An efficacy, safety and pharmacokinetic study on the short-term and long-term use of METFORMIN in obese children and adolescents

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een santeon ziekenhuis

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Disclosure : no conflicts of interest

Outline

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- Objectives
- Methods
- Results
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- Implementation
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- Acknowledgement
- *Retrospective study*

Rational

8-20% of all Metformin prescriptions is for off label use for obesity

(metformin is registered for type 2 diabetes ≥ 10 years)

In obese children/adolescents with insulin resistance Metformin may reduce

- Body mass index
- Insulin resistance
- % of body-fat

In obese children/adolescents with insulin resistance Metformin may delay

- Progression to T2DM
- Micro- and macro-vascular complications of T2DM

Objectives

Primary

- Determine the effect of adding Metformin treatment to lifestyle-intervention in reducing BMI in obese children/adolescents with insulin resistance.

Secondary

- Determine the safety and tolerability of Metformin in obese children/adolescents with insulin resistance.

Tertiary

- Study the population pharmacokinetics of Metformin in obese children/adolescents

Methods

Design

- Part I: Double-blind randomized placebo-controlled study of 18 months
- Part II: Open, follow up study of 18 months, in which Metformin will be offered to all obese patients with insulin resistance.

Population

- Children/adolescents of Caucasian descent with obesity and insulin resistance

Intervention

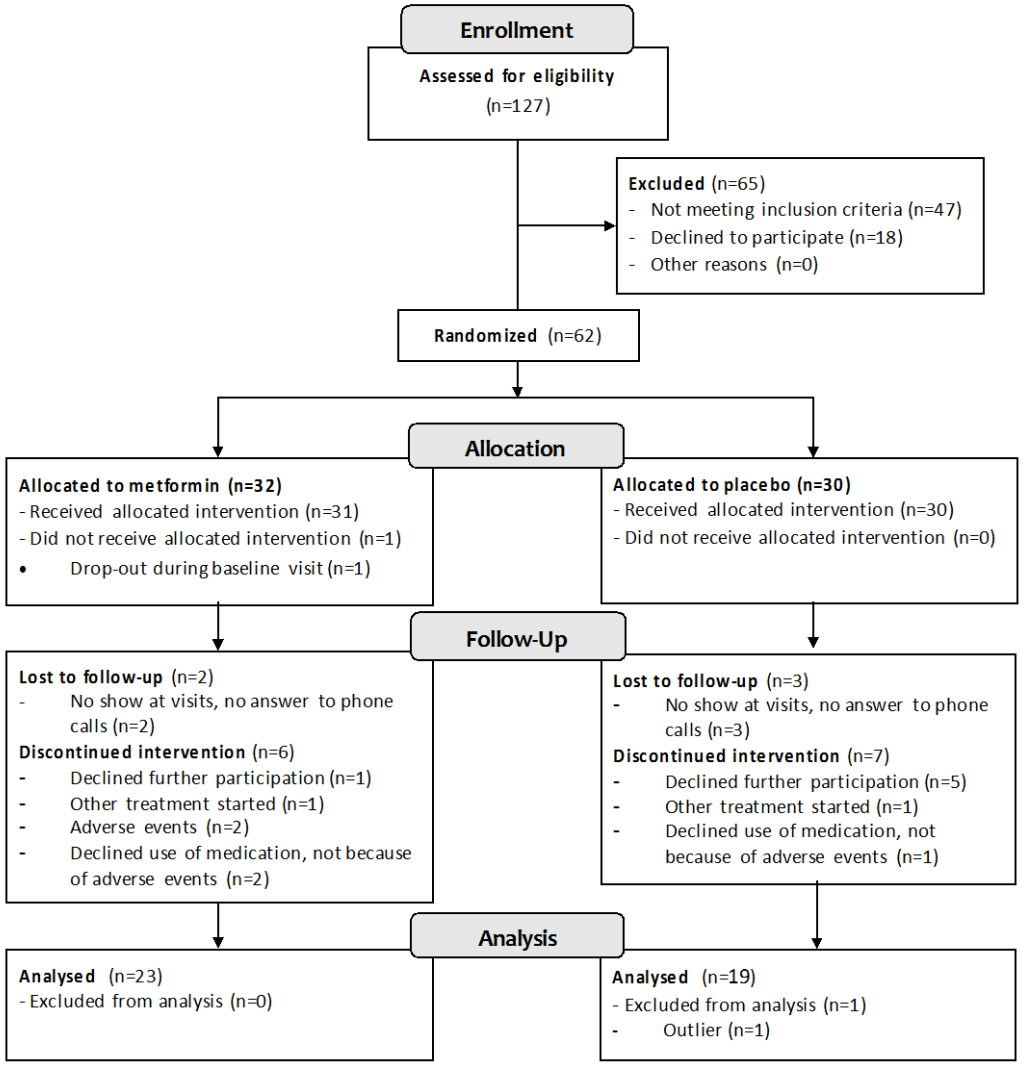
- Assigned to either placebo or Metformin (administered in increasing dosages of 500 mg od - 1000 mg bid)
- Lifestyle-intervention program (twice weekly supervised physical training & individual dietary advise during hospital visits)

In- and exclusion criteria

- Age ≥ 10 and ≤ 16 years at study entry
- Caucasian descent
- Obesity, defined as BMI-SDS > 2.3
- Insulin resistance, defined as HOMA-IR ≥ 3.4
- Informed consent from subjects and parents/caregivers

- T2DM
- Endocrine disorders with steroid therapy
- Suspicion of polycystic ovarium syndrome
- Height < -1.3 SD of target height;
- Syndrome disorders +/- mental retardation
- Use of anti-hyperglycaemic drugs;
- Pregnancy
- (history of) alcohol abuse;
- Impaired renal function,
  defined as GFR < 80 ml/min
- Impaired hepatic function,
  defined as ALAT >150% of normal value for age
- Use of ritonavir;
- Use of ACE inhibitors
- Insufficient knowledge of the Dutch language

Results


Enrollment
Assessed for eligibility
(n=127)
Excluded (n=65)
- Not meeting inclusion criteria (n=47)
- Declined to participate (n=18)
- Other reasons (n=0)
Randomized (n=62)
Allocation
Allocated to metformin (n=32)
- Received allocated intervention (n=31)
- Did not receive allocated intervention (n=1)
• Drop-out during baseline visit (n=1)
Allocated to placebo (n=30)
- Received allocated intervention (n=30)
- Did not receive allocated intervention (n=0)
Follow-Up
Lost to follow-up (n=2)
- No show at visits, no answer to phone calls (n=2)
Discontinued intervention (n=6)
- Declined further participation (n=1)
- Other treatment started (n=1)
- Adverse events (n=2)
- Declined use of medication, not because of adverse events (n=2)
Lost to follow-up (n=3)
- No show at visits, no answer to phone calls (n=3)
Discontinued intervention (n=7)
- Declined further participation (n=5)
- Other treatment started (n=1)
- Declined use of medication, not because of adverse events (n=1)
Analysis
Analysed (n=23)
- Excluded from analysis (n=0)
Analysed (n=19)
- Excluded from analysis (n=1)
- Outlier (n=1)

Patient characteristics (I)

	Metformin (n= 23)	Placebo (n=19)
Age (yr)	13.6 (12.6-15.3)	12.0 (11.3-14.0)
Gender, n (%) -Boys -Girls	 6 (26.1) 17 (73.9)	 8 (42.1) 11 (57.9)
Height (cm)	162.9 (159.0-168.0)	162.0 (160.0-166.0)
Weight (kg)	82.2 (75.4-92.7)	86.1 (74.0-103.0)
BMI (kg/m^2)	29.8 (28.1-34.5)	30.5 (28.7-38.6)
BMI-SDS	3.10 (2.72-3.52)	3.38 (3.10-4.20)
Tanner stage, n (%) -Prepubertal (Tanner stage 1) -Pubertal (Tanner stage 2-4) -Postpubertal (Tanner stage 5)	 3 (13.0) 17 (74.0) 3 (13.0)	 3 (16.7) 12 (66.6) 3 (16.7)

Patient characteristics (II)

	Metformin (n= 23)	Placebo (n=19)
Glucose 0’ (mmol/l)	4.8 (4.7-5.0)	4.8 (4.5-5.0)
Glucose 120’ (mmol/l)	6.0 (5.6-6.6)	5.9 (4.8-7.2)
Insulin 0’ (mU/l)	18.0 (11.0-27.0)	23.0 (12.0-26.0)
HOMA-IR	4.00 (2.30-6.36)	4.85 (2.40-5.78)
HbA1c (mmol/mol)	33 (31-34)	32 (31-34)
Body fat (%)	38.6 (36.5-43.2)	41.2 (36.9-44.1)
Fat mass (kg)	31.8 (25.0-39.4)	33.6 (27.6-48.5)
Fat free mass (kg)	48.9 (45.4-53.0)	50.4 (42.6-54.5)

Study endpoints

For efficacy

- Δ BMI
- Δ insulin resistance
- Δ HbA1c
- Δ % of body fat

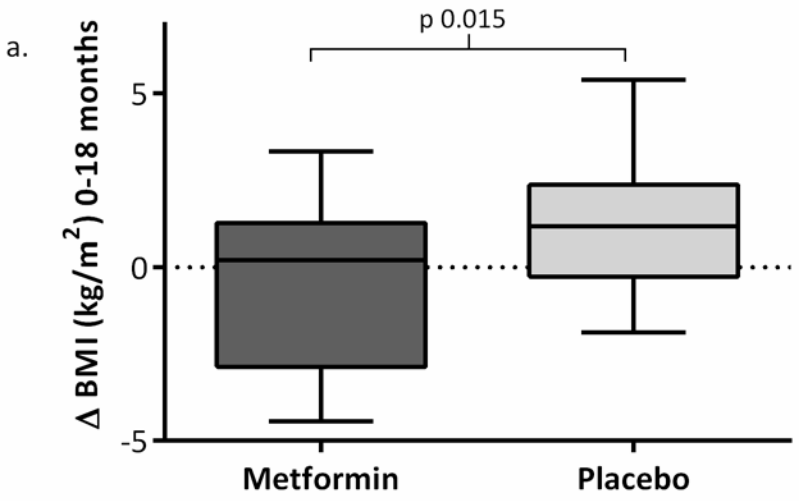
For safety and tolerability

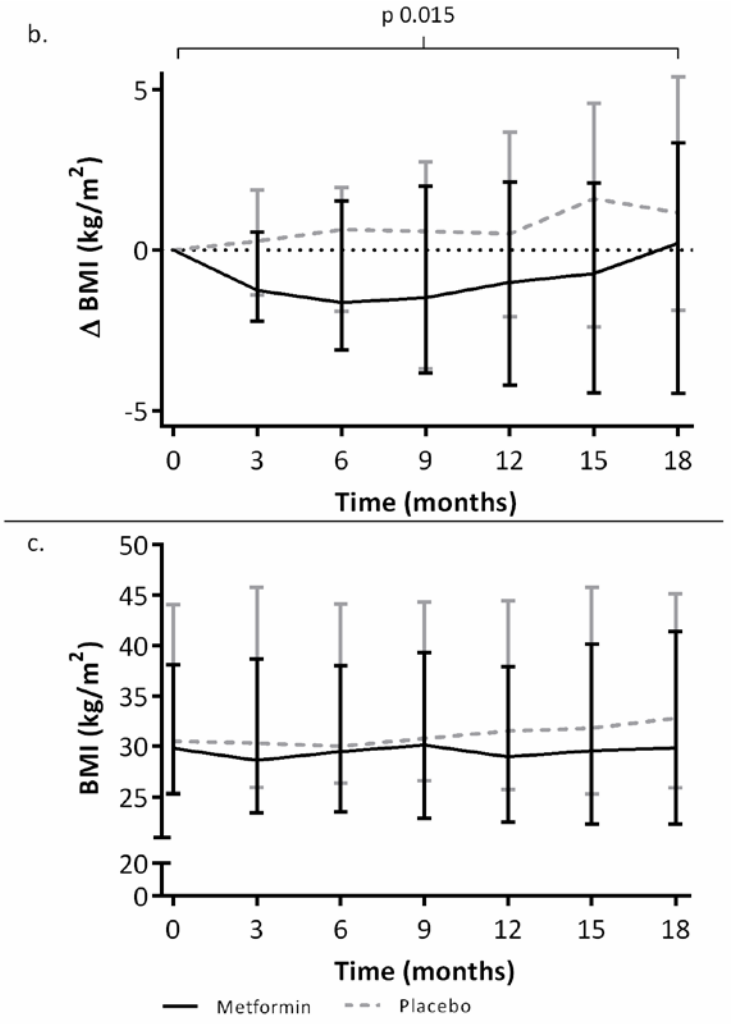
- Hepatic and renal function tests
- Number of adverse effects (in relation to the achieved dose level)

For pharmacokinetics

- PK of Metformin

Δ BMI





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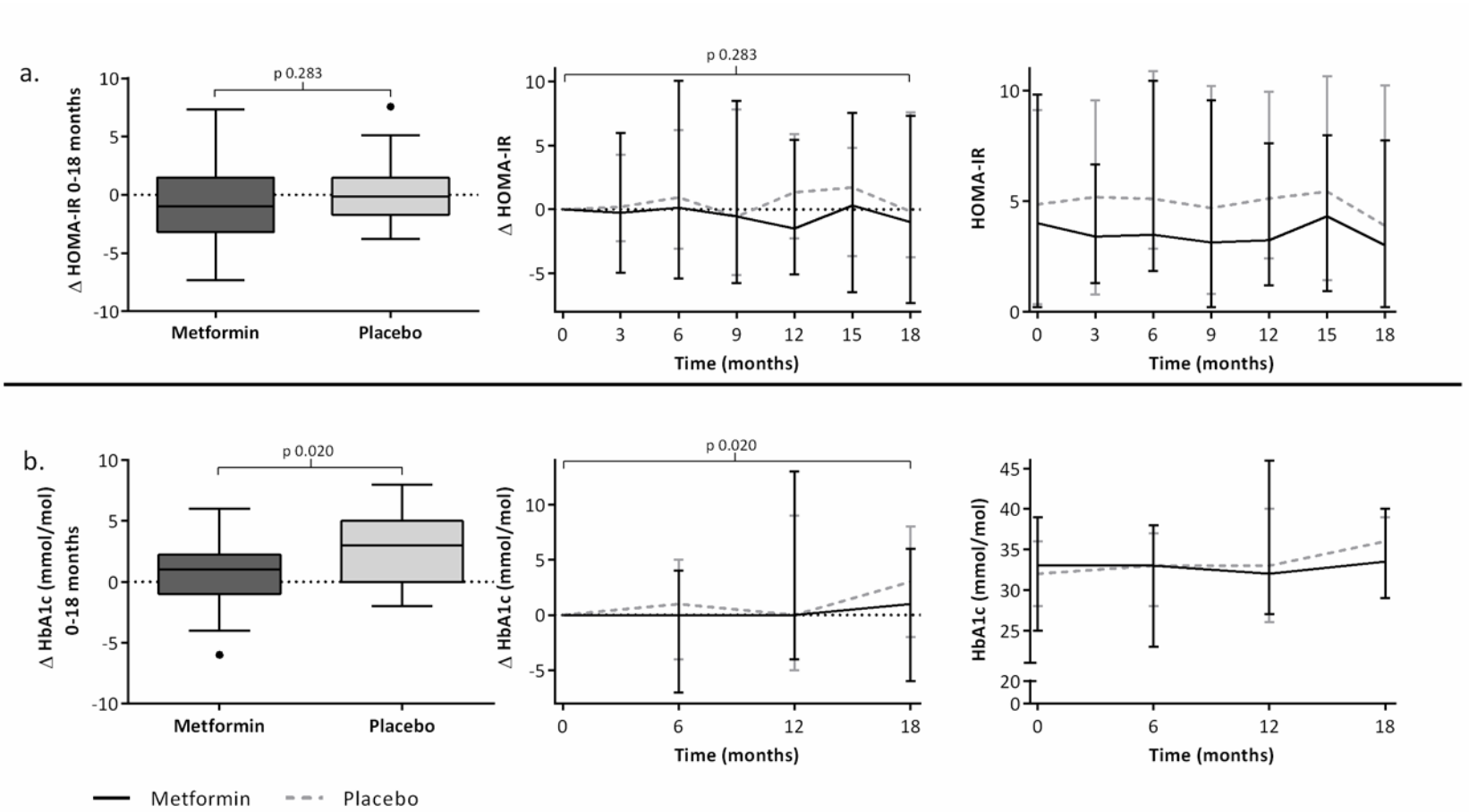
Δ HOMA-IR & Δ HbA1c



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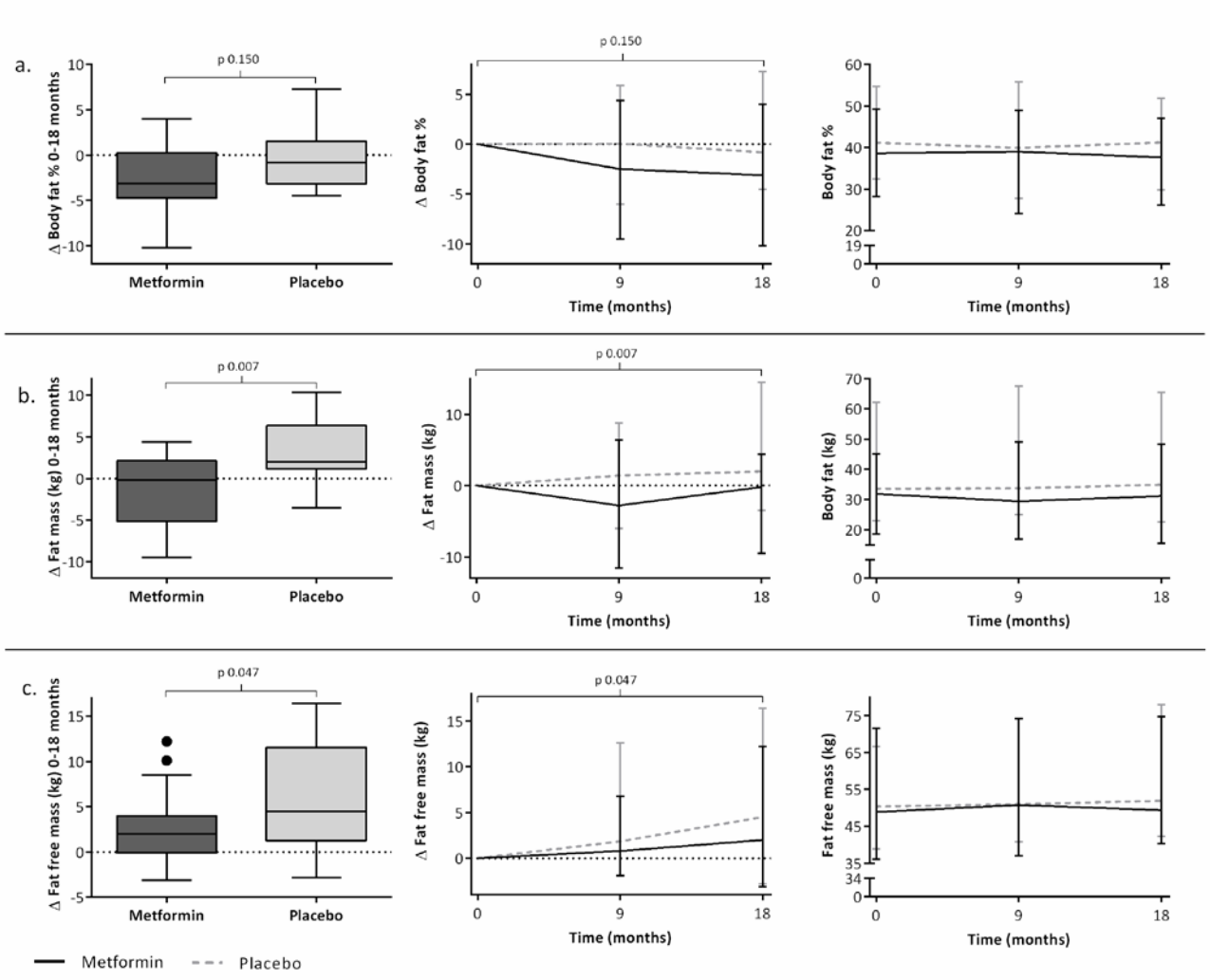
Δ Body composition



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Safety & tolerability

	Metformin (n= 23)	Placebo (n=19)	p-value
Safety, n(%)			
ALT > 69 U/l (girls) or >78 U/l (boys)	0	0	NA
GFR < 60 ml/min	0	0	NA
Vitamin B12 <140 pmol/l	3 (13.0)	0	NA
Tolerability			
Adverse events, n(%)			
Nausea	17 (73.9)	8 (42.1)	**0.04**
Diarrhoea	14 (60.9)	9 (47.4)	0.38

- Two patients (Metformin) discontinued treatment because of adverse events (severe nausea despite dosage reductions/abdominal pain and discomfort)
- Four patients (Metformin) did not tolerate the max dose because of adverse events (1000mg [n=1],1500mg [n=3])

PK of Metformin

Oral clearance of Metformin (CL/F)

- Increases significantly with total body weight in obese adolescents
- Increase in oral clearance is explained by both weight for age and length, and weight excess

Compared to the literature the oral clearance value

- In obese adolescents is increased compared to non-obese adolescents
- In obese adolescents is comparable to non-obese adults
- In obese adolescents was similar or lower to obese adults

Limitations

- Small sample size
- High dropout rate
- Measurement of fasted plasma insulin

Conclusion

- Eighteen months treatment with Metformin in obese adolescents with insulin resistance results in stabilization of BMI and improved body composition compared to placebo. After nine months of Metformin treatment the BMI returned to baseline!

- No effect was observed for HOMA-IR after eighteen months Metformin treatment, probably due to large coefficient of variation in fasted plasma insulin measurement.

- Long-term treatment with Metformin in obese adolescents with insulin resistance is safe, but vitamin B12 deficiency was observed.

- Long-term treatment with Metformin in obese adolescents with insulin resistance was reasonable tolerated, although nausea was significantly more observed compared to placebo.

- High drop-out illustrates that adolescents are difficult to motivate for long-term treatment.

Take home messages

Long-term treatment with Metformin

- May be useful as additional therapy in combination with lifestyle intervention in adolescents with obesity and insulin resistance
- Is safe, but may lead to vitamin B12 deficiency
- Is reasonable tolerated, although nausea is observed

Publications

METFORMIN: an efficacy, safety and pharmacokinetic study on the short-term and long-term use in obese children and adolescents - study protocol of a randomized controlled study. van der Aa MP, Elst MA, van Mil EG, Knibbe CA, van der Vorst MM. Trials. 2014 Jun 5;15:207.

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Long-term treatment with metformin in obese, insulin-resistant adolescents: results of a randomized double-blinded placebo-controlled trial. van der Aa MP, Elst MA, van de Garde EM, van Mil EG, Knibbe CA, van der Vorst MM. Nutr Diabetes. 2016 Aug 29;6(8):e228.

Definition of insulin resistance affects prevalence rate in pediatric patients: a systematic review and call for consensus. van der Aa MP, Knibbe CA, Boer A, van der Vorst MM.J Pediatr Endocrinol Metab. 2017 Feb 1;30(2):123-131.

Increased metformin clearance in overweight and obese adolescents . A. van Rongen, M.P. van der Aa, M.Matic, R.H.N. van Schaik, V.H.M Deneer, M.M van der Vorst, C.A.J. Knibbe1 2 (submitted)

Implementation

- Protocol for Metformin treatment in adolescents (≥ 10 yr) with obesity (BMI-SDS > 2.3) and insulin resistance (HOMA-IR ≥ 3.4) in St. Antonius hospital.

- After publications and PhD defense (Dr. MP Van der Aa, December 2016) frequently contacted by colleagues concerning Metformin treatment in obese adolescents for indication, dosages and safety measurements.

Future research

Ongoing studies (results expected 2017/2018)

- Part II of the current trial. Open follow up study, in which the participant may decide to continue on metformin treatment, if he/she is still obese and insulin resistant.

- Part II of the retrospective study in which we evaluate the effect off label use of metformin for 36 months in daily clinical practice.

Suggestion for future research:

- An efficacy, safety and pharmacokinetic study in obese children <u>≤10 yrs</u> with insulin resistance on use of METFORMIN. (duration 12-18 months?)

Acknowledgement

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- Dr. MP Van der Aa, MAJ Elst and YF Lentferink, co-investigators
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  for supervising the data analysis

Questions?

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Off label Metformin treatment in daily practice

Rational

- Effect of long-term Metformin treatment on BMI in RCT overestimated?

Objective

- Comparison of Δ BMI in Metformin treated patients in RCT versus patients treated with off lable Metformin in a pediatric out-patient clinic

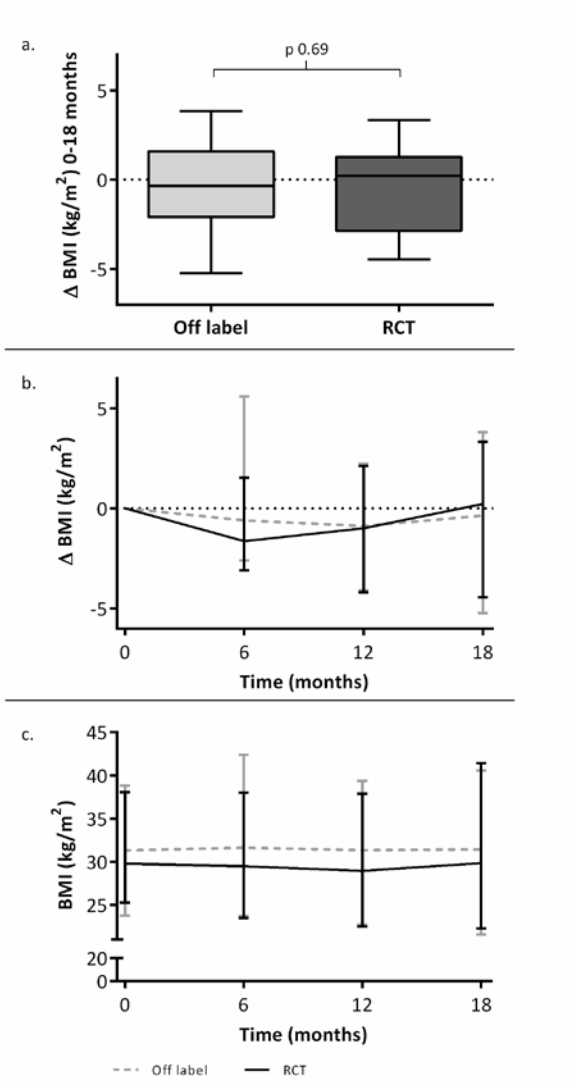
Methods

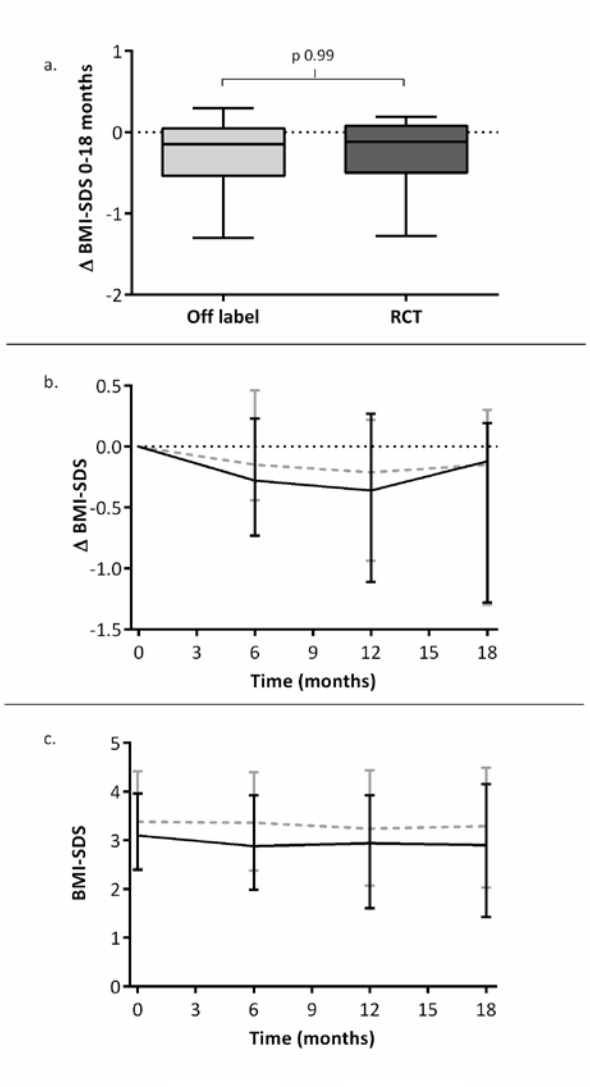
- Retrospective study in obese adolescents of a pediatric out-patient clinic
- Inclusion criteria: age ≥ 10 & ≤ 16 yrs, obesity (BMI-SDS > 2.3), Metformin treatment, follow up ≥ 18 months
- Data collection:
  - baseline : age, gender, height, weight, glucose, insulin and HbA1c
  - follow up: height, weight, glucose, insulin and HbA1c

Metformin: RCT versus off lable: baseline data

	Off label group (n=19)	RCT group (n=23)	P-value chi^2	P-value Mann-Whitney
Gender				
- Boys	-11 (57.9)	-6 (26.1)	**0.037**	
- Girls	-8 (42.1)	-17 (73.9)		
Age (years)	14.3 (11.7-15.7)	13.6 (12.6-15.3)		0.99
Etnicity				
-Caucasian	-11 (57.9)	-23 (100)	NA	
-Other	-8 (42.1)	-0 (0)		
Height (cm)	168.3 (161.5-177.2)	162.9 (159.9-168.0)		0.08
Weight (kg)	92.5 (75.2-104.0)	82.2 (75.4-92.7)		0.16
BMI (kg/m^2)	31.3 (28.8-33.8)	29.8 (28.1-34.5)		0.66
BMI-SDS	3.23 (3.05-3.64)	3.10 (2.72-3.52)		0.37
BMI-SDS ≥ 3.0	15 (78.9)	13 (56.5)	0.13	
Tanner stage:				
-Prepubertal (TS1)	-3 (15.8)	-3 (13.0)	0.42	
-Pubertal (TS2-4)	-4 (26.4)	-17 (74.0)		
-Postpubertal (TS5)	-1 (5.6)	-3 (13.0)		
-Unknown	-10 (52.6)	-0 (0)		
FPG (mmol/l)	5.0 (4.8-5.6)	4.8 (4.7-5.0)		**0.015**
FPG ≥ 5.6 mmol/l	5 (26.3)	0 (0)	NA	
FPI (µU/ml)	31.0 (22.0-41.9)	18.0 (11.0-27.0)		**0.005**
FPI > 15 µU/ml	17 (89.5)	14 (60.9)	**0.036**	
HOMA-IR	7.74 (4.48-8.96)	4.00 (2.30-6.36)		**0.003**
HOMA-IR ≥ 3.4	17 (89.5)	10 (43.5)	**0.019**	
HbA1c (mmol/mol)	36 (32-39)[#]	33 (31-34)		0.052

Δ BMI: RCT versus off label Metformin





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Conclusion

- Treatment with Metformin in obese adolescents in daily practice results in a BMI change comparable to the change observed in the RCT.