# Run in study on the safety and tolerability of a fasting-mimicking diet in relapsing remitting multiple sclerosis

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## Background

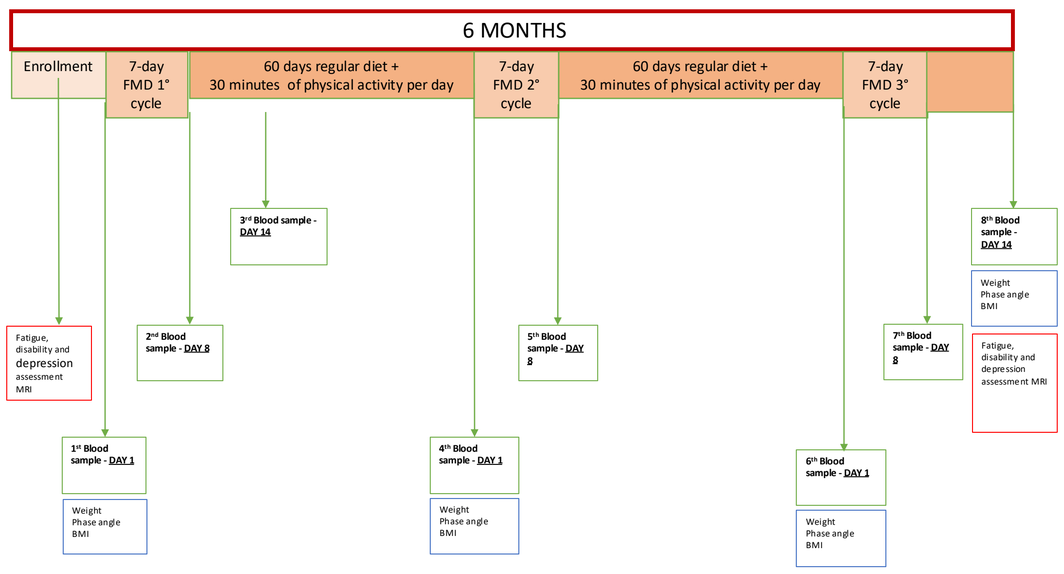
Fasting-mimicking diet (FMD) has shown promise in experimental autoimmune encephalitis. Although cycles of FMD have been demonstrated to be safe and feasible in multiple clinical settings, data regarding the use of FMD in multiple sclerosis (MS) patients are still lacking. Ensuring adherence to diet changes is critical to determining the efficacy of such interventions. However, to date, there is not sufficient evidence to encourage the use of any specific diet for MS patients.

## Aims

The primary objective of the present study is **to investigate safety and tolerability of FMD in patients with relapsing-remitting Multiple Sclerosis (RRMS).** Secondary objectives were **to assess patients' compliance to FMD, changes in nutritional status/body composition, and the effect of FMD on clinical stability, biochemical parameters, and immune cell profile.**

## Methods

- In this phase-II prospective study, we enrolled 22 consecutive **RRMS patients** followed at the MS Center of the University of Genoa undergoing first-line therapies (interferon-beta, glatiramer acetate, teriflunomide and dimethyl fumarate).
- Patients were asked to undergo **three cycles of 7-days FMD (1100 kcal on day one and 800 kcal on days 2-7) every 60** days in addition to standard therapy.
- During days of calorie restriction patients were called every day by the dietician to evaluate the tolerance towards the diet.
- Patients underwent clinical and neurological evaluations, nutritional assessments (bioimpedance), laboratory testing, immune profiling (flow cytometry), serum neurofilament dosage, and MRI at baseline and at six months. Safety was assessed using CTCAE v5.0 criteria.




* Blood sample of day 1 (first cycle), day 14 (first cycle), and day 14 (third cycle) included IF and NfL dosage

## Results

| POPULATION CHARACTERISTICS | | |
|---|---|---|
| Age, mean± s.d. | | 44.4 ± 6.87 |
| Sex, n(%) | Female | 14 (63.6%) |
| | Male | 8 (36.4%) |
| Disease duration (years), mean± s.d. | | 11.7 ± 6.94 |
| EDSS at baseline, median (IQR) | | 1.0 (0.0 - 1.5) |
| DMT, n(%) | Interferon | 5 (22.7%) |
| | Glatiramer acetate | 2 (9.1%) |
| | Dimethyl fumarate | 12 (54.5%) |
| | Teriflunomide | 3 (13.6%) |
| Relapses during the study, n(%) | No | 22 (100.0%) |
| | Yes | 0 (0.0%) |
| MRI activity during the study, n(%) | No | 22 (100.0%) |
| | Yes | 0 (0.0%) |

- Eighteen out of 22 patients (81.8%) completed all FMD cycles.
- Only mild to moderate adverse events (grade G1-G2) were reported, primarily fatigue and headache, with **no serious adverse events.**
- **Nutritional parameters** remained stable or improved. In particular, fat-free mass (FFM) increased significantly between cycle 2 and cycle 3: $p = 0.02$, and between cycle 2 and follow-up: $p = 0.03$; skeletal muscle mass index (SMI) increased significantly between cycle 2 and cycle 3: $p = 0.01$, and between cycle 2 and follow-up: $p = 0.01$; fat mass (FM) slightly decreased between cycle 2 and follow-up: $p = 0.0120$.
- Blood **glucose** showed transient reductions post-FMD but remained within normal ranges.
- No significant lymphopenia or liver/kidney dysfunction was observed.
- **Immunophenotyping** revealed a significant reduction in circulating myeloid dendritic cells after the third FMD cycle ($p < 0.01$).
- No relapses, MRI activity changes, or increased neurofilament levels were observed during the study period.

## Conclusions

- This study demonstrates that three bimonthly 7-day cycles of FMD are feasible, safe, and well tolerated in RRMS patients at low nutritional risk.
- Adherence was high, and the intervention did not negatively affect body composition or hematological parameters.
- Importantly, patients remained clinically stable, with no disease progression or MRI worsening.
- The reduction in myeloid dendritic cells may warrant further investigation.
- There remains a need to define the potential usefulness of FMD in RRMS through clinical studies having efficacy parameters as primary endpoints.

***Bibliography***

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