European Nicotinamide Diabetes Intervention Trial (ENDIT): a randomised controlled trial of intervention before the onset of type 1 diabetes

European Nicotinamide Diabetes Intervention Trial (ENDIT) Group*

Summary

Background Results of studies in animals and human beings suggest that type 1 diabetes is preventable. Nicotinamide prevents autoimmune diabetes in animal models, possibly through inhibition of the DNA repair enzyme poly-ADP-ribose polymerase and prevention of β-cell NAD depletion. We aimed to assess whether high dose nicotinamide prevents or delays clinical onset of diabetes in people with a first-degree family history of type 1 diabetes.

Method We did a randomised double-blind placebo-controlled trial of nicotinamide in 552 relatives with confirmed islet cell antibody (ICA) levels of 20 Juvenile Diabetes Federation (JDF) units or more, and a non-diabetic oral glucose tolerance test. Participants were recruited from 18 European countries, Canada, and the USA, and were randomly allocated oral modified release nicotinamide (1·2 g/m²) or placebo for 5 years. Random allocation was done with a pseudorandom number generator and we used size balanced blocks of four and stratified by age and national group. Primary outcome was development of diabetes, as defined by WHO criteria. Analysis was done on an intention-to-treat basis.

Findings There was no difference in the development of diabetes between the treatment groups. Of 159 participants who developed diabetes in the course of the trial, 82 were taking nicotinamide and 77 were on placebo. The unadjusted hazard ratio for development of diabetes was 1·07 (95% CI 0·78–1·45; p=0·69), and the hazard ratio adjusted for age-at-entry, baseline glucose tolerance, and number of islet autoantibodies detected was 1·01 (0·73–1·38; p=0·97). Of 168 (30·4%) participants who withdrew from the trial, 83 were on placebo. The number of serious adverse events did not differ between treatment groups. Nicotinamide treatment did not affect growth in children or first-phase insulin secretion.

Interpretation Large-scale controlled trials of interventions designed to prevent the onset of type 1 diabetes are feasible, but nicotinamide was ineffective at the dose we used.

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Introduction

Type 1 diabetes might be a preventable disease. Many successful interventions have been described in the non-obese diabetic (NOD) mouse.[1] In human beings, results of prospective studies in high-risk relatives of people with diabetes have shown a long latent period between the first appearance of circulating autoantibodies directed against antigens derived from pancreatic islets and the clinical onset of the disease.[2] Multiple autoantibodies are present in most newly diagnosed cases at the time of diagnosis, and their presence is highly predictive of progression to disease in otherwise healthy first-degree relatives.[3] Type 1 diabetes is a serious and currently incurable disease with a prodrome that offers a long window of opportunity for screening. Inexpensive validated methods are available. On this basis, screening and intervention before the onset of type 1 diabetes would be justified if there were a cost-effective means of intervention.

Pretreatment with high dose nicotinamide has been known for many years to prevent the development of diabetes in rats treated with streptozotocin. Nicotinamide also prevents or delays the onset of diabetes in the non-obese diabetic mouse, and results of in-vitro studies have shown that it can prevent β-cell damage. Nicotinamide affords a degree of protection to β cells after the diagnosis of diabetes in humans[4] and has been reported to prevent the development of diabetes in schoolchildren with islet-cell antibodies (ICA).[5] The results of small pilot studies of nicotinamide in high-risk relatives were also promising.[6] As the safety profile in humans seems favourable,[7] we aimed to assess whether high dose nicotinamide could delay or prevent the onset of diabetes in people at high risk of progression to the disease.

First-degree relatives of a patient with type 1 diabetes provided an accessible and highly motivated population for such an intervention. Furthermore, the risk of progression to disease associated with ICA and other antibody markers has been accurately quantified for this group of people, with remarkable consensus between studies throughout the world.[8-10] However, the logistics of such a study are daunting, since only a small proportion of first-degree relatives are at high enough risk of the disease to justify intervention. Of the 84 228 relatives screened for the Diabetes Prevention Trial—Type 1 (DPT-1), only 339 participants were identified for inclusion in the trial of parenteral insulin to prevent type 1 diabetes in high risk individuals.[11] A screening exercise of this size needs the resources of a whole continent, and therefore, this investigator-led study included participants from 18 European countries, Canada, and a group in the USA.

Methods

The protocol and outcome of the screening stages of ENDIT have been published elsewhere.[12]

Participants

We screened first-degree relatives of patients who developed type 1 diabetes before age 20 years, and who were themselves aged between 3 and 40 years. The original upper age limit of 60 years was lowered to 40 years in 1995 after results of a multicentre analysis showed that relatives older than 40 years with ICA were at low risk of progression to diabetes.[10] We explained this finding to family members older than 40 years of age who had been screened and recruited, and they were allowed to remain in the trial and be included in the randomisation process if they so wished. We screened more than 30000 eligible relatives for ICA. Participants were recruited through 354 clinical centres in 18 European countries, Canada, and the USA between 1990 and 1998. We included patients who had an ICA level of 20 Juvenile Diabetes Federation (JDF) units or more in at least one sample, as measured in the central laboratory, and an ICA level of 5 JDF units or more in the other sample. We excluded people who: had a chronic disease that was likely to affect outcome, toxicity, or adherence to the protocol; women who were breastfeeding, pregnant, or of childbearing age and not using effective contraception; and anyone taking vitamin preparations containing nicotinamide. Participants who were shown to have diabetes on oral glucose tolerance testing were also excluded.

The protocol was approved by the research ethics committee or equivalent in each participating centre, and also by the appropriate national drug regulatory authorities. Written informed consent was obtained from all participants.

Procedures

Participants were randomly allocated either oral modified release nicotinamide (Ferrosan AC, Copenhagen, Denmark) at a dose of $1\cdot2$ g/m^2 daily up to a maximum of 3 g/day or placebo for 5 years in two divided doses. The randomisation sequence was generated with a computerised pseudorandom number generator and had balanced blocks of size four. Randomisation was stratified by age (younger and older than age 20 years) and by national group. Because some national groups recruited small numbers of participants, we pooled randomisation for Austria and Switzerland; for Italy, Greece, and Croatia; and for Belgium and the UK. Randomisation codes for the appropriate age-group were allocated sequentially by the national coordinator. All study personnel remained unaware of the patients' treatment allocation for the duration of the study. Study medication was supplied by the manufacturers to the national coordinating centres labelled only with the randomisation code. Emergency unblinding could be done by opening sealed code envelopes held at each national coordinating centre. The study monitor checked that these envelopes were intact at least once a year and at the end of the study.

We reviewed participants at baseline, 1 month, and 6 months after study entry and every 6 months thereafter. At each visit we did a clinical examination and recorded height and weight, adverse events, checked biochemical and haematological variables, and the number of returned tablets. Oral glucose tolerance testing was mandatory at baseline and 6, 18, 30, 42, 54, and 60 months. An intravenous glucose tolerance test (IVGTT) was also mandatory at baseline and whenever possible, was repeated at 12, 24, 36, 48, and 60 months.

We tried to keep in contact with all participants who had withdrawn from the study for reasons other than development of diabetes, to determine their diabetes status.

Our primary outcome was the development of diabetes, as defined by WHO criteria. Additional prespecified outcomes were first-phase insulin release in the intravenous glucose tolerance test, and growth in children.

Testing procedures and assays

Oral glucose tolerance test (OGTT)

Oral glucose ($1\cdot75$ g/kg bodyweight, up to a maximum of 75 g) was administered after an overnight fast. We took venous plasma samples at 0 and 120 min and tested for glucose in the local study centre laboratory. Diabetes and impaired glucose tolerance were defined by WHO criteria.[13]

Intravenous glucose tolerance test

Tests were done in accordance with the Islet Cell Autoantibody Register Users Study (ICARUS) protocol.[14] A glucose dose of $0\cdot5$ g/kg, up to a maximum of 35 g, was infused over 3 min (+ or – 15 s), and we took blood samples at –5, 0, 1, 3, 5, and 10 min. First-phase insulin response (FPIR) was calculated as the sum of the insulin concentrations at 1 and 3 min after the end of the infusion.

Islet autoantibodies

Baseline samples from all participants were tested for ICA and autoantibodies to glutamic acid decarboxylase (GAD), IA-2, and insulin in the laboratories of the Division of Medicine, University of Bristol as previously described.[15] Samples were judged positive if concentrations were at or above the $97\cdot5$th percentile of concentrations in a control population of 2860 schoolchildren.

The ICA assay was shown to have 81% sensitivity with 86% specificity in the First Immunology of Diabetes Society (IDS) Combined Antibody Workshop; and radiobinding assays for autoantibodies to GAD, IA-2, and insulin, had 91% sensitivity with 99% specificity, and 74% sensitivity with 99% specificity, and 58% sensitivity with 99% specificity , respectively.[16]

Insulin assay

Plasma insulin was measured in one laboratory at the Steno Diabetes Centre, Gentofte, Denmark in an enzyme-linked two-site immunoassay.[17] To allow for comparison of intravenous glucose tolerance test results with age-specific percentiles for FPIR obtained in the University of Washington, Seattle, USA and used for DPT-1,[11] 105 samples spanning the range 0–500 pmol/L were assayed in both laboratories. The regression equation of insulin concentration measured in Seattle on the insulin concentration measured in the Steno laboratory was used to derive a correction factor to standardise the measurement to the Seattle assay.[18]

Statistical analysis

We calculated that our target sample size was 528 participants for the study to have 90% power to detect a 40% reduction in the rate of progression to type 1 diabetes over a 5-year period, with a two-tailed significance of $0\cdot05$. We assumed that non-diabetic first-degree relatives under the age of 40 with confirmed ICA level of 20 JDF units or more have a 35% risk of insulin therapy within 5 years. Sample size calculations showed that a minimum of 211 subjects in each group would be needed to detect a reduction in progression to diabetes from 35% to 21%. We estimated that about 20% of participants would withdraw during the trial and, therefore, we aimed to recruit a minimum of 264 people to each group.
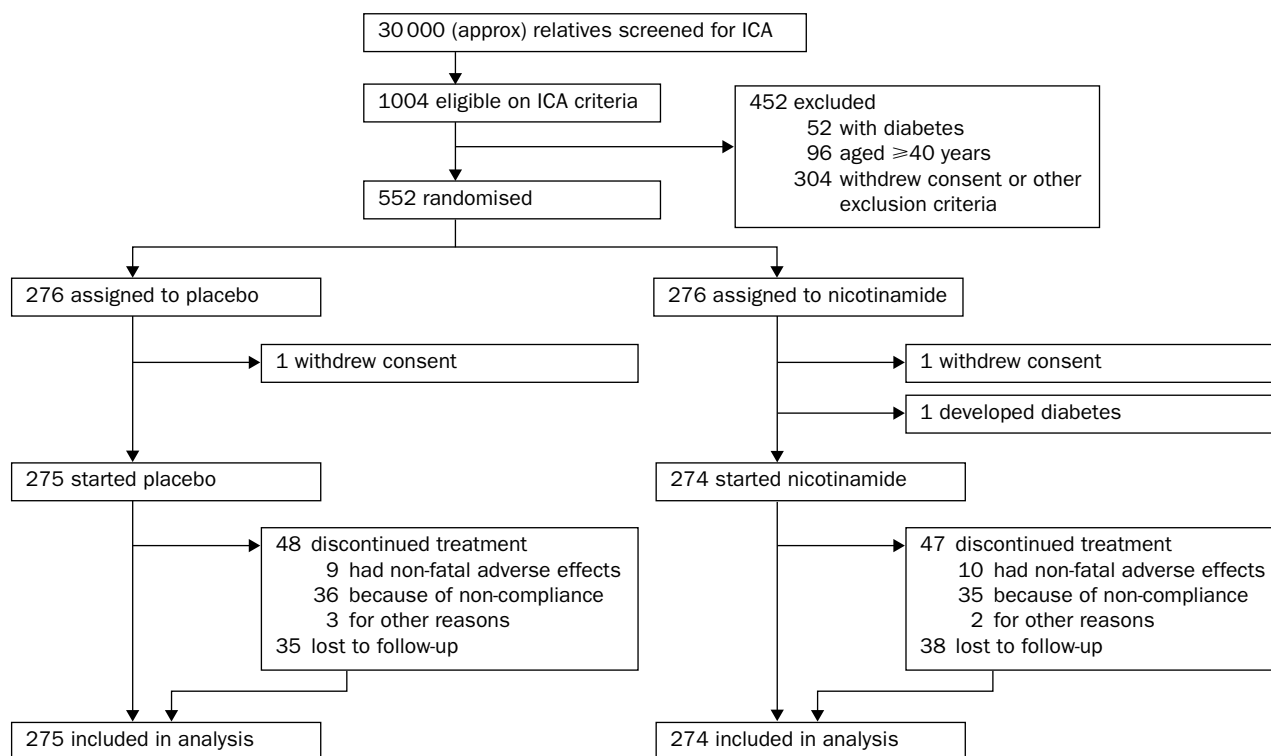
Figure 1: **Trial profile**

An independent data and safety monitoring committee reviewed safety data every year. We planned to do an interim analysis of the primary outcome after half the participants had completed 3 years of follow-up. The prespecified rules for stopping the trial were, for efficacy, a decrease in the incidence of diabetes of more than 50% with p less than 0·0001 (two sided logrank test) and, for harm, an increased progression to diabetes with p less than 0·05. The interim analysis was completed in March, 1999. The original plan was to do the final analysis in May, 2003, after all participants had completed 5 years of follow-up. Recruitment to the study, however, took longer than originally foreseen, and the data and safety monitoring committee decided that a second interim analysis should be undertaken in December, 2001, because, by that time, 484 participants (88%) had either developed diabetes or had completed 5 years follow-up, and another 28 people (5%) had withdrawn from the study and were lost to follow-up. On the basis of results from the interim analysis, the trial was stopped in May, 2002, because the treatment was deemed futile. Analysis of other outcomes and of subgroups was then completed.

Statistical analyses was done by an independent statistician in accordance with a predefined plan. All analyses were by intention-to-treat. Cox proportional hazards models were used to analyse the time-to-event outcome, and estimates of both the unadjusted and adjusted (controlling for the baseline covariates; age, glucose tolerance and number of antibodies ≥97·5th centile) treatment effect was obtained. Results are reported as number of participants and events for each treatment group, and hazard ratios (95% CI) and p values from the Cox model analyses. The treatment effect was assessed in a small number of prespecified subgroups based on sex, age, oral glucose tolerance, number of islet autoantibodies, and FPIR. Time-to-event curves were constructed with the Kaplan-Meier method.

We calculated SD scores for height and weight using cross sectional stature and weight reference curves for the UK.[19] The effect of treatment on height or weight SD scores and FPIR over time was investigated with a generalised estimating equation approach, taking into account the correlation between the repeated

	Placebo (n=276)	Nicotinamide (n=276)
Started randomised treatment	275	274
Age at randomisation (years)		
<5	8 (3%)	7 (3%)
5–9	56 (20%)	57 (21%)
10–14	61 (22%)	63 (23%)
15–19	38 (14%)	39 (14%)
20–24	15 (5%)	16 (6%)
25–29	10 (4%)	10 (4%)
30–34	26 (9%)	21 (8%)
35–39	45 (16%)	38 (14%)
≥40	16 (6%)	23 (8%)
Male sex	143 (52%)	144 (53%)
Relationship to diabetic relative		
Child	26 (9%)	22 (8%)
Sibling	163 (59%)	171 (63%)
Mother	57 (21%)	47 (17%)
Father	29 (11%)	34 (12%)
120 min plasma glucose (mmol/L)		
<7·8	247 (90%)	250 (91%)
≥7·8	28 (10%)	24 (9%)
Islet autoantibodies ≥97·5th percentile:		
ICA only	108 (39%)	89 (32%)
+1 additional antibody	35 (13%)	46 (17%)
+2 additional antibodies	57 (21%)	54 (20%)
+3 additional antibodies	75 (27%)	85 (31%)
Age-specific FPIR*		
Below 10th percentile†	96 (37%)	90 (36%)
≥10th percentile	160 (63%)	159 (64%)

Data are number (%). *FPIR missing for 19 participants in placebo group and 25 in nicotinamide group. †10th percentile is equivalent to 430·5 pmol/L for participants younger than 8 years and 717·5 pmol/L for those older than 8 years, standardised to the Seattle assay.[11]

Table 1: **Participants' baseline characteristics**

	Placebo (n=83 [30%])	Nicotinamide (n=85 [31%])
Age at randomisation (years)		
<5	2 (2%)	1 (1%)
5–9	10 (12%)	9 (11%)
10–14	13 (16%)	18 (21%)
15–19	13 (16%)	18 (21%)
20–24	8 (10%)	7 (8%)
25–29	8 (10%)	3 (4%)
30–34	11 (13%)	12 (14%)
35–39	15 (18%)	10 (12%)
≥40	3 (4%)	7 (8%)
Male sex	42 (51)	40 (47)
Glucose at baseline (mmol/L)		
<7.8	78 (94%)	82 (96%)
≥7·8	5 (6%)	3 (4%)
Number of antibodies at baseline		
≥ICA only	41 (49%)	33 (39%)
≥+1	14 (17%)	19 (22%)
≥+2	15 (18%)	21 (25%)
≥+3	13 (16%)	12 (14%)
Age-specific FPIR at baseline*		
≥Low (below 10th centile)†	23 (29%)	28 (35%)
≥Normal	57 (71%)	51 (65%)

Data are number (% of participants who withdrew from the trial). *Of 44 participants with missing FPIR data, 3 of 19 on placebo and 6 of 25 on nicotinamide withdrew from study. †10th percentile is equivalent to 430·5 pmol/L for participants younger than 8 years and 717·5 pmol/L for those older than 8 years, standardised to the Seattle assay.[11]

Table 2: **Characteristics of participants who discontinued treatment or who were lost to follow-up**

measurements on individuals. A Gaussian distribution was assumed for all of the three outcomes (we noted that FPIR was positively skewed and, therefore, we did a log transformation) and the identity link was used. Independent and autoregressive correlation structures were tested, both producing very similar results. SEs were calculated with the sandwich estimator.

Role of the funding source
Ferrosan A/C, which at the start of the study was a wholly-owned subsidiary of Novo-Nordisk, provided all the trial medication and the randomisation list was generated by Novo-Nordisk. Neither this company nor the major sponsors of the study (The European Union and Juvenile Diabetes Research Foundation) had a role in

	Placebo (n=275)	Nicotinamide (n=274)	Hazard ratio (95% CI)	p
Overall	77 (28%)	82 (30%)	1·07 (0·78–1·45)*	0·69
			1·01 (0·70–1·38)†	0·97
Sex				
Male	47 (33%)	48 (33%)	0·99 (0·66–1·48)*	0·97
Female	30 (23%)	34 (26%)	1·17 (0·71–1·90)*	0·53
Age at baseline (years)				
<20	66 (40%)	64 (39%)	0·98 (0·69–1·39)*	0·91
≥20	11 (10%)	18 (17%)	1·42 (0·70–2·90)*	0·33
Glucose intolerance				
Normal	60 (24%)	64 (26%)	1·04 (0·73–1·48)*	0·81
Impaired	17 (61%)	18 (75%)	1·56 (0·80–3·03)*	0·19
Antibodies ≥97·5th percentile:				
ICA only	0 (0%)	3 (3%)	NA	-
ICA with ≥1 additional antibody	77 (46%)	79 (43%)	0·91 (0·66–1·24)*	0·54
FPIR				
Normal (≥10th percentile)	23 (14%)	28 (18%)	1·23 (0·71–2·13)*	0·47
Low (below 10th percentile)	50 (52%)	41 (46%)	0·82 (0·55–1·25)*	0·36

Data are n (%) unless otherwise stated. *Unadjusted model. †Adjusted for baseline covariates; age, glucose tolerance, and number of antibodies ≥97·5th centile.

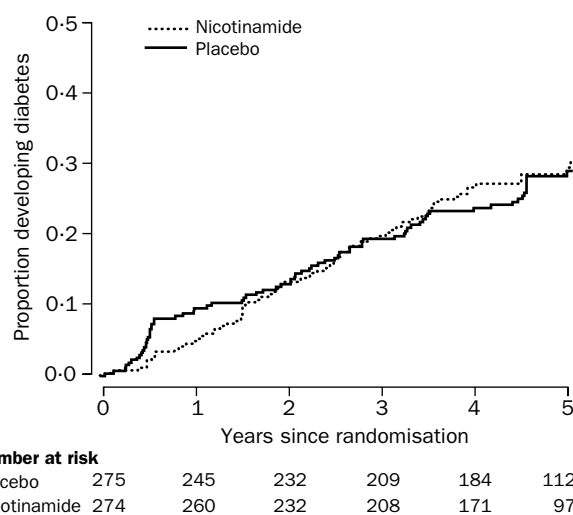Table 3: **Hazard ratios for developing diabetes within 5 years**

Figure 2: **Kaplan-Meier failure curve**

Number at risk						
Placebo	275	245	232	209	184	112
Nicotinamide	274	260	232	208	171	97

study design, data collection, data analysis, data interpretation, or the writing of the report.

Results
Between between June, 1994, and May, 1998, we enrolled 552 participants. The interval between collection of samples for ICA positivity and randomisation was less than 18 months in all but 11 participants, and less than 2 years in all but one who was randomly allocated to treatment 26 months after ICA positivity was confirmed. Figure 1 shows the trial profile. Of 552 individuals randomly allocated to a study group, 549 started their trial medication.

Participants' baseline characteristics are shown in table 1.

The primary outcome variable of diabetes status after 5 years of follow-up was established in 447 of 549 participants (87%), including 95 participants who discontinued treatment before the end of the follow-up period but who remained in contact with local investigators. Figure 1 shows the group allocation and reasons for treatment discontinuation for these 95 people. Another 73 participants (13%) were lost to follow-up before completion of the trial (figure 1). Median follow-up in people lost to follow-up was 3·3 years (IQR 2·3–4·0 years). The distribution of discontinued treatment and loss to follow-up did not differ across demographic and risk-factor subgroups (table 2). Emergency unblinding was done for four participants

The main outcomes of the trial are shown in table 3 and figure 2. Nicotinamide treatment did not have any discernible effect on the primary outcome—ie, progression to diabetes. 159 participants developed diabetes within 5 years of randomisation to treatment, 82 (30%) in the active treatment group and 77 (28%) in the placebo group. The unadjusted Cox proportional hazard estimate showed no difference between the placebo and nicotinamide groups on an intention-to-treat basis (table 3). Nor did we note any difference between groups after adjustment for age at baseline, glucose concentrations at 2-h glucose in the OGTT, and number of islet autoantibodies (table 3). We did not adjust the hazard ratio for FPIR at baseline, because these data were missing for 19 people in the placebo group and 25 in the active treatment group.

Data in table 3 show that there was no evidence of a treatment effect in groups divided on the basis of age, sex,
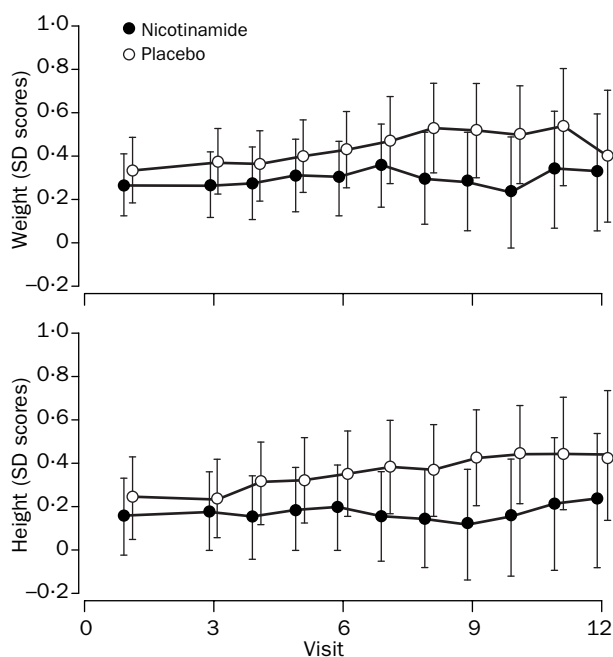
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Figure 3: Mean changes in weight and height in participants younger than 20 years
Vertical bars show 95% CI.

oral tolerance status, antibody status, or first-phase insulin response.

Secondary outcomes relating to the effects of treatment on growth and FPIR were analysed using the generalised estimating equation. Figure 3 shows the changes in weight and height during the trial of participants of age less than 20 years at the start of the trial and figure 4 shows changes in FPIR during the trial for all participants. There were no differences between groups for any of the secondary outcomes (height: p=0·71, weight: p=0·64, FPIR: p=0·81).

Regular safety analyses done throughout the trial showed no differences between the treatment groups with respect to adverse events. 35 serious adverse events were reported in 18 participants in the active treatment group and 15 in the placebo group, not including hospital admission at diabetes onset. At every visit, the two groups did not differ with respect to the number of adverse events reported, the systems of the body affected, or the severity of events (data not shown). Increased concentrations of alanine transaminase, aspartate transaminase, or gamma glutamyl transpeptidase (more than three times the upper limit of
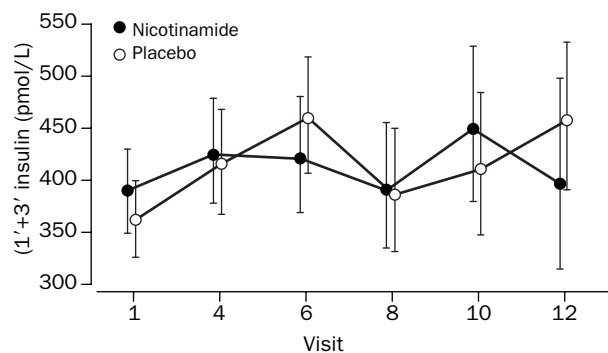

Figure 4: Changes in first-phase insulin response
Data are geometric means and vertical bars show 95% CI.

normal in the local laboratory) were noted in nine participants during the trial. Of these, five were taking active treatment group and four were on placebo. Six women became pregnant during the trial, four in the nicotinamide group and two in placebo. Trial medication was stopped as soon as pregnancy was confirmed. No congenital abnormalities were reported in the offspring.

Discussion

We have shown that at the doses used, nicotinamide is ineffective in the prevention of type 1 diabetes. The proportion of relatives who developed diabetes within 5 years was almost identical in those treated with nicotinamide and those on placebo, and there was no suggestion of a treatment effect in any of the subgroups defined by well established markers of additional risk. Type 1 diabetes meets every criterion for a disease for which screening would be justified [20] save one: we lack an effective form of intervention. Excellent predictive markers exist in the form of circulating autoantibodies directed against a range of islet antigens. These antibodies can be detected many years before the clinical onset of type 1 diabetes and they mark a prodromal phase during which there is progressive β-cell destruction,[21] thus providing an opportunity for intervention to halt or delay the disease process before hyperglycaemia occurs.[22] Our study was based on detection of high-titre ICA, a well validated marker of risk for progression to type 1 diabetes.

Nicotinamide is a component of vitamin B3 that has been known for many years to offer protection in animal models of diabetes induced by alloxan or streptozotocin,[23] and against spontaneous diabetes in the NOD mouse.[24] In type 1 diabetes, β cells are destroyed by a cellular immune response which involves cytotoxic T cells and macrophages and results in release of proinflammatory cytokines. Downstream events include single strand DNA damage leading to activation of the DNA repair enzyme, poly(ADP-ribose) polymerase (PARP), which shuttles onto and repairs DNA strand breaks. In doing so it consumes nicotinamide adenine dinucleotide (NAD), transferring the dinucleotide moiety of NAD to poly (ADP-ribose), resulting in a rapid fall in available intracellular energy levels. Excessive activation of PARP and depletion of intracellular NAD are precursors of cell death, and the protective effect of nicotinamide on β cells is thought to be mediated by inhibition of this pathway.[12,25] Nicotinamide has been tried in human type 1 diabetes both at diagnosis and before clinical onset of the disease with varying results. A meta-analysis of nicotinamide treatment following diagnosis showed better preservation of C-peptide secretion at 12 months, although metabolic control was unaffected,[4] and studies in ICA-positive relatives and in schoolchildren with no family history of diabetes have been reported to delay or prevent the onset of diabetes.[5,6] Our review of published work suggested that nicotinamide at the dose tested could achieve partial PARP inhibition in humans and its safety profile seemed good.[26] We, therefore, set out to assess whether treatment with nicotinamide at the high doses used in previous studies could produce a clinically useful reduction in development of diabetes in relatives of people with type 1 diabetes.

Our findings contrast with results from most earlier studies in humans,[5,6] although they do accord with findings from a small German trial in young siblings of patients with type 1 diabetes.[27] Our study was adequately powered to detect a 35–45% reduction in the risk of developing diabetes within 5 years, and the close overlap

between the treatment groups makes it unlikely that smaller treatment effects have been overlooked. Despite the logistical difficulties of running a study in 18 European countries, Canada, and the USA, we were able to deliver a high quality study with few protocol violations. The overall number of participants who failed to complete the study according to protocol was 31%, somewhat higher than the 20% we anticipated, but we did exceed our recruitment target and the power of the study was not greatly affected. Of 168 who discontinued treatment, 95 remained under follow-up for the duration of the study, and the primary outcome could therefore be ascertained in 87% of those randomised. The numbers of patients from each treatment group and their baseline characteristics were evenly balanced in those who were lost to follow-up and the remainder; therefore, these withdrawals are unlikely to have affected the validity of our main conclusions. The cumulative risk of progression to diabetes in our placebo group was lower than we expected, probably because our risk estimates were based on observational studies which included all cases, whereas intervention studies will not include early progressors who develop diabetes while the screening programme is underway. Although our own safety review was reassuring,[7] concerns have been raised about the potential effects of nicotinamide on growth in children[28] and on residual insulin secretion.[27] These concerns were shown to be unfounded, and no adverse effects of nicotinamide were identified even at doses 30–50 times higher than the recommended daily intake.

The failure to confirm findings in animal studies might be related to the lower dose used in humans, or to the fact that nicotinamide was given at a much later stage of the disease process in humans than in rodents. Another possible explanation relates to species-related differences in the islets themselves. It has, for example, been shown that nicotinamide protects isolated human islets against chemically-induced necrosis, but not against cytokine-induced apoptosis.[29]

Although both trials were negative, the enduring lesson from ENDIT and DPT-1 is that such trials can be done at all.[30] The logistics remain daunting, however, especially when there is a lack of substantial central funding, as was the case with ENDIT. Europe currently has no effective funding mechanism to support long-term trials on the scale of ENDIT, and therefore, this investigator-led study relied heavily on the motivation of investigators and participants. Results from both trials re-emphasised that diabetes can be predicted, and in ENDIT 29% of first-degree relatives, identified simply on the basis of high concentrations of ICA, progressed to diabetes within 5 years. Our results also lent support to the assertion that risk of progression to diabetes increases in proportion to the number of autoantibody markers present in the circulation. Because of improved screening strategies, future trials will require fewer participants, and nearly all participants selected for inclusion and exposed to potential risks of intervention will at some stage develop the disease. High-throughput automated screening methods will greatly simplify future trials of this type, and the resulting improvement in screening efficiency would have enabled two interventions to be tested within the ENDIT screening population.[31]

Our work shows the feasibility of large-scale multinational studies of interventions to delay or prevent the onset of type 1 diabetes. The limiting factor for these studies remains the lack of a safe and validated intervention. In view of the massive investment of time and energy needed to do trials on this scale, it may be necessary to test other interventions in people with newly diagnosed diabetes before trials in non-diabetic people at high risk of the disease, despite the fact that the therapeutic effect might differ at different stages of the disease. An important lesson from DPT-1 and ENDIT is that both animal studies and small pilot studies in humans can be very misleading, and international consensus on the scale, design, and interpretation of future pilot studies will be needed. The twice daily dosage schedule in ENDIT was difficult for participants to sustain over a long study, and simplicity of administration should be a major consideration in planning future interventions. The doctor seeing a patient with new-onset type 1 diabetes has until now been in the position of a nephrologist unable to diagnose renal failure until his patients require dialysis. Results from ENDIT and DPT-1 have shown that this era is coming to an end, and give us hope that type 1 diabetes will, in time, be a preventable disease.

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