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The Close Reciprocal Relationship Between Diet And Thc-Based Therapy: A Comprehensive Narrative Review Of Literature.

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Abstract

The increasing use of THC-based therapy in various fields of medicine, requires dedicated attention to maximizing efficacy and minimizing possible side effects in frail patients' population. Especially with regard to oral and/or sublingual THC administration, the optimal dosage is extremely variable from patient to patient and influenced by many factors including nutrition. In this perspective, this article explores the reciprocal interaction between diet and cannabinoid and focuses on the usefulness of certain type of foods as a tool to improve oral/sublingual THC absorption and bioavailability as well as their potential effectiveness in reducing acute side effects of treatment. In this narrative review we also explore the possible changes induced in the diet by the chronic use of THC, in order to prevent its potential negative impact on the patient's nutritional status and therapeutic goals, especially in the setting of oncological patients.

Keywords: delta-9-tetrahydrocannabinol (THC), chronic pain, lipidic foods, cyclodextrins, intestinal absorption, bioavailability, hypercaloric fat food craving, diet imbalance.

INTRODUCTION AND AIM

The increased usage of delta-9-tetrahydrocannabinol (THC) in medical practice has been observed over the past decade, addressing different pathological areas such as chronic pain, oncological anorexia, and neurological and psychiatric disorders. [1]

The employment of this drug in these frail patient populations requires caution and great attention, in order to prevent and/or minimize the possible collateral effects of treatment. In fact, even if severe acute adverse events are not known to be associated with THC overdosage, many acute and chronic gastrointestinal, cardiovascular and psychiatric disorders have been described, including hyperemesis, diarrhea, tachycardia, orthostatic hypotension, dyspnea, chest pain, anxiety and dysphoria, among others. [2,3,4]

The appearance of these side effects may discourage the chronic usage of medical cannabis and push the patient to discontinue the treatment. [5]

In this view, it is crucial to define the optimal individual dosage to achieve the target therapeutic effect with the minimal amount of THC intake. However, especially concerning the oral intake of THC, it can be difficult to define the exact dose in relation to the complex pharmacodynamics of this molecule. [6]

The aim of this narrative review is to describe reciprocal relationship between diet and THC which, as described below, can be crucial in optimizing the dosage and reducing the side effects of the cannabis-based medical therapy.

THE IMPACT OF DIET ON THC ABSORPTION AND BIOAVAILABILITY

THC is a lyophilic and hydrophobic molecule that, when orally taken, is slowly and poorly absorbed in the small intestine with a resulting low bioavailability (5-10% of ingested amount). Its oral use is also negatively affected by extensive first hepatic passage inactivation of THC after intestinal absorption. [7, 8]

This results in a markedly low effective dose after oral

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ingestion of THC, which is moreover extremely variable from patient to patient in relation to multiple individual factors, including age, sex, race, genetic polymorphism of metabolism hepatic cytochrome, eventual diseases and pharmacological treatment. Last, but not least, diet can significantly modify both the absorption and metabolism of THC. [6, 7, 8]

Due to its hydrophobic nature, transepithelial absorption of THC through intestinal tight junctions is less than 10% of ingested dosage; however, it may be increased in the presence of lipidic food and/or when using a pharmacological lipidic formulation of this molecule. [6, 9]

In vitro and animal (rat) model experiments have reported a 2.5- to 3-fold increase in THC intestinal absorption in the presence of lipids. About one-third of lipophilic THC and CBD molecules were found to be solubilized in mixed spherical micelles in the presence of lipids and biliary salt in the proximal small intestinal environment. Therefore, it was assumed that the resulting chylomicron–cannabinoid complex could be better absorbed by intestinal cells and released not only into vascular but also lymphatic circulation. The THC fraction released into vascular circulation underwent high first hepatic metabolism passage, while the supposed THC–chylomicron complex released into the lymphatic vessels may reach the systemic circulation and, thus, its target sites before being metabolized by the liver enzymes. [9, 10]

Thus, lipid co-administration could increase the oral bioavailability of THC, due to both higher epithelial absorption and alternative lymphatic release.

A 2019 randomized double-blind study in 28 healthy human volunteers demonstrated that taking THC oral tablets after a lipid meal significantly increased (2.5-fold) the area under the curve with respect to fasted intake of the drug. [11]

A recent (2025) study in healthy men and women confirmed that the consumption of a high-fat meal also significantly increased the bioavailability and biphasic absorption of cannabidiol in humans, which is a molecule that is structurally and pharmacologically very similar to THC. [12]

Therefore, it is appropriate to take oral THC immediately after or in co-administration with a high-fat meal, in order to increase its bioavailability and reduce the amount and number of daily dosages of treatment. It is also advisable to avoid taking soluble fiber at the same time of THC therapy, as it can reduce the absorption of lipids and liposoluble molecules.

It is also conceivable that the sublingual administration of THC could benefit from similar dietary measures as, even with this route of intake, a non-negligible part of the drug is swallowed, ingested and absorbed into intestine. [13]

The co-administration of lipids is not the only dietary strategy to enhance the oral absorption of THC.

Cyclodextrins (CD) are a family of cyclic oligosaccharides, consisting of a macrocyclic ring of glucose subunits joined by α-1,4 glycosidic bonds. These hydrophilic molecules may create an internal hydrophobic cavity inside their proper ring structure, making them capable of blinding and driving host lipophilic molecules such as cannabinoid drugs, into the surrounding water environment. This CD–THC circular inclusion complex maintains hydrophilic characteristics on the outside of its ring structure, preserving the water solubility which is crucial to allow for intestinal permeability. [14]

Therefore, even a simple preparation obtained by mixing CD and THC in water solution, followed by co-precipitation, can significantly enhance the water solubility and oral absorption of cannabinoid-based drugs and, consequently, their bioavailability in chronic pain management. [14]

Furthermore, nutritive factors may modify not only the absorption, but also the metabolism of the drug.

Piperine is an alkaloid food supplement (the major active component found in black paper), which displays multiple anti-inflammatory, antioxidant and immunomodulatory properties. Different in vitro and in vivo experimental models have revealed that piperine has the potential to reduce Phase I and Phase II metabolism in the intestine and liver, and can inhibit the major drug-metabolizing enzyme CYP3A4 and P-gp efflux pumps. Lessons from animal models highlight a lipid-based self-emulsifying drug delivery system (Pro-NanoLipospheres, PNL) supplemented with piperine, which exhibited high effectiveness in increasing the oral bioavailability of THC. Pharmacokinetic experiments on rats demonstrated that a single oral administration of the THC–piperine–PNL complex resulted in a 1.47-fold and 9.3-fold increase in the AUC, compared to THC-PNL and THC alone, respectively. [15]

It is therefore conceivable that taking THC in conjunction with lipids and piperine-based food supplements can also enhance its bioavailability in humans.

THE EFFECTS OF THC THERAPY ON THE QUALITY OF THE PATIENT'S DIET AND NUTRITIONAL STATUS

The relationship between THC and alimentation is not a unique one, as nutrition influences the absorption and metabolism of the drug as much as the latter influences the amount and quality of diet. Several studies have extensively established the great appetite-stimulating properties of THC, which are mediated by modulation of CB1 and CB2 receptor activity in the central (via the thalamus–hypothalamus and hippocampus–amygdala axes) and peripheral (olfactory and gustatory apparatus) nervous system, as well as through its effects on glucose and lipid metabolism. [16]

The resulting complex multi-modal effect of THC is not only limited to stimulating increased hunger, but also influences the palatability and flavor of food, creating a specific and selective desire for certain types of food in patients. [16]

Since the first experimental studies in the 1980s, It has been observed that THC intake is associated with voracious appetite and a craving for hypercaloric sweet and fatty foods. Older literature has reported numerous anecdotal accounts from cannabis users indicating that the consumption of these foods may attenuate the more acute effects of THC; however, empirical human research in this regard remains very limited.[17, 18]

A 2019 randomized, single-blind placebo-controlled study in 17 healthy volunteers highlighted that THC increased "liking" and "wanting" ratings of high-calorie, but not low-calorie images, compared with placebo. Participants consumed significantly more milkshake after THC than after placebo. THC also increased plasma motilin and decreased ghrelin concentrations before milkshake consumption compared to placebo, without any differences in their levels after food ingestion between the two groups. [19]

In contrast, increased levels of ghrelin after oral THC intake in a fasting state were observed in a more recent randomized double-blind placebo-controlled study conducted in 20 patients. [20]

Motilin and ghrelin are two hormonal peptides, which are involved in gastric motility (motilin) and anxiety, hunger and blood pressure control (ghrelin). [21]

Altered concentrations of these molecules after THC intake in the pre-feeding phase could be responsible for certain side effects (anxiety, nausea, hypotension, tachycardia), which may be attenuated after food ingestion and the consequent normalization of their levels. However, the results of the available studies are conflicting, and more data and evidence are needed to confirm or refute these interesting suggestions.[19, 20, 21]

Therefore, food intake stimulated by THC could cause a reduction in its peak acute effects, thus serving as an effective tool to counteract undesirable side effects in patients under pharmacological therapy; however, at the same time, with chronic use this could cause negative dietary imbalances.

A recent prospective study has shown that chronic THC consumers exhibit significantly lower values in the Healthy Eating Index (a measure evaluated by questionnaire for assessing whether a set diet aligns with the Dietary Guidelines for Americans), as compared to non-users. [22]

In accordance with these findings, another recent report observed that adolescent current marijuana users were less likely to meet obesity prevention guidelines and/or the sugar-sweetened beverages recommendation. [23]

As an example, such dietary imbalances may be reflected in the worse control of diabetes in THC users. A recent systematic review reported poor glycemic control in people with type 1 diabetes (T1D) who consumed recreational cannabis, as well as a higher risk of cardiac and renal complications in THC users with type II diabetes. [24]

It is therefore crucial to practice adequate nutritional counseling before starting a new medical cannabis-based therapy, in order to avoid chronic worsening of the patient's diet and nutritional status. This is particularly important in the treatment of cancer and HIV-related cachexia.

Cannabis-based medical therapy is, in fact, effective in stimulating the appetite; however, its impact on cachexia and weight loss in cancer patients still remains unclear, as highlighted by two recent meta-analyses and systematic reviews. [25, 26]

Some studies included in these analyses actually showed that the drug's effectiveness in improving muscle mass and body weight could be related to several factors, possible including an unbalanced diet. In fact, a diet that is hypercaloric but low in proteins may not be able to counteract the loss of protein muscle mass underlying oncological cachexia. [25, 26]

SUMMARY AND CONCLUSION

In summary, there exists a close reciprocal correlation between THC and diet, where one significantly influences the other and vice versa. In particular, studies assessing the effects of lipid ingestion during or immediately before oral and/or sublingual drug intake provide good evidence in terms of its effectiveness in improving the intestinal absorption and bioavailability of THC.[9,10,11, 12]

We also presented interesting hypotheses regarding the idea that indulging in the high-fat/hypercaloric food cravings induced by THC use may attenuate its acute effects. [16, 17, 18, 19, 20, 21]

Finally, it was highlighted that nutritional counseling is needed in subjects treated with THC, as chronic cannabis use can cause an imbalance in the diet, leading to a certain ineffectiveness of the therapy and potential negative effects on health, especially in the setting of oncological and diabetic patients. [22, 23, 24, 25, 26]

In conclusion, considering that cannabis-based medical therapy is a rapidly expanding field, the relationship between THC and diet is a promising area of research which is yet to be explored in depth. As such, further prospective studies in humans are needed to validate with certainty the interesting hypotheses that have been put forward to date.

Core tip

This comprehensive narrative review explores the reciprocal close interaction between diet and THC and provides recent evidences on the positive contribution of certain types of food and nutrition in improving the effectiveness of THC-based medical therapy. The article also provides practical information useful for minimizing the side effects of the therapy and preventing negative imbalance in the diet of the patient undergoing chronic THC-based therapy.

Author contributions

Piciucchi M and Rossi A, have equally and mainly contributed to conceiving, designing and preparing the study. Satriano A collaborated on the literature review. All authors prepared the draft and approved the submitted version.

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