Stehouwer Coen (Orcid ID: 0000-0001-8752-3223)
Kooy Adriaan (Orcid ID: 0000-0002-8853-0019)

Metformin-associated prevention of weight gain in insulin-treated type 2 diabetic patients cannot be explained by decreased energy intake: A Post hoc Analysis of a Randomized Placebo-Controlled 4.3 year Trial.

Short running title: *Metformin, prevention of weight gain and energy intake*

Mattijs Out[1,2,*], Ida Miedema[3,*], Harriët Jager-Wittenaar[3,4], Cees van der Schans[3,5], Wim Krijnen[3], Philippe Lehert[6], Coen Stehouwer[7], Adriaan Kooy[1,2,8]

[1] Bethesda Diabetes Research Center, Hoogeveen, The Netherlands

[2] Bethesda General Hospital, Care Group Treant, Hoogeveen, The Netherlands

[3] Hanze University of Applied Sciences Groningen, Research Group Healthy Ageing, Allied Health Care and Nursing, Groningen, The Netherlands

[4] University of Groningen, University Medical Center Groningen, Department of Oral and Maxillofacial Surgery, Groningen, The Netherlands

[5] University of Groningen, University Medical Center Groningen, Department of Rehabilitation Medicine, Groningen, The Netherlands

[6] Louvain Academy, Department of Statistics, Faculty of Economics, Mons, Belgium

[7] Maastricht University Medical Centre, Department of Internal Medicine and Cardiovascular Research, Maastricht, The Netherlands

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[8] University of Groningen, University Medical Center Groningen, Department of Internal Medicine, Groningen, The Netherlands

[*] Denotes equal first authorship contribution

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Abstract

Metformin prevents weight gain in patients with type 2 diabetes (T2D). However, the mechanisms involved are still unknown. In this post-hoc analysis of the HOME trial, we aimed to determine whether metformin affects energy intake. Patients with T2D were treated with 850 mg metformin or placebo (1-3 times daily) added to insulin for 4.3 years. Dietary intake was assessed at baseline, after 1 year and after 4.3 years, according to the dietary history method. Of the 310 included participants, 179 completed (93 placebo, 86 metformin) all three dietary assessments. We found no significant difference in energy intake after 4.3 years between the groups (metformin vs placebo: -31.0 kcal/day; 95% CI -107.4 to +45.4; F-value 1.3, df=415, p=0.27). Body weight in placebo-users increased significantly more than in metformin-users during 4.3 years (4.9± 4.9 vs 1.1±5.2kg; t-test: p≤0.001).Linear mixed models did not show a significant effect of energy intake as explanation for the difference in weight gain between the groups (F-value 0.1, df=1, p=0.82). In conclusion, the prevention from weight gain by metformin cannot be explained by reduced energy intake.

1 Introduction

A major side-effect of insulin therapy in type 2 diabetes (T2D) is weight gain, which is associated with increasing insulin resistance and cardiovascular risk.[1] Metformin prevents weight gain in T2D patients.[2] However, the mechanisms involved are still unknown. Less energy intake, malabsorption and metabolic effects may contribute. In animal experiments, metformin reduced food intake.[3] Studies of the effects of metformin on energy intake in human are sparse and inconclusive,[4–9] although a majority of the studies found associations between the use of metformin and lower energy intake.[4–7] However, sample sizes of these studies were small and long-term placebo-controlled trials are lacking. Therefore, we investigated whether treatment with metformin vs placebo during 4.3 years affects energy intake in patients in the *Hyperinsulinemia: the Outcome of its Metabolic Effects (HOME) trial* (ClinicalTrials.gov identifier NCT00375388). The HOME trial is the largest known randomized controlled trial (RCT) to evaluate the effects of metformin vs placebo in patients with T2D treated with insulin. The study showed that metformin when added to insulin in patients with T2D not only improved glycemic control and reduced insulin requirements, but also prevented weight gain.[2] In the HOME trial, both short- and long-term outcomes are available. Moreover, no other glucose-lowering drugs were used, allowing comparison of metformin vs placebo in patients receiving insulin, but no other antidiabetic agents. The main objective of the current study was to investigate whether treatment with metformin affects energy intake.

2 Materials and methods

2.1 Study design, randomization, interventions and follow-up

The HOME trial is a 4.3 year RCT, that included 390 Caucasian patients aged 30-80 years with T2D treated with insulin. Patient selection, study design, data collection and power analysis have been described previously.[2] The HOME trial was conducted in the outpatient clinics of three non-academic hospitals (Hoogeveen, Meppel and Coevorden Hospitals, The Netherlands). All participants provided written informed consent before inclusion. The medical ethical committees of the three participating hospitals approved the trial protocol. The study was conducted in accordance with Good Clinical Practice (CPMP/ICH/135/95; 1996) and with the Declaration of Helsinki (revised version, 2000).

The trial design and description of the recruitment plus retention of patients for the current study are included in the supplements (Figure S1). Patients were randomly allocated to either metformin 850 mg or placebo (one to three times daily, depending on tolerance and renal function), in addition to insulin therapy.

Visits and data collection

Patients visited the clinics at the start of the pre-randomization phase (three months before randomization), at baseline (for randomization to metformin or placebo), one month after baseline (to check tolerance of drug titration), and subsequently every three months until the end of the trial. All participants received dietary counseling. Dietary intake was independently assessed by four trained registered dietitians at baseline, after 1 year, and after 4.3 years. For dietary assessment, patients were asked about their intake during the preceding week according to the validated dietary history method. [10]

Mean energy intake per day (kcal) was calculated using food calculation software (Becel Institute Nutrition Software; Vodisys Medical Software, Groningen, The Netherlands). The dietitians were blinded for treatment allocation. Body weight was measured every three months.

2.2 Statistical Analyses

In the current analysis, our main objective was to test for the effect of metformin vs placebo on energy intake. For our main analysis, we used a linear mixed model assessing time effects (baseline, one year, 4.3 years), treatment effects and their interactions, based on intention to treat. In the model, we statistically controlled for the fixed effects of sex, age, duration of diabetes and smoking habits. Missing measurements on dietary intake and body weight were not part of the analysis.

In addition, we performed three secondary analyses: 1) a per protocol analysis including only those patients who completed the whole study according to the research protocol; 2) an analysis to investigate the degree to which possible differences in energy intake between treatment groups were associated with weight gain during the study. For this secondary analysis, treatment dose, time, smoking habits and sex were taken as fixed factors, energy intake, age and duration of diabetic disease as covariates, and patients as random effects; 3) a mediation analysis to study whether reduction of the daily dose of (DDI) is a significant contributing factor to the reduced weight gain. F-tests were used to for the significance of effects. P-values < 0.05 were considered statistically significant; "±" denotes standard deviation. The analysis of mixed models was carried out with R release 3.03.

3 Results:

3.1 General trial results

Dietary assessments were available from two hospitals, providing data of 334 out of 390 patients randomized in the original HOME study. 24 patients were excluded, as their baseline dietary assessment was performed after having started with metformin or placebo treatment, resulting in inclusion of 310 patients. Of the 310 participants, 179 (93 placebo and 86 metformin) completed all three dietary assessments. Patients in the metformin group were slightly older than those receiving placebo, had a slightly longer duration of diabetes, and were less often smokers. All other characteristics were comparable between the treatment groups (Table 1). The main outcomes of this trial have been reported previously.[2] Mean values of duration of diabetes, previous occurrence of cardiovascular disease, age and weight were similar between the three hospitals and between those who did and did not complete the study.

3.2 Main analysis

Mean daily energy intake after 4.3 years decreased from 1649±419 to 1632±453 kcal in the placebo group and from 1613±426 to 1567±419 kcal in the metformin group (mean difference of 71.0 kcal/day in metformin vs placebo; 95% CI -199.4 to +54.5, p=0.28) (figure 1).

Mixed model analyses did not indicate a significant difference in energy intake after 4.3 years: -31.0 kcal/day in the metformin compared to the placebo group (95% CI -107.4 to +45.4; F-value 1.3, df=415, p = 0.27). In addition, a per protocol analysis of the data of patients with the intended maximum dose of

metformin of 850 mg three times daily showed similar results (-36.8 kcal/day, 95% CI -144.7 to +71.1; F-value 1.3, df=238, p = 0.28).

Body weight of the patients in the placebo group increased by 4.9±4.9 kg in 4.3 years, significantly more than in the metformin group (+1.1±5.2kg; t-test: p<0.001). However, linear mixed models taking random patient effects into account did not indicate a significant effect of energy intake on weight gain between treatment and control groups (F-value 0.1, df=1, p = 0.82), after controlling for several factors. A mediation analysis showed that at the end of the study, a patient on the actual mean dose of metformin (2050mg), had 3.2kg±0.5 less weight gain (p=0.0001), as compared to placebo, of which 1.2kg±0.0 (p<0.0001; 37.5%) could be explained by a reduction of insulin intake by the use of metformin. (p=0.0001,details are in the supplements).

4 Discussion

This long-term RCT has previously shown that metformin prevents weight gain in T2D patients with insulin therapy [2]. The present analysis shows that metformin did not reduce energy intake. Therefore, in this study, the prevention of weight gain by metformin cannot be explained by a reduction of energy intake.

Our present findings are not consistent with the majority of previous studies. Previously, metformin was associated with reduced food intake in two very small short term placebo-controlled trials[4,5] a small open label trial[6] and a post-hoc trial with matched controls. [7] On the other hand, two RCTs in T2D patients showed no change in energy intake by metformin, as compared to placebo. [8,9] In our study, we analysed the effect of metformin on energy intake after 1 and 4.3 years. Therefore, we cannot entirely exclude

that metformin reduces energy intake at the very short term. However, the current evidence suggests that other mechanisms must be involved in the prevention of weight gain by metformin during insulin therapy.

Reduction in insulin requirements. Our mediation analysis showed that reduction in insulin requirements by the use of metformin [2] prevents weight gain. Several effects of insulin may cause weight gain.[11] First, in the months after initiation of insulin therapy, weight gain is attributed to the improvement in glycemic control and correction of fluid balance. Second, insulin has anabolic effects and stimulates lipogenesis. Third, genetic factors may contribute to the sensitivity to gain weight due to insulin therapy. Fourth, insulin acts independently of glycaemia and may induce hypoglycemia and lead to enhanced hunger, inducing reactive eating behavior and inhibiting an active lifestyle.[11]

Malabsorption by metformin. Metformin may cause malabsorption of nutrients possibly through reducing ileal bile salt reabsorption.[12] To what extent this may affect weight development remains to be established.

Effects of metformin through the incretin system. Metformin may affect the incretin system at different levels by acting as an incretin mimetic, as an incretin enhancer, and as an incretin sensitizer.[13] Such a composite effect increases the bioavailability and efficacy of glucagon-like peptide-1 (GLP-1), the most relevant incretin. GLP-1 is known to slow gastric emptying, to improve glycemic control, to prevent hypoglycemia (and reactive eating behavior), and to prevent weight gain.

Potential other effects of metformin affecting regulation of body weight. An important effect of metformin is the activation of AMP-activated protein kinase (AMPK), the cell's principle energy sensor.[14] AMPK affects cell energy metabolism and might influence body weight regulation. In obese mice,

metformin improves the balance of white adipose tissue and brown adipose tissue, which also might affect body weight control.[15] Next, metformin alters the microbiome in mice and humans, which may cause an increase of intestinal gluconeogenesis.[12] In rodents, increased intestinal gluconeogenesis decreases body weight, despite comparable food intake.[16] Such an effect may contribute to the prevention of weight gain in metformin use. Finally, metformin might affect energy expenditure or physical activity. However, several studies found no influence of metformin on energy expenditure or physical activity.[4]

Strengths and limitations of the study

Strengths of our study include the randomized, placebo-controlled, double-blind design and its relatively long period of follow-up, as well as the relatively large sample size. A limitation is the assessment of dietary intake by the dietary history method, which usually underestimates intake.[10] Intake may have been further underestimated, as we did not assess snacking in case of hypoglycemia. However, the frequency of hypoglycemic events was similar in both groups.[2] Thus, the occurrence of hypoglycemia and related snacking probably will not have influenced the results. In addition, we did not register physical activity during the present trial. Finally, it is difficult to unravel 'cause-and-effect relationships' between insulin requirement and weight development, even in an RCT like the HOME trial since they might be bi-directional.

In conclusion, in this long-term RCT in patients with T2D treated with insulin, metformin treatment did not affect energy intake as compared to placebo. Therefore, reduced energy intake cannot serve as an explanatory factor for the earlier found prevention of weight gain by metformin in insulin therapy on the long term. However, approximately one third of difference in weight gain between metformin and

placebo users can be explained by the reduction of insulin requirements by metformin. Further research is needed to determine the degree of involvement of potential other mechanisms discussed.

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Conflict of interest

All authors declare that there is no duality of interest associated with their contribution to this paper.

Author contributions

AK and CS designed the study. MO and IM did literature searches. MO, IM, WK and PL researched the data; MO, IM and WK performed the statistical analyses; MO, IM and AK wrote the article. HJW, CS, WK, PL and CS contributed to the discussion and reviewed and edited the article. MO, IM, WK and AK are guarantors. All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Legends

Figure 1

Mean energy intake at baseline, after 1 year and 4.3 years for the placebo and metformin group

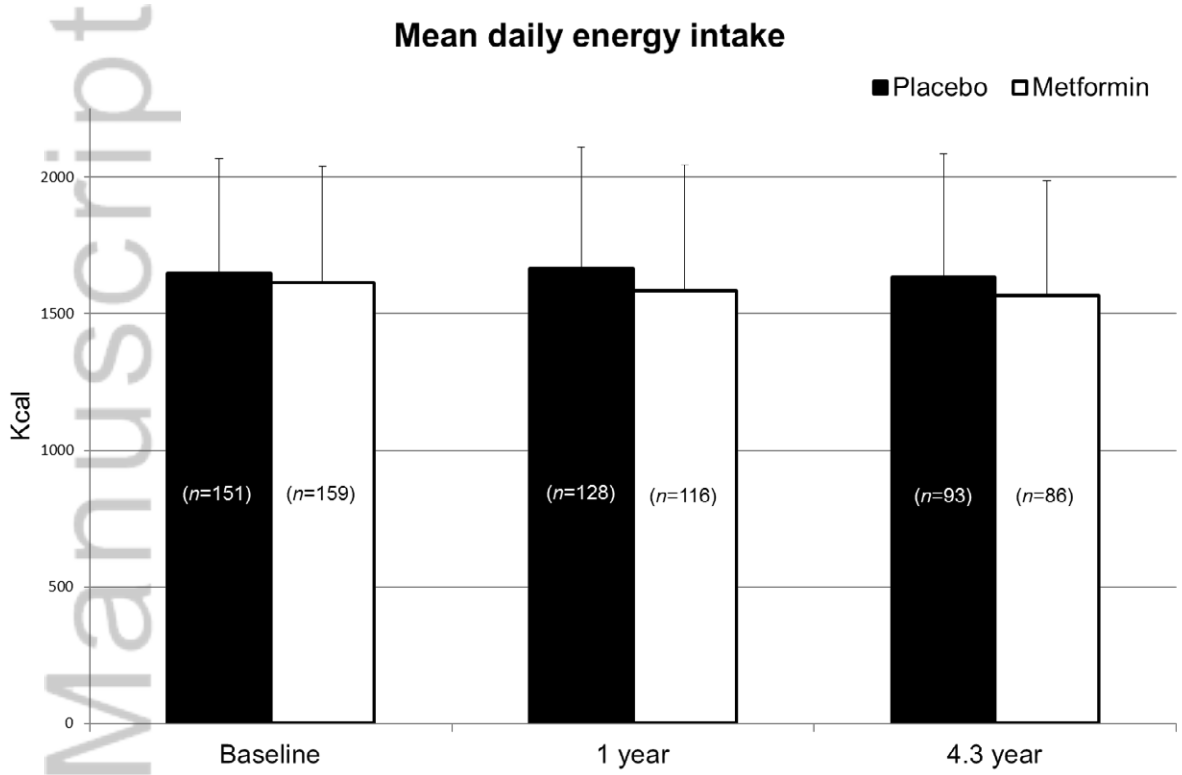
Table 1

Baseline characteristics

**P < 0.05 compared with placebo group*

Figures

Figure 1



Tables

Table 1

	Placebo (n=151)	Metformin (n=159)
Demographic Characteristics, mean±SD		
Men/ women, No.	72/79	72/87
Age (years)	59±11	63±9*
Duration of diabetes (years)	12±8	14±9*
Insulin treatment (years)	6±6	7±8
Current smoking, No. (%)	39 (26)	33 (21)*
Use of alcohol (U/day)	0.7±1.2	0.7±1.2
Metabolic variables, mean±SD		
Weight (kg)	87±16	86±16
Body mass index (kg/m^2)	30±5	30±5
Plasma HbA1c (%)	7.9±1.2	7.9±1.2
Daily dose of insulin (IU/day)	64±25	62±29
Energy intake (kcal)	1649±419	1613±426

References

1. DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care.* 1991;14(3):173-94.

2. Kooy A, de Jager J, Lehert P, et al. Long-term effects of metformin on metabolism and microvascular and macrovascular disease in patients with type 2 diabetes mellitus. *Arch Intern Med.* 2009;169(6):616-25.

3. Lv WS, Wen JP, Li L, et al. The effect of metformin on food intake and its potential role in hypothalamic regulation in obese diabetic rats. *Brain Res.* 2012;1444:11-9.

4. Lee A, Morley JE. Metformin decreases food consumption and induces weight loss in subjects with obesity with type II non-insulin-dependent diabetes. *Obes Res.* 1998;6(1):47-53.

5. Paolisso G, Amato L, Eccellente R, et al. Effect of metformin on food intake in obese subjects. *Eur J Clin Invest.* 1998;28(6):441-6.

6. Makimattila S, Nikkila K, Yki-Jarvinen H. Causes of weight gain during insulin therapy with and without metformin in patients with Type II diabetes mellitus. *Diabetologia.* 1999;42(4):406-12.

7. Yki-Jarvinen H, Nikkila K, Makimattila S. Metformin prevents weight gain by reducing dietary intake during insulin therapy in patients with type 2 diabetes mellitus. *Drugs.* 1999;58 Suppl 1:53,4; discussion 75-82.

8. Aviles-Santa L, Sinding J, Raskin P. Effects of metformin in patients with poorly controlled, insulin-treated type 2 diabetes mellitus. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med.* 1999;131(3):182-8.

9. Jacob AN, Salinas K, Adams-Huet B, Raskin P. Weight gain in type 2 diabetes mellitus. *Diabetes Obes Metab.* 2007;9(3):386-93.

10. Jain M, Howe GR, Johnson KC, Miller AB. Evaluation of a diet history questionnaire for epidemiologic studies. *Am J Epidemiol.* 1980;111(2):212-9.

11. McFarlane SI. Insulin therapy and type 2 diabetes: management of weight gain. *J Clin Hypertens (Greenwich).* 2009;11(10):601-7.

12. McCreight LJ, Bailey CJ, Pearson ER. Metformin and the gastrointestinal tract. *Diabetologia.* 2016;59(3):426-35.

13. Cho YM, Kieffer TJ. New aspects of an old drug: metformin as a glucagon-like peptide 1 (GLP-1) enhancer and sensitiser. *Diabetologia.* 2011;54(2):219-22.

14. Pryor R, Cabreiro F. Repurposing metformin: an old drug with new tricks in its binding pockets. *Biochem J.* 2015;471(3):307-22.

15. Kim EK, Lee SH, Jhun JY, et al. Metformin Prevents Fatty Liver and Improves Balance of White/Brown Adipose in an Obesity Mouse Model by Inducing FGF21. *Mediators Inflamm.* 2016;2016:5813030.

16. De Vadder F, Kovatcheva-Datchary P, Goncalves D, et al. Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits. *Cell.* 2014;156(1-2):84-96.

Author/s:
Out, M; Miedema, I; Jager-Wittenaar, H; van der Schans, C; Krijnen, W; Lehert, P; Stehouwer, C; Kooy, A

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