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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 1

General Introduction

shared authorship

Type 2 diabetes

Type 2 diabetes (T2D) is a complex disease that is characterized by chronic hyperglycaemia(1). Multiple factors play a role in the development of the disease, including genetic and environmental factors(2, 3). Poor dietary habits and physical inactivity are key environmental factors involved in the pathogenesis, leading to a positive energy balance(1). Furthermore, the gut microbiome plays a role, which is also affected by dietary alternations(4-6). An increase in muscle insulin resistance is one of the first indicators of the development of T2D, which prevents glucose from being stored in muscles, giving rise to increased plasma glucose levels(7). In turn, this causes de novo lipogenesis, leading to an increase in subcutaneous and visceral fat storage(8). Furthermore, especially when the subcutaneous fat storage capacity is exceeded, ectopic fat will start to accumulate in several tissues, including the liver and pancreas, leading to hepatic insulin resistance and a reduction of insulin secretion(1, 8-10). These processes reinforce one another and are further mediated by other factors such as inflammation, resulting in a continuous rise in plasma glucose levels(1, 9-11). Over time, beta cells fail to produce sufficient insulin to compensate for insulin resistance and T2D ensues(1, 12).

The global prevalence of T2D continues to rise worldwide. In 2021, the number of individuals with diabetes was estimated to have exceeded 536 million globally, and by 2045, it is projected that diabetes will affect approximately 12% of the world's population, amounting to an estimated 783 million people(13). In the Netherlands, the prevalence of T2D increased from 2.3% in 2004 to 6.3% in 2020 in men and in the same period from 2.3% to 5.3% in women, while the incidence rate in this period remained relatively stable(14). Both the Dutch and global data indicate that T2D is a common chronic disease that needs global attention, given its significant impact on affected individuals.

Regarding the effects on the individual, a diagnosis of T2D is significantly related to a decrease in quality of life(15). In addition, T2D can result in various complications that further reduce quality of life, including microvascular complications such as retinopathy and nephropathy, as well as macrovascular complications including cardiovascular diseases(16, 17). T2D also affects life expectancy, causing a reduction of about two life years per person(18, 19). It is estimated that for every year with an HbA1c > 58 mmol/mol, someone loses around 100 life days(18). In addition, the impact on society must be taken into account. The rising prevalence of T2D is accompanied by increasing healthcare costs, particularly related to disease management of complications, which account for the majority of healthcare expenses in individuals with T2D(20-22). Although projecting future costs is uncertain, estimates suggest that the global economic burden will rise from U.S.$1.3 trillion in 2015 to $2.2 trillion by 2030, which represents a growth in costs as a share of global gross domestic product from 1.8% in

2015 to 2.2% by 2030(23). In conclusion, T2D significantly affects individual mortality and quality of life, while also imposing a considerable economic burden on society. To reduce the effects of T2D, it is crucial to provide evidence-based treatment options.

Treatment of type 2 diabetes

Lifestyle interventions form the foundation of T2D treatment and there are two key pillars(24, 25). First, increasing physical activity can optimize glycaemic control, even in the absence of weight loss(26, 27). Second, various dietary programs have shown to improve glycaemic regulation(28-30). When lifestyle modifications are insufficient to improve glycaemic control, additional treatment options are available for individuals with T2D which include various types of glucose-lowering medication(24, 25). However, glucose-lowering medication targets specific disease symptoms, such as an increased blood glucose level, and is not able to reverse the disease process, whereas lifestyle interventions including dietary interventions address the entire metabolic system(12, 31). For instance, dietary interventions not only have the capability to improve glucose metabolism, but also have the potential to reduce weight, improve lipid profiles, and lower blood pressure at the same time(32). Therefore, dietary changes are a fundamental component of treatment for T2D, even when additional medication is required. Ideally, healthcare providers should be able to offer patients a variety of dietary options that are proven effective in the treatment of T2D, to match an individual's needs and capabilities(47).

Currently, several diets have shown to be effective in the treatment of individuals with type 2 diabetes(28-30). Some examples are continuous energy restriction, low-carbohydrate diets without energy restriction and the Mediterranean diet(29, 30, 33-35). However, guidelines do not recommend one specific diet over another for individuals with T2D(24, 25). In general, guidelines encourage to follow the same healthy eating advice as the general population(24, 25). However, a weight loss target of 5-10% is recommended for individuals with T2D who are overweight, as it can lead to significant metabolic improvements(36). Recently, several studies have shown that T2D remission can be achieved by continuous energy restriction, and that the amount of weight loss is related to achieving successful remission(34, 37). However, to remain in remission it is essential to sustain weight loss, and additional support after the initial weight loss phase may be necessary(38, 39). Sustaining long-term caloric restriction can be challenging(40). Moreover, prolonged caloric restriction has also been shown to lower basal metabolic rate, even when adjusted for body weight reduction(41). This suggests that continuous caloric restriction not only leads to the loss of weight, but can also induce metabolic changes that can make achieving and maintaining a healthy weight particularly difficult(41).

Intermittent and periodic fasting

Since sustaining long-term caloric restriction can be difficult and this is not without side-effects, other dietary programs have been developed over the past years. Intermittent fasting (repetitive fasting periods ≤ 48h each) and periodic fasting (any fasting regimen repeated at regular intervals, including short-term fasting for 2-3 days and prolonged fasting ≥ 4 days) are gaining popularity as alternatives to continuous energy restriction(42). These diets refer to eating patterns in which individuals go through short time periods of restricted food intake, alternated with periods of unrestricted food intake(42). Since water-only fasting is difficult to sustain, several dietary regimens have been developed that mimic the effects of fasting while not requiring complete abstinence of eating for extended periods of time. Some examples are modified fasting, which provides up to 25% of energy needs on a fasting day, and time restricted eating, which limits the restriction of energy intake on specific time periods per fasting day (typically between 12 and 16 hours) (42-44). Short-term trials have found that these diets can be effective in improving glucose metabolism in persons with T2D(45, 46).

Fasting-mimicking diet

A fasting-mimicking diet (FMD) is another form of periodic fasting, which has a specific macronutrient composition that mimics the endocrine and metabolic effects of complete fasting, while still providing light meals during fasting days(48). FMDs achieve their effects by containing minimal refined sugar or starch, low protein levels, and relatively more complex carbohydrates and healthy fats, all from plant based sources(49). In a pilot study of 38 healthy individuals, three monthly 5-day FMD cycles led to weight loss and reduced visceral fat compared to continuation of a normal diet(49). A larger study with 100 healthy participants found that three monthly 5-day FMD cycles reduced body weight, total body fat and blood pressure(50). A post hoc analysis showed that in participants with increased fasting glucose level (defined as ≥5.5 mmol/L), FMD cycles brought glucose within the healthy range. The FMD was well tolerated without significant side effects(49, 50). These results suggests that a FMD could potentially be beneficial for individuals with T2D.

Aim and outline of this thesis

The overall aim of the studies presented in this thesis is to gain a deeper understanding of the role of intermittent and periodic fasting, more specifically in the form of an FMD programme, for individuals with T2D receiving treatment in primary care. Individuals with T2D in primary care often face not only the challenges of managing their T2D but also issues related to weight management, comorbidities such as hypertension and

hypercholesterolemia, and extensive medication use. A common complaint among these patients is their inability to lose weight despite multiple attempts. To illustrate the associated challenges and potential benefits, we present the medical history of an "average" individual with T2D, usually under primary care surveillance:

Mrs. Riet Suiker
Mrs. Suiker is a 62-year-old woman who attends her regular check-up with her general practitioner for the management of her type 2 diabetes (T2D). She was diagnosed with T2D six years ago and began treatment with metformin three years ago. Her diabetes is acceptably regulated, with an HbA1c of 51.6 mmol/mol. Although she tolerates metformin well, she also uses medication for hypertension and hypercholesterolaemia, and she expresses a desire to reduce her overall medication use if possible. Mrs. Suiker is aware of the importance of weight reduction already for a long time, and she currently weighs 88 kg (BMI 30.4 kg/m^2). Despite multiple attempts to follow various diets, she has struggled to sustain them in her daily life and eventually discontinued them. Recently, she has heard about intermittent fasting and wonders whether it could be a suitable option for her, leading her to seek advice from her general practitioner.

What recommendations can be offered to her? Is following an FMD programme, a form of periodic fasting, a feasible option for her? Moreover, could it lead to health improvements, including an improved glucose metabolism and a reduction in medication use, and potentially aid in weight loss?

The studies presented in this thesis are carried out by a team of two PhD fellows, Elske van den Burg and Marjolein Schoonakker. Both researchers are specialist trainees in General Practice and each took a leading role in specific manuscripts. However, both were working closely together in all parts of this thesis. The presentation of manuscripts that are the content of this thesis, is structured in three parts, each comprising several chapters (**Figure 1**). In **part I**, an overview of the available literature at the time of writing is presented regarding dietary interventions, specifically regarding treatment effects of intermittent and periodic fasting for individuals with type 2 diabetes (**chapter 2, van den Burg**), an overview of intermittent fasting and its effects on weight, fat mass and visceral fat (**chapter 3, Schoonakker**), and the impact of diets with different types of macronutrient restrictions on the human gut microbiome (**chapter 4, Schoonakker**).

In **part II**, the design of the Fasting In diabetes Treatment (FIT) trial and it's clinical outcomes is discussed. In short, the FIT trial was a 12-month randomised, controlled, assessor-blinded intervention trial on the effects of the intermittent use of an FMD in individuals with T2D, who were treated with lifestyle advice only and had an HbA1c > 48

mmol/mol, or who were treated with the combination of lifestyle advice and metformin. Participants were recruited from general practices in and around Leiden and The Hague. While the FMD programme and the trial follow-up were coordinated from the Leiden University Medical Centre, the treatment for T2D remained under regular surveillance in general practice. In the Netherlands, the vast majority (90%) of individuals with T2D are treated in primary care, typically by a general practitioner who is often supported by a practice nurse dedicated to chronic disease management(51). As participants in the FIT trial remained in regular primary care, the clinical response to monthly 5-day FMD cycles in a 'real world' setting was assessed. In **chapter 5** (**van den Burg**), the study protocol of the FIT trial is presented, which includes an elaborate description of the rationale, it's methods, inclusion criteria and prespecified outcomes. **Chapter 6** (**shared first authorship van den Burg and Schoonakker**) presents the primary outcomes of the FIT trial, specifically examining the effects of following an FMD programme for 12 months on HbA1c levels and glucose-lowering medication use. In this chapter, also several secondary outcomes of the FIT trial are presented, including anthropometrics, blood pressure and laboratory values. Thereafter, the secondary outcomes derived from MRI are discussed. In **chapter 7** (**van den Burg**), the effects of following an FMD on MRI-derived biomarkers for liver fat and liver inflammation/fibrosis are presented, and in **chapter 8** (**Schoonakker**) the effects on abdominal visceral fat, subcutaneous fat and muscle mass are analysed.

In **part III**, results of the FIT trial which are important for implementation of the FMD programme in primary care are presented. **Chapter 9** (**Schoonakker**) is a mixed-methods study, which discusses the feasibility of following the FMD programme by combining quantitative data including reasons for discontinuation, serum ketone levels and treatment satisfaction, and qualitative data from focus group discussions. Also **chapter 10** (**van den Burg**) is a mixed-methods study which explores the effects of following the FMD programme on self-initiated lifestyle changes by combining quantitative data from questionnaires with qualitative data from focus group discussions. Finally, **chapter 11** (**van den Burg**) describes the cost-effectiveness of following an FMD programme, for which a trial-based analysis and a lifetime model-based analysis have been performed.

Chapter 12, the general discussion (**shared authorship van den Burg and Schoonakker**), places the main findings of this thesis in a broader context, examining their implications for clinical practice and future research. Additionally, the case of Mrs. Suiker is revisited to reflect on how these findings may apply to her situation.

Figure 1. Chapters in this thesis.

This thesis is written jointly by Elske van den Burg and Marjolein Schoonakker, as introduced earlier. Both have contributed equally to the design and coordination of the FIT trial. Together, they have a shared responsibility for the coherence of the whole dissertation, as well as for the chapters 1, 6 and 12. Furthermore, they are individually responsible for a designated part of this dissertation: Elske van den Burg is primarily responsible for the chapters 2, 5, 7, 10 and 11, while Marjolein Schoonakker is primarily responsible for the chapters 3, 4, 8 and 9.

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