

Cancer Cachexia and Cannabinoids

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Key Words

Cancer · Cachexia · Anorexia · Cannabinoids · Cannabis

Summary

Anorexia and cachexia are diagnosed in more than two-thirds of all cancer patients with advanced disease, and are independent risk factors for morbidity and mortality. Anorexia, nausea and vomiting often are described as more significant inhibiting factors for quality of life of cancer patients than even intense pain. In 1986, delta-9-tetrahydrocannabinol (THC), the main effective constituent of cannabis, was licensed as an anti-emetic drug in cancer patients receiving chemotherapy. In addition, in clinical studies THC has shown significant stimulation of appetite and increase of body weight in HIV-positive and cancer patients. The appetite-stimulating effect of cannabis itself has also been well documented in many anecdotal cases. There are strong indications that cannabis is better tolerated than THC alone, because cannabis contains several additional cannabinoids, like cannabidiol (CBD), which antagonize the psychotropic actions of THC, but do not inhibit the appetite-stimulating effect. Therefore, we intend to compare the therapeutic effects of whole-plant extracts of cannabis to those of THC (dronabinol) alone in controlled studies.

Schlüsselwörter

Krebs · Kachexie · Anorexie · Cannabinoide · Cannabis

Zusammenfassung

Kachexie und Cannabinoide

Anorexie und Kachexie werden bei mehr als zwei Drittel der Krebspatienten im fortgeschrittenen Krankheitsstadium klinisch manifest und stellen nicht nur einen unabhängigen prognostischen Faktor für die Mortalität dar, sondern beeinträchtigen auch stark die Lebensqualität. Appetitlosigkeit, Übelkeit und Erbrechen werden von Krebspatienten häufig als gravierende Einschränkung ihrer Lebensqualität beschrieben als selbst starke Schmerzen. In der Folge umfassender präklinischer und klinischer Studien wurde Delta-9-Tetrahydrocannabinol (THC) als Hauptwirkstoff von Cannabis 1986 in den USA als ein wirksames Antiemetikum für die Chemotherapie bei Krebspatienten zugelassen. Untersuchungen wiesen aber auch eine signifikante Appetitstimulation und Gewichtszunahme nach. Neben einer Fülle von Einzelfallberichten ist der appetitstimulierende Effekt auch von Cannabis gut dokumentiert. Sowohl anekdotische Berichte als auch Forschungsergebnisse geben Hinweise auf eine bessere Verträglichkeit von Cannabis im Vergleich zur Monosubstanz THC, da Cannabidiol und andere Cannabinoide im Gesamtpflanzenextrakt die psychotrope Wirkung von Delta-9-THC antagonisieren, die Appetitstimulation aber nicht einschränken. Vor diesem Hintergrund sollten die therapeutischen Effekte von Cannabis-Extrakt und Dronabinol (THC) in kontrollierten klinischen Studien miteinander verglichen werden.

Cancer Cachexia

The word 'cachexia' is derived from the Greek 'kakos' (meaning 'bad') and 'hexis' (meaning 'condition'). It may occur in numerous

disease states, including AIDS, malabsorption, major trauma, surgery, severe sepsis, and, not the least of all reasons, cancer. Cachexia is characterized by unintentional weight loss involving depletion of skeletal muscle mass and adipose tissue.

Cachexia in cancer patients differs from weight loss found in simple starvation because it is a more complex process. While during long-time starvation body fat is used as a fuel (free fatty acids are released from adipose tissue and converted into ketone bodies, which are utilized for energy by peripheral tissues and the brain) and the muscle mass is conserved, in cancer cachexia, there is equal loss of body fat and muscle.

Weight loss in cancer patients has long been recognized as an important prognostic factor which affects response to chemotherapy [7] and duration of survival [8]. In a retrospective study of the Eastern Cooperative Oncology Group analyzing data of 3,047 patients, the frequency of weight loss ranged from 31% for favorable non-Hodgkin's lymphoma to 87% in gastric cancer [3]. Most evidence suggests that cancer cachexia results from a combination of metabolic abnormalities (increased protein degradation to meet high tumor requirement for amino acids associated with decreased protein synthesis [12]), malnutrition (decreased food intake due to anorexia, difficulty swallowing, pain or psychological depression [1]) and circulating humoral factors (increased release of catabolic hormones, tumor necrosis factor alpha, interleukins 1 and 6, interferon gamma [13]).

The central purpose of the pharmacological treatment of cachexia is to antagonize its two main symptoms, anorexia and chronic nausea. The latter should be controlled adequately before any pharmacological intervention for the patient's anorexia is attempted [2]. This finding suggests that a pharmacotherapy aimed at reversing chronic nausea and improving appetite may enhance quality of life in cancer patients and plays an important role in the overall management of the wasting syndrome in advanced cancer.

Delta-9-Tetrahydrocannabinol

Already in the 1970s Regelson et al. [11] studied delta-9-THC, the major psychoactive component of cannabis, in 54 advanced cancer patients in a crossover study. He found significant weight gain while the subjects were on THC versus weight loss while they were on placebo. At a dose of 0.1 mg/kg per os t.i.d. (15 mg/day maximum), there was almost complete absence of subjective euphoria com-

monly associated with the compound. In 1985 delta-9-THC (dronabinol) was approved by the FDA as a Schedule-II substance for the treatment of chemotherapy-induced nausea in cancer patients. After another investigations [14] had shown that delta-9-THC not only reversed nausea but also appeared to stimulate appetite and mood at well tolerated doses (5 mg daily) and other authors confirmed these results [10], in 1991 dronabinol also was approved for the treatment of anorexia associated with weight loss in AIDS.

Cannabis and Cancer Cachexia

The plant *Cannabis sativa* L. has long been reported to increase hunger and appetite. For instance, there are some well-documented reports about the appetite-stimulating properties of cannabis from the 19th century [9]. Also today, anecdotally, smoking marijuana has been noted to cause appetite stimulation in both healthy and ill subjects. A growing number of cancer patients experience improvement of nausea, appetite and mood by self-medication with cannabis. Beside anecdotal reports about marijuana-smoking cancer and AIDS patients, the appetite-stimulating effects of cannabis have well been documented [5, 6].

To treat cancer patients with cannabis could improve appetite, leading to weight gain and a better quality of life. In addition, it may lead to a relief of nausea which is often caused by chemotherapy. Finally, if the cycle of malnutrition aggravating the disease process can be broken, cannabis might enhance survival.

In recent years, various studies found evidence that cannabis and its components can modify both cellular and humoral immunity. It is still a widespread view that cannabinoids have negative effects on the human immune system especially in immunocompromised patients. However, new studies show that cannabinoids, under certain circumstances, also have immunostimulating effects. Consequently, some researchers refer to several cannabinoids as immunomodulators. More importantly, it has been shown that in HIV patients long-term marijuana use does not enhance the progression to AIDS [4]. What was found for these severely immunocompromised HIV-positives is bound to be true as well for cancer patients.

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