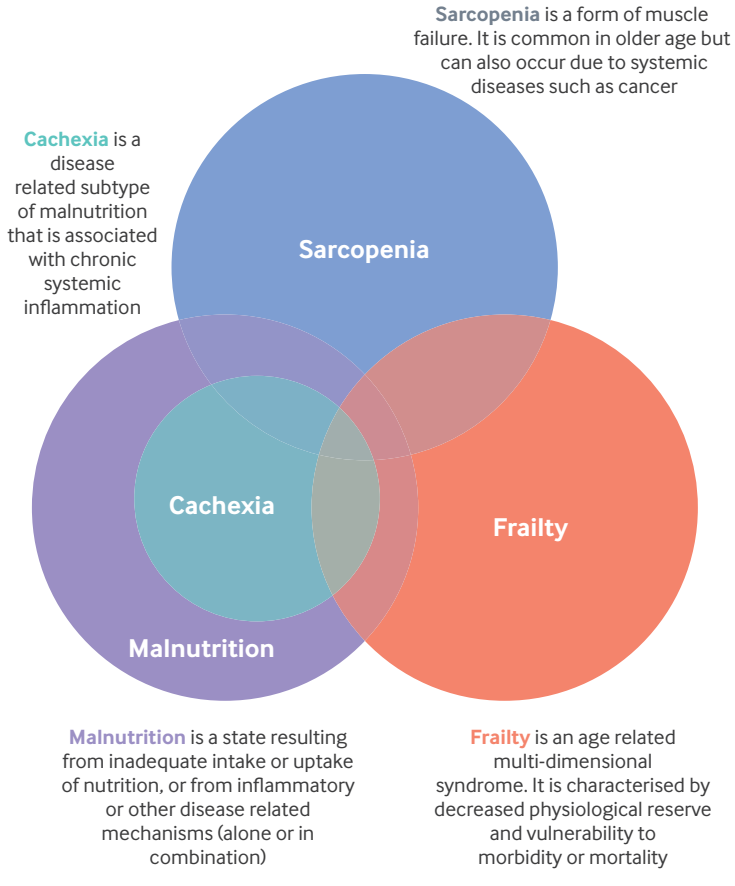

Fig 1 | Characteristics of cancer cachexia

What are the causes of cancer cachexia?

Cancer cachexia is more than just a calorie deficit. It is a complex syndrome involving numerous body systems underpinned by systemic inflammation.[10] It may disrupt the central nervous system, cause hormonal and metabolic alterations, and reduce the benefits of anticancer treatments.

In cancer cachexia, there is an intricate interaction between the tumour and the patient[11]: tumours secrete a range of molecules triggering the cachexia process,[12] and the resulting inflammatory response exacerbates the condition.[11] Here, we highlight some of the key disturbances brought about by these interactions.

Muscle wasting is a key feature and is a result of increased catabolic activity.[13] Although several possible causal mechanisms have been identified, the process is not fully understood and more research is required to inform the development of therapeutic targets.[14] Additionally, changes in adipose tissue are observed whereby white fat (which stores energy) is converted into brown fat (which burns energy). This process is driven by inflammation and contributes to patients' increased energy expenditure.[15]

Appetite loss, fatigue, and social withdrawal are common in patients with cachexia. These symptoms are influenced by the hypothalamus, which also interacts with key appetite hormones such as ghrelin (hunger hormone) and leptin (satiety hormone). A growing body of evidence suggests that hypothalamic dysfunction, resulting from inflammation, contributes to cancer cachexia.[16]

The liver and heart are also affected. Reduced cardiac size and wall thickness are seen in animal models of cachexia,[17] which may precede cardiac dysfunction and ultimately failure. Pre-clinical studies also show changes in hepatic energy metabolism associated with cachexia and evidence of cirrhosis, this leads to increased overall energy expenditure likely exacerbating weight loss and muscle wasting.[18 19]

How do patients present?

Cancer cachexia is a condition with three distinct phases: pre-cachexia, cachexia, and refractory cachexia. In the first phase, patients may show subtle early signs such as anorexia or impaired glucose tolerance that occur before unintentional weight loss.[20] Therefore, it is important to ask patients who are early in a cancer diagnosis about appetite. Refractory cachexia by contrast is associated with cancer progression, low performance status, and the end of life.[20] Cachexia itself is diagnosed using a set of phenotypical and aetiological criteria,[21] initially developed for diagnosing malnutrition (box 1).

Patients with cancer cachexia present to a range of health professionals including GPs, surgeons, specialist nurses, oncologists, dieticians, and palliative care physicians. Symptoms are both physical (anorexia, fatigue, reduced physical function, and weight loss) and psychological (low mood).[23] All can cause considerable distress to patients and family members.

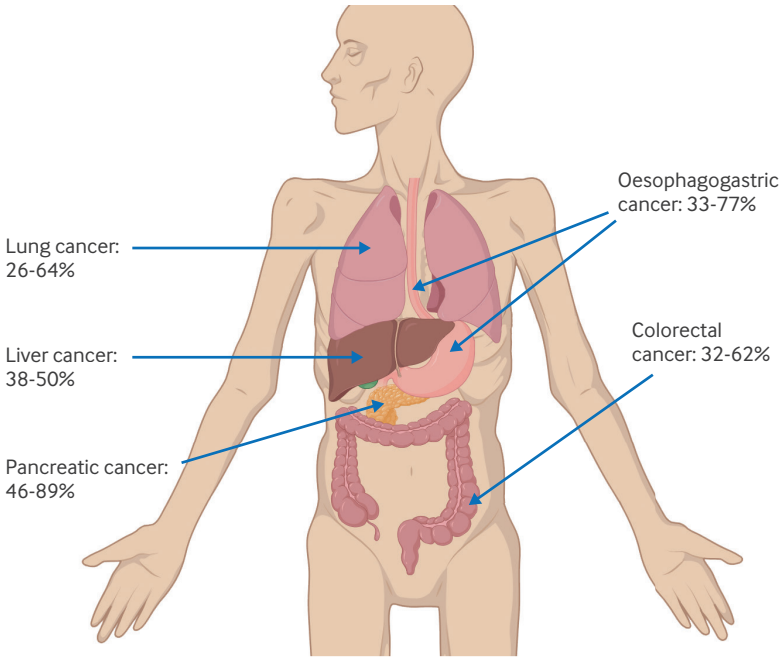

Fig 2 | Tumour sites most strongly associated with cancer cachexia

Many features of cancer cachexia, such as fatigue and low mood, overlap with symptoms secondary to tumour burden or treatment side effects. Termed symptom clusters,[24] these can be challenging to disentangle and likely require longitudinal assessment and astute observation, sometimes necessitating input from palliative care specialists (box 2).

How is cancer cachexia diagnosed?

Cancer cachexia is often underdiagnosed. In one retrospective review of the medical records of 8541 patients with cancer, ICD codes identified 672 patients with cachexia compared with 1257 patients identified by review of patient weights.[25] In total, only 65% of patients had their body weight recorded, suggesting that cachexia was not considered during their care.

Box 1 | Global Leadership Initiative on Malnutrition (GLIM) criteria for malnutrition[22]

Patient must meet at least one phenotypical and one aetiological criterion for a diagnosis of malnutrition

Phenotypical criteria

- Weight loss >5% within the past 6 months or >10% beyond 6 months
- Body mass index (BMI) <20 if <70 years old or <22 if ≥70 years old
- Low muscle mass*

Aetiological criteria

- Reduced food intake or assimilation
- Acute or chronic systemic inflammation†

* Radiology is the optimal method for assessment of muscle mass, but in practice reduced muscle function often accompanies low muscle mass and this would serve as a suitable replacement.

† Clinical judgment can be used to assess if the underlying condition is inflammatory in nature. This can be supported by raised inflammatory markers such as C reactive protein.

Box 2 | When to refer

Offer regular screening for cachexia to all patients with cancer, particularly those with high risk cancer types such as pancreatic cancer. This can be done using the GLIM criteria (box 1) alongside a measure of the systemic inflammatory response (such as raised C reactive protein (CRP) concentration).[21] Depending on prognosis, referral to dietetics or palliative care may be indicated.

The Global Leadership Initiative on Malnutrition (GLIM) developed criteria for the diagnosis and grading of malnutrition (box 1),[22 26] which can also be used for diagnosing cancer cachexia (defined as disease related malnutrition in the presence of inflammation).[21]

Any patient with a cancer known to carry a high risk of cachexia, or any patient with cancer who has symptoms of anorexia, fatigue, or weight loss should be evaluated for cachexia using the GLIM criteria for malnutrition, plus a measure of systemic inflammatory response such as C reactive protein (CRP).[26] A diagnosis should trigger intervention to help slow further functional decline. Note however, that older trials of cancer cachexia interventions may not have included systematic inflammation in their entry criteria, so findings may not be comparable with those of more contemporary studies.

Any of the GLIM phenotypic criteria can be used to diagnose cachexia, although body mass index (BMI) may not be as suitable as weight loss in western populations where pre-morbid obesity is highly prevalent. A combination of BMI and weight loss was a better predictor of overall survival than either measure alone in a study of 8160 European and Canadian adults with cancer.[27] Those with a lower baseline BMI had worse outcomes than those with a higher baseline BMI for the same percentage weight loss (P<0.001).[27] Additional energy stores at the time of a cancer diagnosis may confer a survival advantage.

During the past decade, interest has been growing in the association between radiologically diagnosed low muscle mass and poorer outcomes for patients with cancer.[28] Computed tomography (CT) scans are routinely used for cancer diagnosis, staging, and surveillance. As well as identifying the site and extent of malignant disease, this imaging could be used to assess patients' body composition. Low muscle mass and strength (sarcopenia) are key features of cancer cachexia and often precede clinically apparent weight loss. CT assessment of body composition can be a valuable tool for assessing patients with possible cachexia, but its use is currently confined to research settings.

How does cancer cachexia affect patient outcomes?

Patients with cancer cachexia often undergo systemic anticancer therapy, with both curative and palliative intent. Cachexia may increase the risk of chemotherapy related toxicities which can lead to dose reductions and premature discontinuation of treatment. One systematic review of 63 studies found that 25% reported an increase in chemotherapy related toxicity in patients with cancer cachexia, with treatment discontinuation seen in 20% of the studies.[29]

In patients undergoing surgery with curative intent, preoperative cachexia is associated with poorer survival in pancreatic,[8] oesophagogastric,[9] and other cancers. In patients with advanced lung cancer, cachexia is associated with significant reduction in 1-year survival (37.6% *v* 60.7%).[30] Cachexia can have a detrimental psychological impact on patients and their families, as changes in body composition and eating habits can cause distress and lead to changes in social interactions.[21] One multicentre study of 528 patients with cancer found that patients with cachexia had higher rates of depression and anxiety and an overall poorer quality of life (all P<0.01) compared with patients without cachexia.[31]

A RELATIVE'S PERSPECTIVE

Nearly 10 years on from my dad's death from pancreatic cancer at 55 years old, and the physical symptom now known to me as cancer cachexia, the "cancer look," still haunts me.

To see your once strong, active, healthy dad end his life struggling to eat a small pot of yogurt designed to supress the appetite of a toddler. What hope did he have? Cancer cachexia changes a person's whole demeanour, and no amount of replacement shakes or calorific food could maintain my dad's weight. "I'm just not hungry," was his common phrase. When cancer cachexia develops, being conscious of what you eat disappears, you would give anything for your loved one to eat something, anything.

Normality is all my dad wanted throughout his illness, to go out and enjoy a meal with his daughter on Father's Day. Yet—crippled with fatigue, his meal barely consumed, and beer left untouched—the last Father's Day memory etched in my mind is tainted with sadness.

Hope is something that I never knew the power of until my dad's illness, and I still live in hope that one day cancer will be no more. Let's never, ever, give up hope.

Low muscle mass and strength (sarcopenia) are key features of cancer cachexia and often precede clinically apparent weight loss

What can be done?

Cancer cachexia is a complex condition requiring a multimodal approach. Intervention should aim to reduce symptoms that inhibit food intake (such as chemotherapy induced nausea), support nutrition, reduce muscle wasting, and improve function, alongside psychosocial support.[21]

Prehabilitation programmes and exercise

In patients being treated curatively for cancer, numerous interventions for cachexia have been evaluated during anticancer therapies or before surgery. In randomised trials, a range of single and multimodal "prehabilitation" programmes—including exercise therapy, nutritional supplements, psychological support, optimisation of pre-existing conditions, and smoking cessation—looked particularly promising for improving postoperative outcomes and reducing muscle loss.[32 33] However, at present, practice remains variable and further high

ADDITIONAL EDUCATIONAL RESOURCES

- Cancer Cachexia Society (https://www.cancercachexiasociety.org)
- Society on Sarcopenia, Cachexia, & Wasting Disorders (SCWD) (https://society-scwd.org)

Information resources for patients

- Cancer Research UK. Cachexia (wasting syndrome) (https://www.cancerresearchuk.org/about-cancer/coping/physically/diet-problems/types/cachexia)
- BDA The Association of UK Dieticians (https://www.bda.uk.com). Provides information on the role of dieticians and some advice on the role of nutrition in cancer
- Irish Cancer Society. Cachexia (https://www.cancer.ie/cancer-information-and-support/cancer-information/cancer-treatments-and-side-effects/coping-with-side-effects/cachexia)
- Pancreatic Cancer UK. Vérène & her husband (https://www.pancreaticcancer.org.uk/real-life-stories/verene-her-husband/). A partner's perspective on cachexia in the setting of pancreatic cancer. The website also has information on appetite and weight loss towards the end of life

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

Rachel Waller wrote the "Relative's perspective," reflecting on the death of her father. She is a patient advocate for cancer cachexia and pancreatic cancer.

EDUCATION INTO PRACTICE

- How many patients in your practice with cancer have a positive malnutrition screening test, and what proportion have been referred to a dietician?
- The last time you met a patient with cancer and changes in body composition, how did you address their concerns about their weight? Having read this article, what would you do differently next time?

quality evidence is required to identify the most effective combination of interventions for inclusion in these programmes.[34]

European guidelines deem professionally supervised moderate level exercise to be safe for patients with cancer cachexia and recommend this to maintain and improve muscle mass and aerobic fitness.[21] However, a Cochrane review in 2021 identified only four eligible studies and notes that further research on the benefits and risks of exercise is required. A future update is expected to include at least three further studies.[35]

Supporting nutrition

In advanced cancer, the focus of care should be aligned with expected survival. The European Society for Medical Oncology (ESMO) recommends regular screening for cachexia and appropriate nutritional intervention for all cachexia patients with a survival prognosis longer than a few months.[21] Oral supplements alone are ineffective, and patients require concurrent dietary counselling, preferably from a dietician. Artificial feeding is not recommended in advanced cancer as it does not seem to improve body composition or overall survival.[36]

Artificial feeding is not recommended in advanced cancer as it does not seem to improve body composition or overall survival

Medication

Various appetite stimulants for patients with advanced cancer and cachexia have been evaluated in trials.[37] Based on one systematic review of six randomised trials,[37] ESMO recommended the use of corticosteroids for a short period (weeks) to improve appetite. However, evidence that this results in weight gain or improved survival is lacking.[21]

Anamorelin, a drug that activates ghrelin receptors, has been approved for the treatment of cancer cachexia in Japan. While a phase 3 randomised controlled trial[38] showed that it improved body weight relative to placebo, anamorelin did not improve physical function so was not approved in the US or Europe.

Following a double-blind randomised controlled trial in patients undergoing chemotherapy, ASCO guidelines[39] now advise that olanzapine may be offered to patients with advanced cancer to help with weight gain. The authors found that significantly more patients treated with olanzapine gained >5% of body weight compared with placebo treated controls (60% *v* 9%, P<0.001). Mean weight in the olanzapine group increased from 53.1 kg to 55.7 kg, P<0.001, whereas in the placebo group mean weight decreased from 53.6 to 51.7 kg, P<0.001. Olanzapine also improved participants' appetite scores.[40]

Psychological support and end of life care

Acknowledging the psychological impact of cancer cachexia is important to patients and families, highlighting the need for health professionals to be aware of the condition and its implications, both physical and psychosocial.[41] Cancer nurse specialists are trained in psychological support[42] and are with patients throughout their cancer journey. Palliative care professionals are also experienced in providing psychosocial support,[23] and referral to their services should be considered particularly if life expectancy is short. If the prognosis is for less than a few weeks, then the aim of treatment should be to alleviate any associated distressing symptoms such as thirst and nausea and to plan for end-of-life care.[21]

HOW THIS ARTICLE WAS CREATED

The aim of this article is to provide a clinical update on cancer cachexia for the non-specialist. A search of the Cochrane Collaboration for "cancer cachexia" resulted in six reviews, of which five were relevant to this article. We searched Medline for "cancer" AND "cachexia," and included relevant recent articles. Both the European Society for Medical Oncology and the American Society of Clinical Oncology guidelines on cancer cachexia were consulted for the section on management. Further evidence for this review was suggested to us from experts in the field and from personal archives of references. Figure 2 was created using Biorender.com with a licence to publish.

Competing interests: None declared.

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CASE REVIEW

Gangrene on the finger tip of a long term smoker

A man in his 40s presented to the dermatology outpatient department with a two month history of a painful black, gangrenous tip to his left middle finger, which initially had been dry but progressed to a serous discharge. The patient reported a one month history of erythema, along with pain and mild numbness, of the finger tip before the gangrene had developed. No other fingers, or toes, were involved. The patient did not report any systemic disease or history of trauma. He was a current smoker with a 20 pack year history.

Key findings on physical examination included normal brachial pulses but reduced radial and ulnar pulses. Laboratory data showed normal coagulation and autoimmune profiles, with no evidence of cryoglobulinaemia or antiphospholipid syndrome. Duplex ultrasonography indicated patent artery flow without signs of proximal atherosclerotic disease. Angiography showed gradual tapering of the left ulnar artery with an abrupt termination at a distal branch of the left profunda brachii artery, along with decreased arterial flow and poor perfusion in the affected finger.

1 What are the differential diagnoses?
2 What is the most likely diagnosis?
3 How would you manage this patient?

Submitted by Der-Jr Huang and Yi-Hsien Shih

Patient consent obtained.

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answers

CASE REVIEW **Gangrene on the finger tip of a long term smoker**

1 What are the differential diagnoses?

Differential diagnoses of gangrenous changes in the fingers, or toes, include trauma, infection, thrombotic diseases (eg, cryoglobulinaemia type 1, antiphospholipid syndrome, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura). The changes could also be drug related, for example thrombosis as a rare side effect of anticoagulants, or vasoconstriction due to beta blockers and adrenaline (epinephrine). Other differential diagnoses are embolic conditions, Buerger disease, atherosclerosis, and peripheral artery disease.

2 What is the most likely diagnosis?

Buerger disease—Buerger disease, also known as thromboangiitis obliterans, is a non-atherosclerotic segmental inflammatory and thrombotic disease that predominantly affects the small and medium arteries of the hands and feet. Incidence is higher in East Asia, the Middle East, eastern Europe, and the Mediterranean. Tobacco use plays a critical role in the pathogenesis of Buerger disease, and poor oral hygiene, hypercoagulability, and genetic predisposition might also contribute to development.

3 How would you manage this patient?

Complete smoking cessation is crucial for patients with Buerger disease to avoid amputation. Both smokeless tobacco and nicotine replacement therapy can prolong the disease. Additionally, proper local wound care and adequate analgesia are essential. For drug treatment, intravenous iloprost, a prostacyclin analogue, can alleviate rest pain and claudication, aid the healing of ulcers and gangrene, and reduce the risk of amputation. Other vasodilators, including sildenafil, a phosphodiesterase type 5 inhibitor; bosentan, an endothelin-1 receptor antagonist; and alprostadil, a prostaglandin E1 agonist, have shown efficacy in several case reports. Calcium channel blockers are considered effective for patients with vasospasm, and cilostazol, a phosphodiesterase type 3 inhibitor, also shows benefits in promoting healing and reducing the risk of limb amputation. Results for antiplatelet treatment using aspirin or clopidogrel have been inconsistent. For surgical treatment, bypass surgery, sympathectomy, and implantable spinal cord stimulators have shown some efficacy in either reducing symptoms or preventing amputation in limited studies. Although minor areas of gangrene might autoamputate, fully developed and well demarcated dry gangrene of the fingers, after a prolonged trial of smoking cessation and medical management, may ultimately require amputation.

LEARNING POINTS

- Buerger disease or thromboangiitis obliterans is a non-atherosclerotic segmental, inflammatory disease affecting the medium and small arteries of the hands and feet.
- Patients might present with ischaemic-type pain, including intermittent claudication and rest pain, as well as Raynaud phenomenon; in progressive disease, ulcers and gangrene might occur.
- Smoking cessation is the mainstay of management; drugs such as prostacyclin analogues and calcium channel blockers might also be effective in slowing progression of the condition.

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Annular erythema

This man in his early 20s presented with a two month history of swollen erythematous plaques with central grey depigmentation, telangiectasia, and superficial scaling on the left cheek and forehead. Tests showed a raised erythrocyte sedimentation rate, decreased complement C3, antinuclear antibodies, anti-SSA antibodies, and anti-histone antibodies, weakly positive results for anti-Smith antibodies, and negative results for anti-dsDNA antibodies. As the patient had no systemic symptoms or signs of disease, subacute cutaneous lupus erythematosus was diagnosed and confirmed on biopsy.

Subacute cutaneous lupus erythematosus is a photosensitive, non-scarring, and non-indurated form of cutaneous lupus, which can be further classified into annular erythema and papulosquamous subtypes. A comprehensive drug history, including angiotensin converting enzyme inhibitors, anticonvulsants, beta blockers, and immune modulators, is crucial to exclude drug induced subacute cutaneous lupus erythematosus, although drugs were not identified as a trigger in this patient. After the patient was treated with low dose hydroxychloroquine and mycophenolate mofetil, the lesions completely resolved.

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Patient consent obtained.

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Air pollution and Parkinson's disease

Air quality in many countries has vastly improved since the days of coal fired power stations and steam trains but, paradoxically, air pollutants are increasingly implicated in disease causation. A case-control study from the US (*JAMA Netw Open* doi:10.1001/jamanetworkopen.2024.33602) links exposure to airborne particulate matter and nitrogen dioxide to an increase in the risk of Parkinson's disease. People in the top fifth of exposure were 10% to 20% more likely to develop the condition than people in the lowest fifth.

Gastrointestinal mucosal damage and Parkinson's disease

Another idea about the aetiology of Parkinson's disease is the gut-first hypothesis, which postulates that the initiating pathology originates in the gastrointestinal tract and travels to the brain via the vagus nerve. It gets some support from a retrospective analysis of 9000 patients who had undergone upper gastrointestinal endoscopy (*JAMA Netw Open* doi:10.1001/jamanetworkopen.2024.31949). People with evidence of mucosal damage—erosions, oesophagitis, or ulcers—were almost twice as likely to develop Parkinson's disease over 15 years of follow-up as those without mucosal damage.

Expanding the prion paradigm

Scrapie in sheep and Creutzfeldt-Jakob disease in humans are caused by a misfolded protein, known as a prion. Unlike pathogens such as viruses, bacteria, and protozoa that replicate through a nucleic acid genome, prions are self-propagating. Laboratory evidence that amyloid-β peptide, tau protein, and α-synuclein protein have similar properties raises the possibility that neurodegenerative conditions such as Alzheimer's disease, multiple system atrophy, and Parkinson's disease are also prion diseases (*JAMA Neurol* doi:10.1001/jamaneurol.2024.2464).

History of Alzheimer's disease

Alois Alzheimer's original report, in 1906, of the disease that bears his name described pathological features of plaques and tangles in the brain of a woman who had experienced memory loss and hallucinations. *Nature* has a timeline illustrating how ideas about the disease have evolved since (https://www.nature.com/immersive/alzheimers-disease-history/index.html). It ends on an optimistic note, focusing on diagnostic advances and recent treatments, but Minerva couldn't help thinking that it also shows how slow progress has been.

Ultraviolet treatment at home for people with psoriasis

Although narrowband UV-B phototherapy is often effective in people with plaque or guttate psoriasis, treatment usually requires multiple visits to a dermatology centre. A trial from the US shows that it can be delivered at least as effectively at home (*JAMA Dermatol* doi:10.1001/jamadermatol.2024.3897). After 12 weeks, more patients receiving home based phototherapy achieved clear, or almost clear, skin when compared with those who travelled to a phototherapy centre. There were no discontinuations of home based treatment because of adverse events.

Fasting before cardiac catheterisation

Patients are usually advised to fast for six hours before undergoing cardiac procedures, but the findings of a trial from Australia provide no support for this tradition (*Eur Heart J*https://doi.org/10.1093/eurheartj/ehae573). Among 700 patients randomised either to fasting or to eating and drinking as they wished, the primary outcome, a composite of aspiration pneumonia, hypotension, hyperglycaemia, and hypoglycaemia, occurred more often in people who had been told to fast than in those who hadn't.

Intracranial arterial disease and dementia

Cerebral small vessel disease certainly contributes to the development of dementia. So does atherosclerosis of the larger intracranial arteries, according to longitudinal data from the Atherosclerosis Risk in Communities study (*Circulation* doi:10.1161/CIRCULATIONAHA.123.067003). Magnetic resonance angiography detected intracranial atherosclerotic disease in a third of participants at baseline. Over 6 years of follow-up, their risk of dementia was nearly twice that of people without arterial disease.

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