DOWNLOAD PDF METFORMIN AS AN ADJUNCT TO INSULIN THERAPY IN ADOLESCENTS WITH TYPE 1 DIABETES A PHILOT STUDY

Chapter 1 : No Long Term Benefit to Adjuvant Metformin in Type 1 Diabetes

We hypothesized that metformin could be used adjunctively with insulin to improve glycemic control in type 1 diabetes mellitus (DM). We conducted a 6-month open-label pilot study in 10 adolescents and young adults with type 1 DM, +/- years, 4 males, 6 females, and body mass index +/- kg/m2.

Received Nov 8; Accepted Aug 8. Copyright Lund et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are properly credited. This article has been cited by other articles in PMC. Abstract Background Despite intensive insulin treatment, many patients with type-1 diabetes T1DM have longstanding inadequate glycaemic control. Metformin is an oral hypoglycaemic agent that improves insulin action in patients with type-2 diabetes. We investigated the effect of a one-year treatment with metformin versus placebo in patients with T1DM and persistent poor glycaemic control. Thereafter, patients were randomized baseline to treatment with either metformin 1 g twice daily or placebo for 12 months double-masked. Patients continued ongoing insulin therapy and their usual outpatient clinical care. The primary outcome measure was change in HbA1c after one year of treatment. At enrolment, mean standard deviation HbA1c was 9. Minor and overall major hypoglycaemia was not significantly different between treatments. Treatments were well tolerated. Nevertheless, adjunct metformin treatment was associated with sustained reductions of insulin dose and body weight. Further investigations into the potential cardiovascular-protective effects of metformin therapy in patients with T1DM are warranted. As recently reviewed by deVries et al. The Diabetes Control and Complication Trial demonstrated the beneficial effect of improving glycaemic control on the long-term risk of late-diabetic complications [3] , [4]. Decreased muscle glucose uptake in response to insulin i. Metformin is an oral anti-hyperglycaemic agent that has been extensively used in the treatment of patients with type-2 diabetes. Enhanced insulin action and decreased hepatic glucose output have been suggested as the primary modes of action of metformin [6]. For the same degree of blood glucose reduction, metformin treatment is associated with a lower risk of hypoglycaemia than with insulin secretagogues and insulin treatment in patients with type-2 diabetes [7] , [8]. Metformin also has a beneficial effect on the risk of macrovascular complications in obese patients with type-2 diabetes [8]. Previous studies have demonstrated an insulin-sparing effect of metformin treatment as an adjunct therapy to ongoing insulin treatment in patients with type-1 diabetes. In contrast, the results concerning glycaemic control and other metabolism-related variables e. Marked differences between studies in baseline levels of glycaemic control for example, HbA1c ranged from 7. Hence, the effect of metformin treatment on glycaemic control and other cardiovascular risk factors in patients with type-1 diabetes remains a matter of controversy. We hypothesized that metformin treatment might reduce glycaemia as well as other non-glycaemic cardiovascular risk markers in patients with type-1 diabetes and persistent poor glycaemic control. Here, we report the results of a one-year trial of metformin versus placebo as an adjunct therapy in patients with type-1 diabetes and persistent poor glycaemic control. Study design The study was an investigator-initiated, single-centre, randomized, double-masked, parallel trial of metformin versus placebo treatments. Participants Inclusion, exclusion and withdrawal criteria are presented in Table 1. Table 1 Inclusion, exclusion and withdrawal criteria Inclusion criteria: Exclusion and withdrawal criteria: According to local guidelines, suggested cut-off levels for C-peptide indicative of type-1 diabetes were: The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Copenhagen County, Denmark. Interventions Patients continued ongoing insulin therapy as well as their usual outpatient clinical care throughout the study period i. Adjustments in life-style, home-monitored blood glucose measurements, insulin dose and concomitant medications were made at the discretion of the patients and the clinicians in the outpatient clinic. After the screening visit, patients entered a one-month run-in period, during which they began a single-masked treatment with one placebo tablet per day. The dose of metformin or

placebo was gradually increased by forced titration once weekly the starting dose of metformin was mg once daily reaching the maximum dose 1 g twice daily, i. Doses were reduced if adverse events occurred that could possibly have been associated with the study medication. Once free of adverse events, the drug dose was increased again and, if adverse events recurred, the lower dose was resumed. Otherwise, through four regular scheduled telephone consultations at one and three months post-randomization and hereafter approximately every third to fourth month the study nurse ensured adequate study medication dose titration. Active and placebo tablets were identical in appearance, taste and smell. The near-maximum dose of metformin was chosen since previous dose-response studies showed only slight additional lowering of blood glucose and a tendency for more side effects with higher doses of metformin [25]. Patients were advised to take tablets just before or during their morning and evening meals. Objectives The objective of the trial was to assess the efficacy and safety of adjunct metformin treatment during one year in adult patients with type-1 diabetes and persistent poor glycaemic control. Outcomes The level of HbA1c after 12 months intervention. Secondary outcomes Pre-specified secondary outcomes were additional variables related to glycaemic control fasting plasma glucose, insulin dose, body-weight, waist- and hip-circumferences and adverse events including hypoglycaemia. Safety variables included blood concentrations of haemoglobin, creatinine, sodium, potassium, bicarbonate, cobalamin, folate, alkaline phosphatase, aspartate aminotransferase as well as platelets and white blood cell counts. Compliance with the study medication. Endpoints were assessed at enrolment screening visit: Patients were asked to report immediately important medical occurrences. Otherwise, through the four telephone consultations see above , the study nurse collected intermediate information about insulin doses and adverse events, including hypoglycaemia. Information about type and dose of concomitant medications was collected at each of the three study visits screening, baseline and end of treatment. Ancillary outcomes The change in HbA1c during the run-in period. Intermediate HbA1c measurements collected from visits in the outpatient clinic between baseline and end of treatment visits. Insulin doses at the three months telephone consultations. The number of outpatient clinic visits during follow-up. Unconsciousness during hypoglycaemic events. This value was equal to the difference reported between the conventional and metformin-treated groups in the UK Prospective Diabetes Study [8]. There was an estimated standard deviation SD of 1. Accordingly, enrolled subjects were needed if up to ten drop-outs were to occur. Randomizationâ€”Sequence generation Randomization was performed using a pre-established computer-generated sequence in blocks of three and four, with the block size masked during the trial. Randomizationâ€”Allocation concealment Double-masked treatments were allocated using numbered drug containers. Concealed treatment allocation was by central randomization by email correspondence. A sealed copy of the randomization sequence was available at the investigation site in case of need for emergency unblinding. The trial clinicians enrolled patients. A person unconnected with the study assigned participants to their groups. Blinding Treatment allocation was masked for participants, clinicians and those evaluating outcomes until after database lock. After close-out the code was two-step encrypted first step: Blood sampling At baseline and 12 month study visits, blood samples were drawn in the fasting state. At enrolment, blood was collected as random, non-fasting samples. HbA1c was measured twice on each study visit and the mean of the measurements of the two separately drawn blood samples was used in all statistical analyses mean [SD] absolute intra-subject difference between HbA1c measurements, in percentage points, baseline: The mean of the two measurements was analyzed. Safety variables were measured using routine procedures at the Steno Diabetes Center. Body weight and height as well as waist and hip circumference were measured with the patient standing upright wearing only underwear. At the periodical recordings i. At enrolment, patients were asked to choose from one or more of five categories of reasons for having unsatisfactory glycaemic control: Adverse events Information about adverse events was collected with a standardised questionnaire. A serious adverse event SAE was defined as one fulfilling any of the following criteria: Minor episodes of hypoglycaemia were considered to be those in which the hypoglycaemic symptoms were treated by the patient; major hypoglycaemic episodes were considered to be those in which the condition induced loss of

consciousness or when third-party intervention was required to obtain treatment. Events of unconsciousness during major hypoglycaemia were captured using a separate category for this in the case-report form. Compliance Compliance and drug exposure during the study were assessed by tablet counting. Compliance with the tablet consumption schedule was calculated as the actual study drug consumption as a percentage of the expected consumption according to the currently prescribed study drug dose. Study drug exposure was calculated as the actual consumption averaged over the total number of days between the first and last study visits in the treatment periods. The number of outpatient clinic visits was estimated by the number of HbA1c measurements between i. Statistical methods Subject characteristics At enrolment, normally distributed variables were compared using unpaired t-tests, whereas non-normally distributed variables were analyzed with the Mann-Whitney test. Primary outcome, primary analysis Differences in treatment effects between the randomized interventions were evaluated by comparison between end of treatment and baseline levels i. An analysis of covariance ANCOVA model was developed with treatment type metformin or placebo as the fixed effect and baseline level as the covariate. Primary outcome, secondary analyses Further pre-specified analyses of the primary outcome, HbA1c, included adjustment for the current i. The following subgroups of patients were analyzed: A Substantial changes in the insulin regimens during the trial i. The dichotomization of BMI, HbA1c and insulin dose was done since these patient characteristics have been proposed as markers of insulin resistanceâ€”a suggested target of metformin treatment. Hence, any interaction of treatment by subgroups of patients according to the dichotomized baseline levels of these variables could potentially discriminate responders to non-responders of metformin therapy. Secondary outcomes, primary analysis Continuous variables were analyzed using the baseline adjusted ANCOVA model as for the primary outcome. Ancillary analyses The HbA1c measurements were investigated during the run-in period with adjustment for HbA1c at enrolment. Subsequently, the first and the last available of these follow-up HbA1c data as well as insulin dose after three months, were analyzed as for the primary outcome. In addition to hypoglycaemia being evaluated as a categorical variable i. Absolute numbers of hypoglycaemic events during follow-up as well as changes from enrolment or the run-period were evaluated. The number of hypoglycaemic events and outpatient clinic visits during follow-up i.

Chapter 2 : Adjunctive Metformin for Insulin Resistance in T1D: A Clinical Perspective

Abstract. OBJECTIVEâ€”To evaluate whether, in adolescents with type 1 diabetes, the addition of metformin to insulin and standard diabetes management results in 1) higher insulin sensitivity and 2) lower HbA 1c, fasting glucose, insulin dosage (units per kilogram per day) and BMI.

Advanced Search Abstract Context: Metformin therapy for adults and children with type 2 diabetes is well established. However, its role in the treatment of insulin resistance and obesity in children and adolescents is less clearly defined. We assessed the effect of metformin on body composition and insulin sensitivity in pediatric subjects with exogenous obesity. Patients referred to a pediatric endocrine clinic were enrolled in a randomized, double-blind, crossover trial. Twenty-eight patients 13 males aged 9â€”18 yr participated in the study. Patients received metformin 1 g twice daily and placebo for 6 months, each with a 2-wk washout period. Body composition anthropometry, dual-energy x-ray absorptiometry, and abdominal magnetic resonance imaging , and insulin sensitivity Si; minimal model, fasting insulin and glucose were measured at baseline and 6 and 12 months. Mean age of subjects at baseline was Metformin therapy for obese insulin-resistant pediatric patients results in significant improvement in body composition and fasting insulin. Although improvement in Si was noted in many individuals, Si was a less useful parameter for analysis of group data, possibly because of effects of variable compliance and changing Si during puberty. Metformin is a well-established oral hypoglycemic agent in the treatment of adults with type 2 diabetes mellitus and other conditions with insulin resistance. The beneficial role of metformin in young patients with type 2 diabetes has been demonstrated in a randomized, controlled trial 1. Metformin is also beneficial in pediatric patients with type 1 diabetes mellitus and insulin resistance 2 â€” 4 ; girls with, or at high risk of developing, polycystic ovarian syndrome 5 â€” 8 ; and young patients with nonalcoholic fatty liver disease 9. There are few data on the role of metformin in insulin resistance associated with obesity before the development of type 2 diabetes in children. The potential clinical application of metformin in the pediatric population was first described in a small study in the s with a beneficial effect on weight and insulin concentrations in 8- to yr-old obese children Subsequent pediatric randomized, controlled trial data have shown improvement in body mass index BMI , fasting serum glucose, and insulin and improved lipid profile in patients on metformin therapy for exogenous obesity with insulin resistance 11 , 12 as well as psychotropic drug-induced weight gain However, insulin sensitivity, as measured by minimal model, did not significantly improve in adolescents receiving metformin, compared with placebo, in a case-controlled, randomized, controlled trial 12 , raising the question of whether metformin specifically improves peripheral insulin sensitivity. By conducting a crossover, randomized, controlled trial, we sought to clarify the role of metformin therapy in pediatric patients with obesity, specifically addressing the effect on anthropometry, body fat compartments, and insulin sensitivity parameters. All parents and patients were given verbal and written information about the study before providing written consent. All participants were invited to give verbal and written feedback of individual results at the end of the study. Study design Participants were randomized to receive metformin and placebo for 6 months each in a crossover design, with a 2-wk washout period in between. Block randomization blocks of four with stratification by pubertal stage Tanner 1â€”2 or Tanner 3â€”5 was performed by computer-generated random number allocation, and placebo or metformin was dispensed by the hospital pharmacy. All participants and investigators were blinded to the intervention. Unblinding occurred after final data analysis. Both metformin and placebo doses were gradually built up over a 3-wk period to a final dose of 1 g twice daily. Standardized information on healthy eating and exercise was given to all patients. Investigations The time line for investigations is illustrated in Fig. At 3 and 9 months, participants underwent clinical assessment and fasting biochemical profile. Liver function tests, serum creatinine, and serum lactate levels were measured every 3 months to assess metformin safety profile. Pill counts were conducted every 3 months by the hospital pharmacy to calculate percent adherence to therapy based on number of capsules

consumed vs. Time line for investigations. Clinical assessment and anthropometry Height was measured to the nearest 0. Waist circumference was calculated from the average of three measures at the level of the umbilicus. BMI was calculated using the following formula: BMI for age z-scores were calculated from the U. Centers for Disease Control and Prevention reference data Waist circumference z-scores were calculated from recent multiracial American reference data Pubertal stage was assessed using the standards of Tanner and Whitehouse Blood pressure was measured on the right arm with an appropriately sized cuff using a DynaMap machine with the subject seated. The lowest of three measures was recorded. Routine physical examination was performed before each set of investigations to rule out significant intercurrent illness. Acanthosis nigricans was assessed for severity at the neck by a validated scale ranging from grade 0 not present to grade 4 severe: This was performed clinically by the principal investigator S. Frequently sampled iv glucose tolerance test After an overnight fast, subjects underwent a min iv glucose tolerance test for minimal model analysis of parameters of insulin sensitivity An iv cannula was inserted into each arm, one for sampling and the other for glucose and insulin boluses. After taking baseline samples, 0. At 20 min 0. Paired insulin and glucose samples were taken at 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 23, 24, 25, 27, 30, 40, 50, 60, 70, 80, 90, , , , , and min. Glucose was analyzed immediately on the Dade Dimension ARX using hexokinase-glucosephosphate dehydrogenase method. The insulin assay was performed on the Immulite analyzer Diagnostics Products Corp. All analyses were performed by the same investigator S. Participants were positioned on the scanner table using standard procedures, and total body cuts were positioned as per standard manufacturer specifications. MRI of the abdomen All subjects were scanned on a 1. Five cross-sectional images, each 10 mm thick, of the abdomen were acquired. The center image slice 3 was positioned at mid-L-4 with two images acquired above slices 1 and 2 and below slices 4 and 5. Analyze software version 4. The mean of the five slices was used in the final analysis. To assess the effect of metformin vs. These tests were applied to period 1 and period 2 differences for groups A and B. The difference between the means of the two groups was taken as twice the size of the treatment effect Linear mixed model analysis was performed to assess possible confounding effect of change in pubertal stage and poor adherence to therapy on insulin sensitivity. Results Thirty-four patients were referred to the study; five refused to participate and one did not meet the inclusion criteria. Twenty-eight patients 13 males participated in the study. Thirteen were randomized to metformin first and then placebo group A , and 15 were randomized to placebo first and then metformin group B. One participant in group A and three participants in group B discontinued the study due to nonadherence to therapy or social circumstances. Two participants in group A had difficult iv access and did not have a full set of insulin sensitivity data. The flow of patients through the study is summarized in Fig.