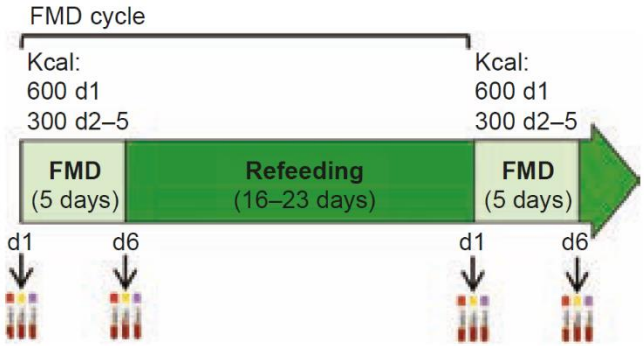
Nutriphyt

Cyclisch vasten verbetert de immuunrespons bij mensen met kanker

Bron: PlaceboNocebo ©Hilde Maris

Vasten is een van de beste manieren om het immuunsysteem te 'resetten' en een verstoord metabolisme te herstellen. Echt vasten – een langere periode niet of heel weinig eten – is voor veel mensen niet zo eenvoudig. Ook constante caloriebeperking (alle dagen weinig eten) is vaak moeilijk vol te houden. Er zijn verschillende manieren om het effect van vasten of weinig eten na te bootsen, met gelijkaardige voordelen, maar gemakkelijker om op lange termijn aan te houden. Een daarvan is het vasten-nabootsingsdieet (fasting mimicking diet, FMD). Het bestaat uit vijf dagen heel weinig eten en de rest van de maand 'gewoon' eten. Het wordt ook cyclisch vasten genoemd.

Deze vorm van vasten zorgt ervoor dat het eigen immuunsysteem veel beter in staat is om tumoren te vernietigen. Het versterkt bovendien de werking van chemo- en immunotherapie. Dat is uitvoerig aangetoond bij muizen, maar het werkt ook bij mensen.



Het vasten-nabootsdieet (FMD):

5 dagen heel weinig eten
+
de rest van de maand "gewoon" eten

In een recent onderzoek moesten 101 kankerpatiënten die behandeld werden voor verschillende soorten kanker een vasten-nabootsingsdieet volgen. Dat hield in dat ze vijf dagen na elkaar heel weinig calorieën mochten eten (maximum 600 kcal op de eerste dag en de volgende vier dagen maximum 300 kcal per dag). Deze cyclus werd elke drie tot vier weken herhaald (individueel afgestemd op de behandeling die ze kregen). Tijdens die vijf dagen mochten ze alleen plantaardig

koolhydraat- en eiwitarm voedsel eten (vooral groenten, fruit, noten en een beetje extra vierge olijfolie). Tussen de vastencycli mochten ze eten wat ze wilden, maar ze werden wel aangeraden om gezond te eten en te leven.

Dit cyclisch vasten had een bijzonder gunstig effect op het metabolisme, met een aanzienlijke daling van de bloedsuikerspiegel (gemiddeld -18,6%), insuline in het bloed (-50,7%) en insulineachtige groeifactor IGF-1 (-30,3%). Een hoge bloedsuikerspiegel en te veel insuline en IGF-1 bieden een ideale voedingsbodem voor kankercellen, en zorgen ervoor dat tumoren beter in staat zijn om te groeien. Ze ondermijnen ook het effect van elke behandeling.

Bij een deel van de patiënten, bij wie de tumor(en) operatief verwijderd werden, werd ook de activiteit van immuuncellen in en rond de tumoren en in het bloed onderzocht. Na een vastencyclus was het aantal actieve kankerceldodende immuuncellen verhoogd. Het immuunsysteem schakelde over naar een sterkere antitumor-immuniteit (Vernieri C, 2021).

Als je zelf van plan bent om cyclisch te vasten, overleg dit dan met je behandelende arts, zodat de cycli afgestemd kunnen worden op je behandeling. Sommige mensen kunnen in het begin last hebben van een te lage bloedsuikerspiegel (hypoglycemie), vermoeidheid, duizeligheid en flauwte. Dat gaat meestal over na een paar cycli, maar het is aangeraden om dit goed op te volgen.

I. Referentie

Vernieri C, Fuca G, Ligorio F, et al. Fasting-mimicking diet is safe and reshapes metabolism and antitumor immunity in cancer patients. Cancer Discov. 2021 Nov 17:candisc.0030.2021. doi: 10.1158/2159-8290.CD-21-0030. Epub ahead of print. PMID: 34789537.

RESEARCH ARTICLE

Fasting-Mimicking Diet Is Safe and Reshapes Metabolism and Antitumor Immunity in Patients with Cancer

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ABSTRACT In tumor-bearing mice, cyclic fasting or fasting-mimicking diets (FMD) enhance the activity of antineoplastic treatments by modulating systemic metabolism and boosting antitumor immunity. Here we conducted a clinical trial to investigate the safety and biological effects of cyclic, five-day FMD in combination with standard antitumor therapies. In 101 patients, the FMD was safe, feasible, and resulted in a consistent decrease of blood glucose and growth factor concentration, thus recapitulating metabolic changes that mediate fasting/FMD anticancer effects in preclinical experiments. Integrated transcriptomic and deep-phenotyping analyses revealed that FMD profoundly reshapes anticancer immunity by inducing the contraction of peripheral blood immunosuppressive myeloid and regulatory T-cell compartments, paralleled by enhanced intratumor Th1/cytotoxic responses and an enrichment of IFNγ and other immune signatures associated with better clinical outcomes in patients with cancer. Our findings lay the foundations for phase II/III clinical trials aimed at investigating FMD antitumor efficacy in combination with standard antineoplastic treatments.

SIGNIFICANCE: Cyclic FMD is well tolerated and causes remarkable systemic metabolic changes in patients with different tumor types and treated with concomitant antitumor therapies. In addition, the FMD reshapes systemic and intratumor immunity, finally activating several antitumor immune programs. Phase II/III clinical trials are needed to investigate FMD antitumor activity/efficacy.

INTRODUCTION

In tumor-bearing mice, cyclic fasting or calorie-restricted, low-carbohydrate, low-protein diets, collectively referred to as fasting-mimicking diets (FMD), have convincingly demonstrated additive or synergistic antitumor activity in combination with cytotoxic chemotherapy (ChT), immunotherapy, or endocrine therapies (1–6). These anticancer effects are mostly mediated by fasting/FMD-induced reduction of blood glucose, insulin, and insulin-like growth factor 1 (IGF1) concentration, which results in the inhibition of anabolic processes that sustain unrestrained growth/proliferation and the repair of chemotherapy-induced genotoxic and proteotoxic effects in cancer cells (2, 6). More recently, fasting and FMD were shown to boost tumor infiltration by $CD8^+$ T cells—the effectors of antitumor immune responses—and to reduce immunosuppressive regulatory T cells (Treg) in syngeneic mouse models (3, 5).

On the basis of this preclinical evidence, clinical trials have been initiated to investigate the feasibility and antitumor activity of cyclic FMD in combination with standard antitumor therapies in different clinical contexts (NCT03709147, NCT04248998, NCT03700437). The only study whose results have been reported so far is the phase II trial "DIRECT" (NCT02126449), which was prematurely interrupted because of poor patient compliance with the proposed FMD regimen and because the FMD failed to reduce ChT-induced adverse events (7).

Here we report on the final results of a first-in-human clinical trial (NCT03340935) that investigated the safety, feasibility, and metabolic and immunomodulatory effects of a severely calorie-restricted, five-day FMD regimen in patients with cancer. We also report on results of an interim analysis in which we investigated FMD-induced systemic and intratumor immune responses in 22 patients with breast cancer enrolled in the ongoing DigesT trial (NCT03454282).

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Note: Supplementary data for this article are available at Cancer Discovery Online (http://cancerdiscovery.aacrjournals.org/).

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Supplementary Table S1: Daily calorie and macronutrient composition of the FMD regimen used in the NCT03340935 and NCT03454282 trials

Day (n)	Allowed foods/beverages	Kcal/day	Macronutrient composition (%Kcal)
1	**Breakfast:** one tea or non-caloric tisane at the choice of the patient (without sugar) **Lunch:** a dish of mixed vegetables (up to 300 grams), including spinach, cabbage, cauliflower, broccoli, lettuce or zucchini, consumed as raw, boiled or steamed (~72 Kcal), together with a tablespoon (12 grams) of extra virgin olive oil (118 Kcal); 100 grams of whole wheat breas (~224 Kcal) **Dinner:** 150 grams of green salad (~30 Kcal) with a teaspoon of extra virgin olive oil (~54 Kcal); 1 orange, 1 apple or 1 pear (average weight 250 grams) (~100 Kcal).	~ 600	Carbohydrates: 52-56% Proteins: 11-15% Lipids: 31-35%
2	**Breakfast:** one tea or non-caloric tisane at the choice at the choice of the patient (without sugar). **Lunch:** 200 grams of green salad (~40 Kcal) with a teaspoon of extra virgin olive oil (~54 Kcal). Alternatively, an equivalent amount (~200 grams) of the following vegetables: spinach, cabbage, cauliflower, broccoli, lettuce, zucchini, or 50 grams of onions. Up to half a lemon per day. **Dinner:** 20 grams of shelled walnuts (~180 Kcal) or 30 grams of almonds (~180 Kcal).	~300	Carbohydrates: 8-12% Proteins: 12-16% Lipids: 74-78%
3	**Breakfast:** one tea or non-caloric tisane at the choice at the choice of the patient (without sugar). **Lunch:** 200 grams of green salad (~40 Kcal) with a teaspoon of extra virgin olive oil (~54 Kcal). Alternatively, an equivalent amount (~200 grams) of the following vegetables: spinach, cabbage, cauliflower, broccoli, lettuce, zucchini, or 50 grams of onions. Up to half a lemon per day. **Dinner:** 20 grams of shelled walnuts (~180 Kcal) or 30 grams of almonds (~180 Kcal).	~300	Carbohydrates: 8-12% Proteins: 12-16% Lipids: 74-78%
4	**Breakfast:** one tea or non-caloric tisane at the choice at the choice of the patient (without sugar). **Lunch:** 200 grams of green salad (~40 Kcal) with a teaspoon of extra virgin olive oil (~54 Kcal). Alternatively, an equivalent amount (~200 grams) of the following vegetables: spinach, cabbage, cauliflower, broccoli, lettuce, zucchini, or 50 grams of onions. Up to half a lemon per day. **Dinner:** 20 grams of shelled walnuts (~180 Kcal) or 30 grams of almonds (~180 Kcal).	~300	Carbohydrates: 8-12% Proteins: 12-16% Lipids: 74-78%
5	**Breakfast:** one tea or non-caloric tisane at the choice of the patient (without sugar). **Lunch:** a dish of mixed vegetables (up to a total of 300 grams), including spinach, cabbage, cauliflower, broccoli, lettuce or zucchini, consumed as raw, boiled or steamed (~75 Kcal), together with a tablespoon (12 grams) or extra virgin olive oil (~108 Kcal). 1 orange, 1 apple or 1 pear (average weight 250 grams) (~100 Kcal). **Dinner:** 100 grams of green salad (~20 Kcal) with a teaspoon of extra virgin olive oil (~54 Kcal).	~300	Carbohydrates: 43-47% Proteins: 13-17% Lipids: 38-42%