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Effect of Intensive Weight Loss Programs on Diabetes Remission in Newly Diagnosed Patients with Type 2 Diabetes: A Systematic Review

Axelsen M*, Jansson L and Svanqvist L

Department of Clinical Nutrition, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Sweden

Abstract

Background: A systematic literature review was conducted to assess the strength of the evidence on intensive weight loss programs on diabetes remission, in individuals with newly diagnosed type 2 diabetes, compared with standard diabetes care.

Methods and findings: Relevant studies were identified using PubMed and Scopus. Search date: 2018-02-12. Inclusion criteria: energy-reduced diet, randomized controlled trials (RCT), overweight or obese patients >18 years, diagnosed with type 2 diabetes <6 years. Exclusion criteria: insulin therapy, bariatric surgery and non-standard control treatment. Two reviewers independently reviewed and extracted relevant data; disagreements were settled by consensus. The strength of the evidence was graded by the international system GRADE. Two studies met the eligibility criteria, one with high and one with moderate quality. Both studies compared a weight loss program with standard diabetes care and had 52 weeks follow up period. One study featuring an intensive weight loss program (>15 kg), with 3 month low calorie diet initiating the program, showed improved remission of type 2 diabetes. The strength of evidence was appraised moderate. One study combining intensive metabolic intervention with antidiabetic drugs for an initial period of a) 8 weeks, or b) 16 weeks, with moderate weight loss (5%), failed to show significant treatment effect. However, the strength of evidence for the program was appraised insufficient.

Conclusions: There is insufficient evidence on the effect of modest weight loss, combined with antidiabetic drugs, on remission in patients with newly diagnosed type 2 diabetes. There is however moderately strong evidence supporting that intensive weight loss program, using low calorie diet, leads to remission in patients with newly diagnosed type 2 diabetes. A major limitation with respect to advancement in this field is the lack of a general consensus on how to define remission. Long-term effects (>52 weeks) are also yet to be established.

Keywords: Systematic review; Type 2 diabetes; Life style; Weight loss; Remission; Beta cell function; Clinical trials

***Corresponding author:** Mette Axelsen

✉ mette.axelsen@nutrition.gu.se

PhD, Associate Professor in Clinical Nutrition, Department Clinical Nutrition, Sahlgrenska Academy, University of Gothenburg, Box 459, 405 30 Göteborg, Sweden

Tel: +46(0)31 786 3709**Fax:** +46(0)31 786 31 01

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Introduction

Type 2 diabetes is regarded as a chronic disease and listed as number six among factors leading to reduced number of years lost due to ill health, disability or premature death according to the Global Burden of Disease Study [1]. On the other hand,

evidence is accumulating arguing that the disease is potentially reversible, at least in people with newly diagnosed type 2 diabetes [2]. When a chronic disease returns to a healthy state, it is called remission. Remission of Type 2 diabetes is defined as the return of blood glucose levels to the normal 'healthy' range in the absence of glucose lowering drugs. At present there is no

exact consensus on how to define remission of type 2 diabetes. An expert panel appointed by the American Diabetes Association (ADA) suggested that remission should be divided into partial or complete remission, and that the state should be maintained for at least one year in the absence of oral antidiabetic drugs [3].

The World Health Organization (WHO) highlights, in its global report on diabetes in 2016, that it is possible to achieve remission of type 2 diabetes [4]. In 2011 Lim et al. [5] published a weight loss study using low calorie diet replacement for 8 weeks in obese patients with type 2 diabetes. The low calorie diet restored fasting blood glucose and insulin sensitivity after seven days. As the participants continued to lose weight, the fat deposits decreased and the function of the insulin producing cells in the pancreas improved. On average, participants had maintained a weight loss of 12 kg and the blood glucose was in the normal range when the study was terminated at 20 weeks [5].

The LookAHEAD trial, a randomized controlled trial, compared 'Intensive Lifestyle Intervention' to less intensive 'Diabetes Support and Education' in overweight and obese patients with type 2 diabetes [6]. Post-hoc analyses showed that 9.2% of participants in the Intensive Lifestyle group went into remission that lasted for at least 2 years, compared to 1.7% in the control group [7]. The predictors associated with long-term remission were <2 years of diabetes, a lower baseline HbA1c, major weight loss during one year of intervention and a clear improvement in physical fitness. There are also studies published after LookAHEAD that investigate energy restriction and weight loss on remission of type 2 diabetes [8-11]. A weakness of these studies is that they do not compare with regular diabetes treatment and that they are conducted on small study samples. In two of the studies, the patients were divided into responders and non-responders by post-hoc analyses [10,11]. Again, responders are generally characterized by shorter diabetes duration, and less treatment with oral antidiabetic drugs compared to non-responders.

The purpose of this systematic literature review was to determine if there is scientific evidence from randomized clinical trials, to support the use of intensive weight loss program for remission in individuals with newly diagnosed type 2 diabetes. If it is possible to find an effective way to reverse type 2 diabetes, and implement it in the treatment guidelines, it would be invaluable with respect to the global burden of the disease.

Methods

Literature searches were conducted systematically in PubMed and Scopus by use of building-block strategy (**Table 1**). Search date was 2018-02-12. The MeSH terms used were 'Diabetes Mellitus Type 2' and 'Remission Induction' [12]. Remaining search terms were free text words. Two searches were carried out in each database. Free text words used in PubMed were 'remission' and 'reversal', and at the second search 'random*'. Free text words used in Scopus were 'diabetes', 'NIDDM', 'MODY', 'diabetes mellitus Type 2', 'reversal' and 'random*' as well as 'caloric restriction', and 'weight loss'.

Inclusion criteria

Relevant lifestyle treatment was defined as energy-reduced diet (normal or low calorie diet) with or without physical activity. Regular routine was defined as 'usual' lifestyle advice regarding diet and physical activity (low intensive treatment), with or without treatment with oral antidiabetic drugs. The studies were to report the outcome measure remission, expressed according to criteria for HbA1c. HbA1c refers to glycated hemoglobin A1c, and it identifies the average plasma glucose concentration. Participants were to be >18 years of age, diagnosed with type 2 diabetes, and having been diagnosed <6 years. Follow-up was to be at least one year. Only randomized controlled studies (RCT), human studies and studies written in English or Swedish were included.

Exclusion criteria

Studies with participants that had been subjected to former insulin-treatment, and studies on bariatric surgery. Studies where the intensive treatment program was compared to other diets, for instance Mediterranean diet. Also studies conducted on people with obesity, where only a minority had type 2 diabetes, were to be excluded.

The search identified 275 studies (**Table 1**). The inclusion of articles was done by two independent reviewers, and disagreements resolved by consensus. After evaluating the titles, 26 studies remained, out of which 7 were duplicates. The resulting 19 studies were evaluated based on abstract. Five articles were included for review in full text. Of these 5 articles, one was excluded due to inappropriate control treatment [13], one because it did not meet the criteria for RCT [9] and one because it was a subgroup analysis of an already included article [14]. Two articles finally met the inclusion criteria [15,16].

The two studies were retained for assessment of their quality by use of check lists developed for randomized clinical trials, by the Swedish Agency for Health Technology Assessment and Assessment of Social Services [17]. The check-list refers to risk of bias with respect to selection, detection, and performance; attrition; reporting; publication; and conflict of interest (high, moderate or low risk of bias). An overall judgment of the study is then made (high, moderate or low quality) and relevant information is extracted from studies of high or moderate quality. The reliability of the composite results was expressed as the strength of evidence by use of the international evidence grading system GRADE. The grading reflects the quality of the study and how its reliability is affected by factors such as the material's inconsistency, indirectness, imprecision and publication bias. The evidence is graded as strong (++++), moderate (+++), low (++) or very low/insufficient (+) [17].

Results

Two studies were found relevant [15,16]. Study details are shown in **Table 2**. The studies were similar with respect to study population, control group and outcome measure. One used

Table 1: Documentation of the systematic literature search on the effect of intensive weight loss programs on diabetes remission in newly diagnosed patients with type 2 diabetes.

Search	Database Search date	Search terms	Limitation	Items found	Included on [TI]	Included studies
1	Pubmed 2018-02-12	Diabetes Mellitus, type 2 ¹ , AND remission OR reversal	RCT	117	11	2 [15,16]
2	Scopus 2018-02-12	Diabetes OR NIDDM OR MODY OR diabetes mellitus, type 2 AND remission OR Remission Induction ¹ OR reversal AND caloric restriction AND random*	Article	16	1	0
3	Pubmed 2018-02-12	Diabetes Mellitus, type 2 ¹ AND remission OR reversal AND random*	Published in 2017, or later	32	6 (3) ²	2 (2) ² [15,16]
4	Scopus 2018-02-12	Diabetes OR NIDDM OR MODY OR diabetes mellitus, type 2 AND remission OR Remission Induction ¹ OR reversal AND weight loss	Article	110	8 (4) ²	1 (1) ² [16]
Total number of studies				275	26	2 [15,16]

¹ [MeSH] (Medical Subject Headings); Term from the Medline controlled vocabulary, including terms found below this term in the MeSH hierarchy.

²Duplicates [TI]; Title

Table 2: Summary of included studies on the effect of intensive weight loss programs on diabetes remission in patients with newly diagnosed type 2 diabetes.

	Lean et al., 2017, United Kingdom [15]	McInnes et al., 2017, Canada [16]
Study design	RCT (n=306)	RCT (n=86)
Population characteristics	Age 20-65 years Type 2 diabetes with a duration of <6 years HbA1c < 12% (108 mmol/mol) BMI 27-45 kg/m ²	Age 30-80 years Type 2 diabetes with a duration of <3 years HbA1c ≤ 8,5% (69 mmol/mol) BMI ≥ 23 kg/m ²
Intervention	Low calorie diet replacement (825-853 kcal/dag) for 3 months followed by food reintroduction for 2-8 weeks. Monthly support for long-term weight loss maintenance (individualized advice on diet and physical activity). Step counters were provided with goal to reach ≥15 000 steps/day. Withdrawal of oral antidiabetic and blood pressure lowering drugs day 1.	I 1: Oral antidiabetic drugs ¹ for 8 weeks, plus moderate weight loss ² . I 2: Oral antidiabetic drugs ¹ for 16 weeks, plus moderate weight loss ² . ¹ metformin, acarbose och insulin glargine ² energy restriction (minus 500-750 kcal/day) and advice on ≥ 150 minutes physical activity per week (moderat intensity). Stepcounters were provided (goal ≥ 10 000 steps/day).
Control	Standard diabetes care according to guidelines in United Kingdom and Scotland.	Standard diabetes care according to Canadian guidelines. Stepcounters were provided.
Follow-up Drop out rate	52 weeks I: 22% C: 0%	52 weeks I 1: 0% I 2: 0% C: 7%
Results	Remission I: 46% C: 4%	Remission I 1: 25% I 2: 22% C: 11%
Study quality	High	Moderate
Comments	Potential risk of overestimation of treatment effect due to attrition bias	Potential risk of overestimation of treatment effect due to conflicts of interest bias. Questionable relevance of treatment

RCT, randomized controlled trial; BMI, body mass index; I, Intervention group; C; control group

low calorie diet, with a subsequent lifestyle program for weight loss maintenance [15]. The other combined lifestyle treatment with an initial period of oral antidiabetic drugs, subsequently transitioned to lifestyle treatment only [16].

The first study, called DiRECT (Diabetes Remission Clinical Trial) [15], was a cluster-randomized clinically controlled multicenter study. The purpose of the study was to assess whether an intensive weight loss program, with the stated aim of achieving at least 15

kg weight loss, in primary care could lead to remission of type 2 diabetes. The patients had a relatively high HbA1c at baseline (7.7 %, 60 mmol/mol in the intervention group; and 7.5%, 58 mmol/mol in the control group). Remission was defined as an HbA1c <6.5% (<48 mmol/mol) in the absence of oral antidiabetic drugs. A total of 306 participants were recruited from primary care centers in Scotland and England, all of whom were diagnosed with type 2 diabetes less than 6 years ago. The patients were randomized 1:1 into intensive weight loss program or standard

diabetes care (**Table 2**). In the intensive weight loss group, all oral antidiabetic and blood pressure lowering drugs were withdrawn at day 1, and low calorie diet replacement (825-853 kcal/day) was initiated. After 3 months (extendable to 5 months), regular food was reintroduced step-by-step for 2-8 weeks. Step counters were provided at the start of food reintroduction, aiming at 15000 steps per day. Drugs were reintroduced if needed, using standard protocols for drug introduction under national clinical guidelines. The follow up time was 52 weeks. Monthly support for long-term weight loss maintenance was sustained until the end of the study. Several side effects were reported by the participants in the intervention group. Moreover, the study was appraised to have medium risk for systematic bias due to large differences in drop-out rates between the intervention (22%) and control group (0%). In its favor, an intention-to-treat analysis was performed to compensate for any attrition effects. Study quality was therefore considered high.

The second study [16], a Canadian study by McInnes et al., was a randomized controlled study aimed at investigating feasibility, safety and potential for inducing remission by use of a short-term intensive metabolic intervention combined with modest weight loss. Remission was defined as HbA1c <6.0% (42 mmol/mol), and partial remission as <6.5% (48 mmol/mol), both in the absence of oral antidiabetic drugs. A total of 86 participants with BMI ≥ 23 kg/m² were recruited. The life style program aimed at a moderate 5% weight reduction by use of energy reduced diet (minus 500-750 kcal/day) and increased physical activity (150 minutes/week). Step counters were provided and the goal set at a minimum of 10 000 steps per day. There was no maintenance program in between weeks 28 and 52. A total of 83 participants were included, all of whom were diagnosed with type 2 diabetes

less than 3 years ago. The participants were randomized 1:1:1 into to three different groups 1) an 8 week intensive metabolic intervention plus moderate weight loss; 2) a 16 week intensive metabolic intervention plus moderate weight loss; and 3) a control group receiving standard diabetes care. The follow up time was 52 weeks. The study was appraised as having a potential risk of conflicts of interest bias. It also had questionable relevance of treatment. The study quality was thus considered moderate.

In DiRECT (15) 46% of participants had achieved remission (HbA1c <6.5%) at the 52 weeks follow-up (p<0.0001), while the corresponding figure for McInnes et al. was 25% for the 8 weeks metabolic intervention and 22% for the 16 weeks metabolic intervention. The effects in McInnes et al. were not statistically significant at the 52 weeks follow-up (**Table 2**).

The proportion of participants achieving ≥ 15 kg (approximately 15%) weight loss in DiRECT was 24% in the intervention group. In McInnes et al. 35% of participants in both intervention groups met the goal of a weight loss of ≥ 5% of body weight. In DiRECT the number of patients free from oral antidiabetic drugs at week 52, was 74% in the intervention group compared with 18% in the control group. The corresponding figure in the study by McInnes et al. was 29% in the 8 week intensive metabolic intervention group, 41% in the 16 week group, and 36% in the control group.

The severely heterogeneous interventions made composite results on the effect on remission incongruous. Therefore, evidence grading and conclusions were made for each intervention separately (**Tables 3 and 4**). It was concluded that there is moderate scientific evidence (+++) for intensive weight loss using low calorie diet treatment (**Table 3**), but insufficient scientific evidence (+) for intensive metabolic intervention in combination with modest weight loss (**Table 4**).

Table 3: Summary of findings. Effect of intensive weight loss by use of low calorie diet for 3 months, followed by a weight maintenance program, compared to standard diabetes care, in patients with newly diagnosed type 2 diabetes.

Outcome	Sample size (number of studies)	Remission rate with standard treatment	Absolute difference	Quality of evidence	Comments
Remission	306 (1)	4%	42% OR, 19.7 CI, 7.8-49.8; p<0.0001	+ ++ Moderate	Consistency -1

OR; odds ratio
CI; confidence interval
Consistency = One study

Table 4: Summary of findings. Effect of intensive metabolic intervention combining oral antidiabetic drugs for a) 8 weeks, or b) 16 weeks, plus moderate weight loss, compared to standard diabetes care, in patients with newly diagnosed type 2 diabetes

Outcome	Sample size (no. of studies)	Remission rate with standard treatment	Absolute difference	Quality of evidence	Comments
Remission	86 (1)	11%	a) 14% RR, 2.33; CI, 0.67-8.12; NS b) 11% RR, 2.07; KI 0.58-7.47; NS	+ Insufficient	Imprecision -1 Consistency -1 Overall deficiencies -1

RR; relative risk
NS= No statistically significant difference
Imprecision = The study had too few participants in each group to achieve adequate power
Consistency = One study
Overall deficiencies = potential conflict of interest bias and questionable relevance of treatment

Discussion

This systematic literature search identified two studies comparing the effects of intensive weight loss programs with standard diabetes care with respect to remission of type 2 diabetes [15,16]. One used low calorie diet and the other used energy reduced 'normal' diet and exercise combined with initial anti diabetic drug treatment. The program with sufficient evidence strength, in this literature search, was weight loss with low calorie diet [15].

Literature searches have limitations. In this search, only two databases were used. Articles on the subject may thus have been overlooked if they were published in another database, or in another language. Another possible source of error is the use of the outcome measure 'remission' amongst the search terms. This may introduce a risk that the result will be positively skewed, since negative studies may exist that overlook to mention the word 'remission' in the title or abstract. Furthermore, the two articles had severely heterogeneous interventions, and the strength of the evidence was therefore appraised separately for the two studies instead of combining the two. This decision was of key importance for grading the evidence of intensive weight loss by use of low calorie diet as moderate. Combining the two would have led to severely weakened strength of evidence for that treatment.

Participants in DiRECT received in total 825-853 kcal/ day, during the meal replacement period, a so called low calorie diet. As comparison, an energy intake of <800 kcal/day is classified 'very' low calorie diet. However, the clinical difference between the two diets are often marginal, the importance being the duration and the overall energy deficit in the long term. The use of low calorie diet is well established and found to be safe and efficient in people with type 2 diabetes, both with respect to weight loss and blood glucose control [18]. Amongst its effects is an increased insulin sensitivity and glucose mediated insulin secretion [2]. It is possible that the side effects of the low calorie diet experienced by the participants in DiRECT, was responsible for the high drop-out rate in this group. This could potentially lead to an overestimation of the positive effect on remission by low calorie diet compared to standard diabetes care. On the other hand, this was handled carefully by an intention-to-treat analysis and it is to be expected that the treatment is not equally suitable to all patients.

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A major limitation with respect to advancement in this field is the lack of a general consensus on how to define remission. According to ADA's criteria, HbA1c is to be maintained for a year without pharmacological drugs [3]. They also convey more strict criteria for HbA1c than adopted in the two studies included in this review; partial remission 5.7-6.5%; and complete remission <5.7% [3]. The participants receiving low calorie diet had, on average, fairly poor glycemic control at baseline. The benefit needs to be shown also in patients with better glycemic control at baseline. They also had few participants of a non-white ethnicity. Hence, consensus with respect to remission criteria, and longer follow-up periods, are highly warranted. So are studies allowing subgroup analyses on the effect of diabetes duration, baseline HbA1c and ethnicity, to get more exact estimates on the success rate with respect to remission in different populations.

The following is concluded based on the evidence in this systematic literature search:

- There is moderately strong evidence (+++) that an intensive weight loss program with low calorie diet leads to remission (HbA1c <6.5%) in individuals with newly diagnosed type 2 diabetes, compared to standard diabetes care, at 52 week follow up.
- There is insufficient scientific evidence (+) on the effect of intensive metabolic intervention combining antidiabetic drugs for 8 or 16 week combined with moderate weight loss when it comes to remission (HbA1c <6.5%) in individuals with newly diagnosed type 2 diabetes, compared to standard diabetes care, at 52 week follow up.
- There is insufficient scientific evidence (lack of studies) on the effects on remission of type 2 diabetes, by use of weight loss programs, long term (> 52 weeks).

Conflicts of Interest

The first author (MA) has received unrestricted research grants from Lantmännen, a cooperative owned and governed by Swedish farmers. None of the other authors have any conflict of interest to report. (There are no acknowledgements or Funding to declare).

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