Early Satiety in Cancer: A Clinical Review of Definition and Therapeutic Management

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Abstract

Early satiety is defined as the desire to eat with the inability to eat appropriate amounts due to premature fullness. Although a common symptom of cancer, it is rarely recognised in medical practice and poorly elucidated in the literature. This review highlights the importance of early satiety in cancer, and outlines appropriate treatment. A literature search was conducted using EMBASE, CINAHL and SCOPUS. The search was limited to articles available in English and peer-reviewed journals. Articles were screened in four stages by two independent reviewers and the Preferred Reporting Items for Systematic Reviews (PRISMA) was used. 486 articles were identified, of which, five full-text articles were included in the study. The literature outlined that targeting central and peripheral mechanisms are key to symptom management. Peripherally-acting prokinetics such as metoclopramide are considered first line therapy. Agents that target gastric accommodation such as clonidine, sumatriptan and sildenafil may also be useful. Centrally acting pharmacological agents associated with digestion may be effective. Centrally acting agents include: progesterone receptor agonists, cannabinoids and ghrelin agonists. Overall, early satiety is an under-recognised, but important symptom in cancer. Due to the limited studies available, the efficacy of treatments are not well established. High quality studies outlining appropriate therapeutic management are necessary to establish standardised treatment protocols.

Introduction

In advanced cancer states, early satiety appears to be a key determinant of anorexia severity (Walsh et al. 2000). Anorexia is a common symptom in cancer and has significant consequences for morbidity and quality of life (QOL) (Laviano et al. 2017). However, early satiation is poorly defined and under-recognized in medical practice. Diverse descriptors such as "abdominal fullness", "easy filling" or "filling quickly" have been used (Theologides 1979). The present review aims to define early satiety, describe its pathophysiology and conduct a literature review of appropriate therapeutic management.

Definition

Early satiety is a desire to eat, followed by an inability to eat appropriate portions due to a premature sense of fullness (satiety), with consequent decreased food intake (Theologides 1976; Sarhill et al. 2003). It occurs in an anorexia-cachexia cluster of symptoms along with taste changes and weight loss (Aktas et al. 2014). Clinically, early satiety is often misclassified as anorexia or nausea; however it is a distinct symptom that can occur in their absence (Theologides 1979; Theologides 1976).

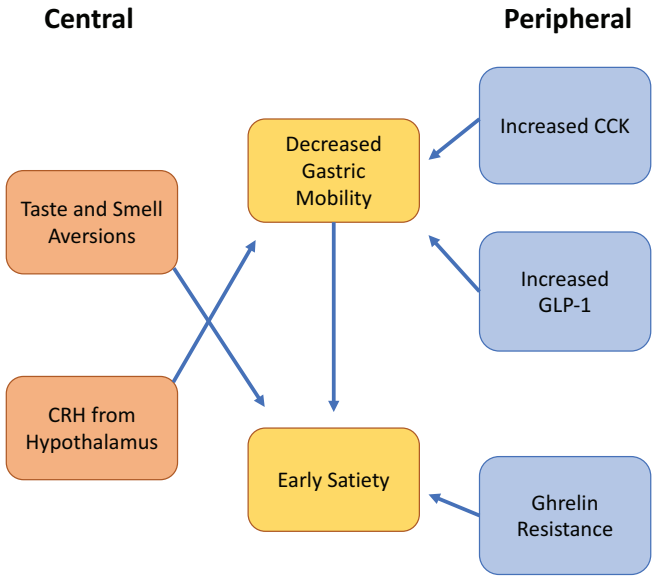
Prevalence

Early satiety is one of the ten most prevalent symptoms in advanced cancer, experienced by 51% of patients (Walsh et al. 2000). This symptom is more common in females and has not been linked to any specific primary cancer site or anti-cancer therapy (Davis et al. 2006; Walsh et al. 2000; Nielsen et al. 1980; Donnelly et al. 1995). It is an independent prognostic indicator of life expectancy (Walsh et al. 2000). Further, patients rarely volunteer information about the symptom spontaneously (Walsh et al. 2000). Consequently, it remains under-treated and poorly understood (Walsh et al., 2000).

Pathophysiology

The pathophysiology is ill-defined but appears to involve both central and peripheral mechanisms (Figure 1). Centrally, food intake is tightly regulated to match energy expenditure to body weight (Davis et al. 2006). Taste and smell aversions reduce food consumption and promote satiation (De Graaf et al. 1999; de Graaf et al. 2004). Corticotropin-releasing hormone (CRH) secreted from the hypothalamus reduces gastric motility and may induce satiety (Beglinger & Degen 2002).

Peripherally, food ingestion induces satiety signals from the gastrointestinal tract (Woods 2004). Important mediators include cholecystokinin (CCK), glucagon-



like peptide 1 (GLP-1), and ghrelin. Most of these elicit satiety as a meal progresses (Woods 2004). CCK is released from the small intestine due to fat and protein intake (Davis et al. 2006). GLP-1 is associated with fat and carbohydrate consumption and released by the ileum (Davis et al. 2006). Both CCK and GLP-1 inhibit gastric emptying, promote satiety, and reduce food intake (de Graaf et al. 2004; Woods 2004; Wilson et al. 2002). Conversely, ghrelin is a stomach hormone that stimulates appetite and gastric motility (Edholm et al. 2004; Davis et al. 2004). Elevated ghrelin levels occur in advanced cancer but there is resistance to ghrelin-associated appetite stimulation (Davis et al. 2006).

Inflammatory cytokines may play a role in the pathogenesis of early satiety in cancer. Studies have demonstrated that tumour associated pro-inflammatory cytokines, tumor necrosis factor-α (TNFα), Interleukin (IL)-1 and 6, and vascular endothelial growth factor (VEGF)-A and VEGF-C are key mediators in cancer-associated anorexia (Davis et al. 2012). Furthermore, early satiation occurs in insulin-dependent diabetes mellitus as a complication of diabetic autonomic neuropathy (Hasler WL 2008; Patrick et al. 2008). There is some evidence of autonomic dysfunction in non-diabetic cancer patients perhaps as a paraneoplastic syndrome (Donthireddy et al. 2007). It is presumed that early satiety reflects gastric dysmotility. Early satiety is a complex multifactorial symptom and appropriate treatment should target both its central and peripheral aetiologies.

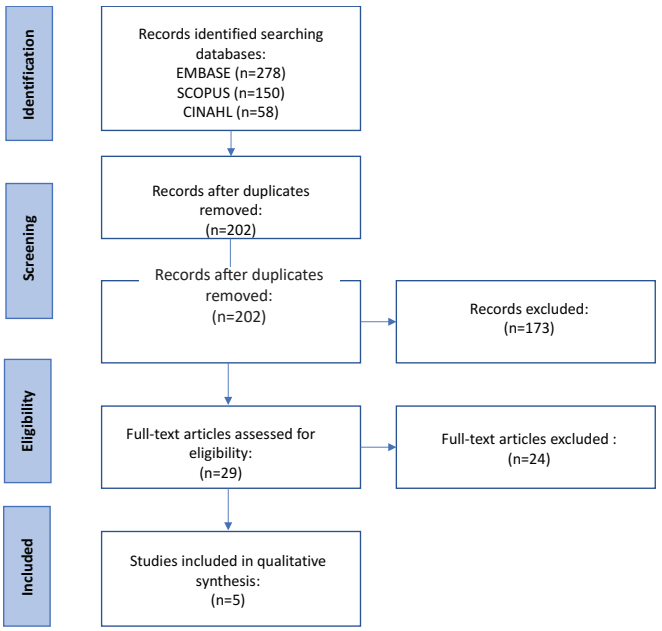
Methods

Literature Search

A systematic literature search was conducted using three electronic databases: EMBASE, CINAHL and SCOPUS. Variations of the following keywords were used: early, premature, satiety, satiation, fullness, and cancer. The search was limited to peer-reviewed journals and texts available in English language.

Study Selection

The review had four stages. To reduce selection bias, each stage was conducted independently by two reviewers. The reviewers screened eligible studies and papers were excluded if they did not pertain to therapeutic management or have full-text available. Articles were also excluded if they did not study the correct population or evaluate early satiety as a primary symptom.



Results

A total of 486 articles were identified and 284 duplicates removed. After screening titles and abstracts, 173 articles were excluded. Twenty-four articles were excluded after full-text assessment. Results were reported by Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (Figure 2). Five items (three original articles and two reviews) were included and full analysis was conducted (Table 1).

Source	Intervention	Study Sample / Literature Reviewed	Study Design	Limitations	Outcomes
Davis et al. 2006	None	Defining early satiety in advanced cancer	Narrative Review	Selection bias Publication bias Qualitative rather than quantitative	Treatments: small frequent meals, increased dietary fat, megestrol acetate, cannabinoids, ghrelin agonists, prokinetic agents (domperidone; metoclopramide)
Davidson et al. 2007	None	Treatments for ingestive behaviour in critical disease states (included cancer)	Narrative Review	Publication bias Selection bias Qualitative rather than quantitative. Conclusions related to all critical disease, not cancer-specific.	Treatments: cannabinoid agonists, ghrelin, megestrol acetate, thalidomide
Andrew et al. 2008	Clinical audit of cancer symptoms and drug history	Advanced cancer with cachexia syndrome (n=32)	Clinical Audit	Small sample (n=23) Did not evaluate treatment effects	Identified early satiety as a common symptom. Treatments: domperidone and metoclopramide
Chasen et al. 2011	OHR118- novel peptide nucleic acid, (TNF-alpha and IL-6) immunomodulatory effects	Advanced cancer with anorexia (n=21; 15 males, 6 females)	Non-randomised interventional study	Small study (n=8 completed) Non-randomised No control Short term study	Effectiveness not established. Significant appetite increase (p=<0.01) (n=8). Total PG-SGA score improved (p ≤ 0.01). Early satiety improved on the DSSI** (p=0.04).
Davis et al. 2012	Thalidomide, (TNF-alpha and IL-1) immunomodulatory effects	Advanced cancer with anorexia (n=35)	Non-randomised, phase II study	Small study (n=33 completed) Non-randomised No control Short term study	Effectiveness not established. 16 non-responders, of these, 4 who were uptitrated responded. Side effects: constipation, dry mouth, pruritus. Early satiety by the CAT significantly improved (p<0.05).

Table 1. Detailed Source Extraction. PG-SGA- Patient Generated Subjective Global Assessment score, **DSSI-Dyspepsia Symptom Severity Index, CAT- Categorical Scale

Discussion

Limited recognition and understanding of early satiety is reflected in the paucity of studies available. Few studies identify and examine effective therapeutic management. Limitations in the literature were identified (Table 1). Evidence was limited by poor follow-up attributable to high mortality in this cohort. In addition, much of the literature evaluates cachexia treatment, which although related, presents different therapeutic challenges. This literature was not included in our study.

Validated assessment tools for symptoms in advanced cancer symptoms rarely include early satiety, so it is difficult to assess treatments reliably. In Davis et al. 2012, the categorical scale (CAT) was used, however it has poor sensitivity (Davis et al. 2009). In addition, the Patient Generated Subjective Global Assessment (PG-SGA) includes early satiety as a symptom, but does not quantify it (Bauer et al. 2002). Early satietyhas been identified as an "Orphan" cancer symptom. As it occurs as part of a four-item anorexia-cachexia symptom cluster, there is the possibility that they share a common pathophysiology. Effective management of early satiety might improve not just satiety but other closely related symptoms.

Non-Pharmacological Management

With regard to central and peripheral mechanisms, early satiety can be targeted with non- pharmaceutical and pharmaceutical interventions. In terms of conservative management, various strategies can be used. There is a clinical variation in appetite of cancer patients, thus it is recommended to make breakfast the main meal of the day (Davis et al. 2006). Alternatively, it has also been proposed that frequent small meals throughout the day may help reach minimum daily calorie requirements (Davis et al. 2006). Lipid-rich meals cause less satiation

than protein or carbohydrate (Davis et al. 2006; Blundell et al. 1996). Colder food temperatures may also reduce food aversion (Davis et al. 2006). Further, emotional stress and anxiety contribute to early satiety, and psychiatric intervention can be helpful in these patients (Andrew et al. 2008).

Pharmacological Management

Megestrol acetate acts predominantly as a potent progesterone receptor agonist. It has a positive effect on the common symptoms of food aversion including taste and smell changes (Davis et al. 2006; Thorne et al. 2015). Cannabinoids like nabilone down regulate hypothalamic CRH and improve energy intake, thus may help improve satiety (Davis et al. 2006; Thorne et al. 2015). In a randomised, placebo-controlled, cross-over clinical trial, the effects of ghrelin were evaluated based on energy intake and meal appreciation using the visual analogue scale. Overall, ghrelin increased energy intake by 31% and a significant increase in meal appreciation score ($P = 0.02$) was observed (Neary et al. 2004). An additional study also concluded that ghrelin could be an effective, well-tolerated treatment for cancer-associated early satiety (Davis et al. 2006).

Cancer patients with severe early satiety have decreased gastric motility (Davis et al. 2006). A study identified in the present review recommended prokinetics, such as metoclopramide and domperidone for pharmaceutical management (Andrew et al. 2008). This particular study quantified symptom burden and audited prescribing in cancer patients with anorexia–cachexia syndrome (ACS) symptoms (Andrew et al. 2008). Seventy percent (n=23) of those audited had early satiety as a primary symptom by the PG-SGA tool and overall early satiety was identified as an unmanaged symptom. Commencing or increasing the dose of a prokinetic such as metoclopramide and domperidone was recommended (Andrew et al. 2008).

The immunomodulatory effects of OHR118, a novel broad spectrum peptide nucleic acid, on TNF-α and IL-6 were investigated in a small phase II non-randomised study (Chasen et al. 2011). Patients received daily, subcutaneous injections (4.0mL) of OHR118 and the effects on appetite, early satiety, and nutritional intake in advanced cancer were explored in 21 patients (Chasen et al. 2011). Early satiety improved significantly on the Dyspepsia Symptom Severity Index (DSSI). However, of the 21 patients enrolled, only eight continued with OHR118 treatment to completion (Chasen et al. 2011). A larger, randomised clinical trial should validate these findings.

Thalidomide, a TNF-α inhibitor, is an additional immunomodulatory drug associated with improved appetite. A two-stage phase II dose titration study (n=35) assessed appetite response in cancer-associated anorexia (Davis et al. 2012). The severity of early satiety, measured by the CAT, significantly improved ($P<0.05$) after two weeks treatment (Davis et al. 2012). However, many were non-responders (n=16) (Davis et al. 2012). A larger study is required.

Other potential agents such as clonidine, nitroglycerin, sildenafil, or sumatriptan have been outlined in the literature (Davis et al. 2006). These may help to improve gastric accommodation (Davis et al. 2006). In addition, hypersensitivity due to increased enteric afferent signals may be blocked by asimadoline (Delgado-Aros et al. 2003). The effectiveness of these treatments, however is unclear (Delgado-Aros et al. 2003; Davis et al. 2006).

Conclusions

Early satiety is a complex multifactorial symptom and appropriate treatment should target both its central and peripheral aetiologies. Despite its high prevalence, significant association with anorexia, and poor prognosis, early satiety is rarely identified or treated in advanced cancer. Limited high quality studies have specifically evaluated management. Future research should establish both a standardised treatment protocol and a validated tool for long-term assessment. Randomised control trials of large patient populations should be conducted to specifically evaluate the efficacy of proposed therapies. Translational research of the pathophysiology of early satiety may improve the understanding of this neglected symptom and uncover novel therapeutic pathways. Overall, improved recognition and management of early satiety may significantly enhance the quality of life in patients with advanced cancer.

Conflict of Interest Statement

There are no conflicting interests that may have influenced this work.

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