Less is more: effectiveness and feasibility of a fasting-mimicking diet programme in persons with type 2 diabetes in primary care

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Chapter 13

Summary

This thesis aims to provide insight into the role of intermittent and periodic fasting for individuals with type 2 diabetes (T2D), specifically in the form of a fasting-mimicking diet (FMD) programme integrated into routine primary care in the Netherlands.

Part I

In **part I**, an overview of the available literature at the time of writing is presented. First, a systematic review examining the metabolic effects of intermittent and periodic fasting in individuals with T2D demonstrated potential in addressing various anthropometric and metabolic abnormalities, at least in the short term and as long as the interventions are sustained (**chapter 2, van den Burg**). Second, a narrative review on the effects of intermittent and periodic fasting of both animal studies and clinical trials showed positive effects on weight, fat mass, visceral fat, inflammation, cognitive function, mental health, gut microbiome composition and metabolic health (**chapter 3, Schoonakker**). Third, a systematic review of studies evaluating the impact of the restriction of carbohydrates, fats or proteins on gut microbiota composition found that carbohydrate restriction reduces the abundance of several health-promoting bacterial species. In contrast, low-fat diets appear to have the opposite effect on relative abundance of health-promoting bacteria (**chapter 4, Schoonakker**).

Part II

Part II of this thesis describes the rationale, methods and clinical outcomes of the FIT (Fasting In diabetes Treatment) trial. **Chapter 5** (**van den Burg**) provides a detailed account of the trial's rationale and methodology, outlining its randomised, controlled, assessor-blinded design. In the FIT trial, individuals with T2D were included who manage glycaemic control with either lifestyle advice alone or in combination with metformin. The intervention consists of periodic 5-day FMD cycles repeated monthly over a year, next to usual care provided by their own general practice. An FMD is a specific form of periodic fasting, which mimics the metabolic effects of complete fasting because of its specific macronutrient composition: relatively less refined sugars, starch and proteins, relatively more complex carbohydrates and healthy plant-based fats. The FMD in the FIT trial contained ~1100 kcal on the first day and ~750 kcal on the following days. The control group received usual care alone.

The primary outcomes of the FIT trial are changes in HbA1c levels and glucose-lowering medication use after twelve months (**chapter 6, shared first authorship van den Burg and Schoonakker**). Intention-to-treat (ITT) analyses using linear mixed models revealed an adjusted estimated treatment effect of following FMD for 12 months of -3.2 mmol/

mol for HbA1c (95% CI -6.2 to -0.2 mmol/mol; p=0.04) and -0.3 for the medication effect score (a score reflecting the intensity of the glucose-lowering medication regimen; 95% CI -0.4 to -0.2; p<0.001). As plasma HbA1c concentration and glucose-lowering medication use mutually influence each other, these parameters were combined to reflect glucose control in individual participants to yield a categorical outcome measure, for which the term 'glycaemic management' is used. Based on individual changes at the end of study in HbA1c and glucose-lowering medication use, glycaemic management was categorised as 'improved,' 'stable,' or 'deteriorated'. Glycaemic management improved in 53% of participants using FMD vs 8% of control participants, remained stable in 23% vs 33%, and deteriorated in 23% vs 59% (p<0.001).

Secondary outcomes of the FIT trial include anthropometric and laboratory measurements (**chapter 6, shared first authorship van den Burg and Schoonakker**). Regarding the anthropometric data, a reduction was found in weight, BMI, waist circumference and body fat percentage after twelve months of following the FMD programme. There was no difference in fat-free mass, systolic or diastolic blood pressure. Regarding the laboratory measurements, there was a small improvement in HDL-cholesterol after twelve months. There was no effect on fasting glucose, insulin, total cholesterol, LDL-cholesterol, triglycerides or high sensitivity CRP. However, the Matsuda index (a measure reflecting insulin sensitivity) did improve after twelve months, while the disposition index (a measure reflecting the combined function of insulin sensitivity and insulin secretion) did not improve after twelve months.

Chapter 7 and 8 describe secondary outcomes of the FIT trial derived from Magnetic Resonance Imaging (MRI). Two MRI-derived biomarkers were assessed in **chapter 7** (**van den Burg**): proton density fat fraction (PDFF), a marker for liver fat, and iron content corrected T1 (cT1), a marker for liver inflammation/fibrosis. ITT analyses using linear mixed models revealed an adjusted estimated treatment effect of following FMD for 12 months of -2.8 % for PDFF (95% CI -4.7 to -0.8%; p<0.01) and -29.9 ms for cT1 (95% CI -51.8 to -8.0 ms; p<0.01). This indicates that following an FMD programme can reduce liver fat and liver inflammation/fibrosis. In **chapter 8** (**Schoonakker**), abdominal visceral adipose tissue (aVAT), abdominal subcutaneous adipose tissue (aSAT) and abdominal muscle area (aMA) were assessed, measured in cm^2 on a single axial slice at the centre of the third lumbar vertebra. ITT analyses using linear mixed models revealed an adjusted estimated treatment effect of following FMD for 12 months of -37.9 cm^2 for aVAT (95% CI -54.7 to -21.0 cm^2; p<0.01) and -20.9 cm^2 for aSAT (95%CI -34.5 to -7.3 cm^2; p<0.01). No treatment effect of following FMD was found on aMA (-1.6 cm^2, 95% CI -4.6 to 1.4 cm^2; p=0.31).

The combination of results from the FIT trial in **chapter 6, 7 and 8** are particularly relevant in the context of pathological mechanisms underlying T2D development, highlighting FMD as a promising dietary intervention for improving metabolic health.

Part III

The third part of this thesis discusses three aspects of the FIT trial relevant to consider before implementation of the FMD programme in regular primary care.

Chapter 9 (**Schoonakker**) focusses on the feasibility of the FMD programme for individuals with T2D. In the FMD group, 61% completed the FMD programme, while 31% discontinued due to diet-related issues and 8% for other reasons. Serum ketone levels were consistently higher in the FMD group than in the control group ($p<0.01$), indicating adherence with the FMD programme. Focus groups with FMD participants (n=20) revealed facilitators for adherence, such as convenience, short FMD cycles, not feeling hungry, internal motivation, believing in beneficial effects, experiencing health improvements and social support. Barriers included taste, quantity, and frequency of the FMD, environmental temptations, and lack of social support.

Chapter 10 (**van den Burg**) examined self-initiated lifestyle changes during the one year FMD programme, using a mixed-methods approach. No differences in diet quality were found between the FMD and control group. Total physical activity in the FMD participants changed from 34.6 to 38.5 hours per week (h/wk) from baseline to twelve months, while in controls it changed from 34.9 to 29.0 h/wk (between group difference, $p = 0.03$). In focus groups with FMD participants (n=20), individual participants perceived the FMD as an encouragement for (minor) lifestyle changes. Important facilitators related to following the FMD were an increase in awareness of the impact of lifestyle on health, better physical fitness and health improvement. Facilitators unrelated to the FMD included family support and opportunities in the neighbourhood, while barriers unrelated to the FMD were experiencing health problems, work-related issues and social events.

The aim of **chapter 11** (**van den Burg**) was to determine the cost-effectiveness of the FMD programme in the short term and the long term. A trial-based cost-utility analysis with quality-adjusted life-years (QALY) and healthcare costs was performed, and these results were extrapolated to a lifetime horizon using the United Kingdom Prospective Diabetes Study Outcomes Model. In the trial-based (short term) analysis (n=92), QALYs were insignificantly lower (-0.04, 95% CI -0.10 to +0.03), while healthcare costs were significantly higher (+€2241, 95% CI +182 to +2660) in the FMD group. In contrast, from a lifetime horizon (long term), QALYs were insignificantly higher in the FMD group (+0.16,

95% CI -1.16 to +1.48) and costs were insignificantly higher as well (+€1336, 95% CI -753 to +3425), yielding an incremental cost-effectiveness ratio of €8369/QALY. It was found that in the short term, the FMD programme does not appear to be cost-effective in this specific patient group in the context of the Dutch healthcare system, mainly due to the costs of the FMD programme and the relatively low costs of early stage T2D. In contrast, in the lifetime model-based cost-effectiveness analysis, a gain in QALYs in the FMD group was seen and the FMD programme' costs were largely offset by savings in the costs of diabetic complications. This suggests that adding an FMD programme to usual care may potentially be cost-effective in the long term.

Conclusion

This thesis offers novel insights into the role of intermittent and periodic fasting for individuals with T2D, focussing on an FMD programme within Dutch primary care. A 5-day monthly FMD programme can be safely and effectively integrated into the care of individuals with T2D managing glycaemic control through either lifestyle advice alone or in combination with metformin. The FMD programme significantly improves HbA1c levels, several anthropometric measures including weight, MRI-derived outcomes such as liver fat, aVAT, and aSAT, and reduces the use of glucose-lowering medication. It is feasible for individuals with T2D within a primary care setting and may serve as a 'teachable moment' for broader lifestyle changes. Long-term modelling suggests the FMD programme may potentially be cost-effective.