Clinical Nutrition 38 (2019) 1146–1152

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Meta-analyses

Effects of inositol on glucose homeostasis: Systematic review and meta-analysis of randomized controlled trials

Inka Miñambres [a, b], Gemma Cuixart [a], Anna Gonçalves [c], Rosa Corcoy [a, b, d, *]

[a] Hospital de la Santa Creu I Sant Pau, Barcelona, Spain
[b] Universitat Autònoma de Barcelona, Spain
[c] Centro Hospitalar do Algarve, Portugal
[d] CIBER-BBN, Spain

ARTICLE INFO

Article history:
Received 28 March 2018
Accepted 11 June 2018

Keywords:
Inositol
Pinitol
Myo-inositol
Diabetes
Glucose
Supplementation

SUMMARY

Background & aims: The effect of inositol on glucose homeostasis is not well characterized. The aim of the present meta-analysis is to synthesize the effects of inositol on glucose homeostasis in different clinical conditions.

Methods: We performed a systematic review (CRD42017057927) following PRISMA guidelines. Web of Science and Medline were searched for randomized controlled trials (RCTs) that addressed supplementation with compounds of the inositol family in humans and assessed their effects on glucose homeostasis.

Results: We screened 476 abstracts and included 20 RCTs with a total of 1239 subjects. Meta-analysis showed in the treatment arm a reduction in fasting plasma glucose (Mean difference (MD) −0.44 mmol/l, 95% CI −0.65, −0.23), 2 h PG after 75 g OGTT (MD −0.69 mmol/l, 95% CI −1.14, −0.23), abnormal glucose tolerance (Relative risk (RR) 0.28, 95% CI 0.12, 0.66), fasting insulin (MD −38.49 pmol/l, 95% CI −52.63, −24.36), and HOMA-IR (MD −1.96 mmol × mUI/l, 95% CI −2.62, −1.30). No differences were observed in BMI, HbA1c and % of patients requiring insulin treatment. Sensitivity analysis did not change treatment estimates. Mention to adverse events was only present in 13 articles with no sign of seriousness.

Conclusions: Inositol supplementation decreases blood glucose through an improvement in insulin sensitivity that is independent of weight. Assessment of adverse effects is scarce among published trials and should be fully addressed before considering inositol as a therapeutic agent for glucose-related outcomes. The characterization of the subjects achieving benefit from the intervention and the formulations to be used should also be known.

1. Introduction

Inositol is a poliol present in animal and plant cells in nature in up to nine stereoisomeric forms. All cells contain inositol phospholipids as components of their membranes and inositol can be part of the structural basis of intracellular messengers, such as inositol triphosphates, phosphatidylinositol phosphate lipids and inositol glycans. Therefore, inositol has been attributed a variety of functions including cellular growth and survival, nerve functionality, regulation of osteogenesis, reproductive activity and metabolic regulation [1,2].

Abnormalities in inositol metabolism have been associated with the development of insulin resistance and diabetic complications. In animal models of diabetes or insulin resistance, inositol supplementation has been found to lower postprandial glucose [3–5] and initial studies in women with polycystic ovary syndrome in the nineties revealed an improvement in peripheral insulin sensitivity and insulinemia [6–8]. Several randomized controlled trials (RCT) have assessed the effects of inositol supplementation in different clinical contexts such as anovulatory women with polycystic ovarian syndrome, pregnant women at risk of gestational diabetes mellitus (GDM), and patients with type 2 diabetes with beneficial effects [6,9,10]. The aim of the present systematic review

* Corresponding author. Hospital de la Santa Creu i Santa Pau, C/Mas Casanovas 90, 08041, Barcelona, Spain. Fax: +34 935565602.
E-mail address: rcorcoy@santpau.cat (R. Corcoy).

https://doi.org/10.1016/j.clnu.2018.06.957
0261-5614/

and meta-analysis is to synthesize the effects of inositol on glucose homeostasis in humans irrespective of their clinical condition.

2. Material and methods

The study was performed according to PRISMA guidelines [11] and the protocol was published in March 2017 in PROSPERO (CRD42017057927).

2.1. Eligibility criteria

We included randomized controlled trials that assessed the effects of supplementation of inositol or its derivatives (pinitol, D-chiro-inositol) on parameters related with glucose homeostasis in humans in any clinical condition. Exclusion criteria: case series, observational studies, cross-sectional analysis, review studies, and essentially studies not providing original data fulfilling eligibility criteria. RCTs of inositol supplementation not reporting specific outcomes of interest were also excluded.

2.2. Data sources and search strategy

We conducted a search on Web of Science and Medline from their inception to 1st February 2016, accessing through Web of Knowledge. Articles retrieved were limited to English, Spanish, Italian and French languages. Only articles published in full length were included. Search terms were as follows: Topic = (inositol OR pinitol) AND Topic = ((glucose OR insulin OR diabet*)) AND Topic = ((women OR men OR subjects OR patients OR individuals OR human)) NOT Topic = (animals) AND Topic = (double blind OR trial OR supplementation OR placebo OR random* OR controlled).

2.3. Study selection and data extraction

Two reviewers independently assessed each abstract for eligibility. Disagreement at this stage yielded an automatic abstract inclusion. Included abstracts were retrieved as full texts and then screened, again in duplicate. Data from the studies fulfilling inclusion criteria were extracted using a standardized data extraction sheet, including baseline information, quality data and outcomes. Specifically, the following data were extracted: study design, country, patient characteristics (sex, age, ethnicity, inclusion and exclusion criteria of the specific study), drug and dosage of inositol supplementation, and baseline and final glucose-related characteristics (body mass index (BMI), fasting plasma glucose (FPG), 2 h plasma glucose (PG) in the oral glucose tolerance test (OGTT), abnormal glucose tolerance (AGT), insulinemia, Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) and insulin treatment). In studies on pregnant women, gestational age at diagnosis of gestational diabetes (GDM) was also evaluated. Any discrepancies at this stage were settled with a third reviewer while referring to the original text. When data of interest was not reported in the paper but potentially available (i.e. HOMA-IR in a paper reporting fasting plasma glucose and insulin) a query was submitted to the authors, twice if required.

2.4. Quality assessment and risk of bias of individual studies

The risk of bias was assessed using the Cochrane Collaboration tool which takes into account the following items: sample size calculation, randomization method, quality of allocation concealment, blinding, attrition rates, intention to treat analysis, the presence of a published protocol and selective outcome reporting (final manuscript vs. published protocol or, results vs. methods when a published protocol was not available). The assessment is qualitative.

2.5. Statistical analysis

Outcome data from original studies were pooled into either relative risk (RR) for dichotomous outcomes or mean difference (MD) for continuous outcomes using Review Manager 5.1 software and a random effects model. Heterogeneity was assessed for all the comparisons using I^2. Pooled analyses were also used to compare baseline characteristics.

2.6. Risk of bias across studies

Publication bias was assessed for all analyses after visual inspection of funnel plots.

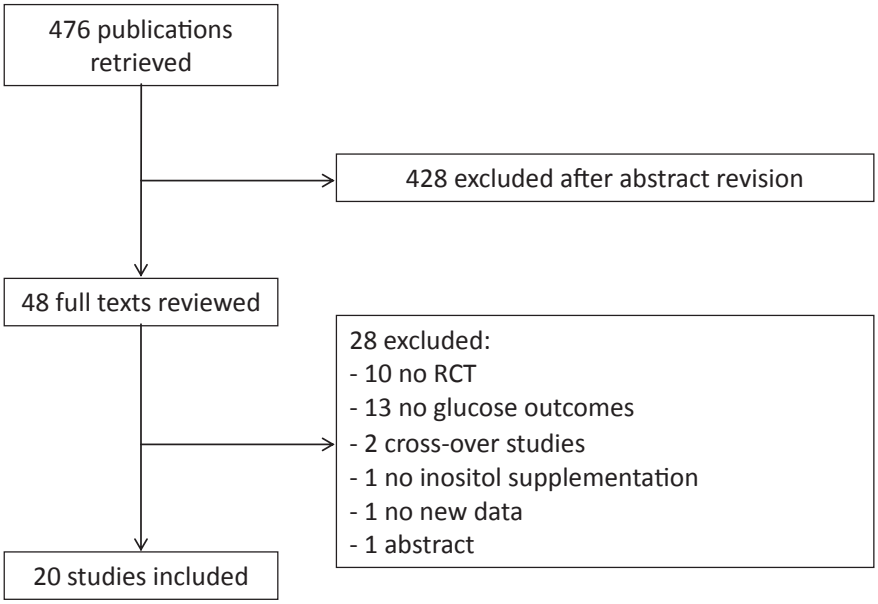

Fig. 1. Flow chart of search results.

Table 1
Characteristics of included studies.

Author	Year (country)	Inclusion criteria	Treatment duration	Drug and daily dose	N	Age	BMI (kg/m^2)	Fasting plasma glucose (mmol/l)	HOMA-IR (mUI/l*mmol/l)	HbA1c (%)	Study excluded in the sensitivity analysis	Reasons for exclusion
Nestler	1999 (Venezuela)	PCOS 18–40 years BMI > 28 kg/m^2	6–8 wk	DCI 1200 mg	22	29	31.3	4.77	–	–	No	
				Placebo	22	26	31.0	5.27	–	–		
Davis	2000 (USA)	BMI > 30 kg/m^2 IGT Stable weight for 6 m	28 d	Acaloric drink + Pinitol 20 mg/kg/d	12	51 ± 12	–	7.6	–	6.8	No	
				Placebo	10		–	7.8	–	6.8		
Iuorno	2002 (Venezuela)	PCOS 18–40 years BMI 20–24.4 kg/m^2	6–8 wk	DCI 600 mg	10	28.2	22.4	4.8	–	–	No	
				Placebo	10	26.5	22.1	4.65	–	–		
Campbell	2004 (USA)	>50 years	6 wk	Diet + acaloric drink + Pinitol 2000 mg	8	66	–	5.36	–	–	No	
				Diet + acaloric drink	8	65	–	5.26	–	–		
Kim	2005 (Korea)	T2DM OAD	13 wk	Diet + Pinitol 1200 mg	15	59.9	24.4	8.72	6.43	8.87	No	
				Diet + lactose	15	61.7	23.8	8.79	6.44	8.79		
Genazzani	2008 (Italy)	PCOS Overweight	12 wk	Folic acid 200 μg + MI 2000 mg	10	–	29	4.86	2.8	–	No	
				Folic acid 200 μg	10	–	27.8	–	2.6	–		
Constantino	2009 (Italy)	PCOS	12–16 wk	Folic acid 400 μg + MI 4000 mg	23	28.8	22.8	4.87	–	–	No	
				Folic acid 400 μg	19	27.1	22.5	4.72	–	–		
Choi	2011 (Korea)	FPG 5.5–8.3 mmol/l	8 wk	Pinitol 1140 mg	20	45.9	24.61	6.98	1.82	–	No	
				Lactose 2000 mg	20	41.7	25.1	6.91	1.74	–		
Corrado	2011 (Italy)	GDM Caucasian	Until delivery	Folic acid 400 μg + MI 4000 mg	28	28.7	–	5.5	6.9	–	No	
				Folic acid 400 μg	56	28.4	–	5.4	7.4	–		
Giordano	2011 (Italy)	Postmenopausal women MetS	6 m	Hypocaloric diet + MI 4000 mg	40	55.6	31.5	6.2	9.4	–	Yes	Differences in protocol vs published paper
				Hypocaloric diet + placebo	40	55.0	30.7	6.4	10.6	–		
Cho	2012 (Korea)	preDM, IFG	9 wk	Pinitol 1140 mg	33	52.63	24.74	6.2	6.1	5.54	No	
				Starch 2000 mg	33	55.17	25.4	6.1	5.1	6.19		
Dona	2012 (Italy)	PCOS	12 wk	MI 1200 mg	18	23.5	21.6	4.79	1.60	–	No	
				Placebo	8	23.6	21.9	4.73	1.40	–		
Kim	2012a (Korea)	PreDM (IFG and/or IGT)	12 wk	Pinitol 1200 mg	12	45.3	27.1	6.17	–	6.01	No	
				Placebo	11	47.2	24.1	6.0	–	6.01		
Kim	2012b (Korea)	DM OAD ≥ 3 m 20–75 years HbA1c > 6.5%	12 wk	Pinitol 1200 mg	33	56.3	25.3	10.31	–	8.38	No	
				Placebo	33	52.9	26.13	9.55	–	8.41		
Santamaria	2012 (Italy)	Postmenopausal women 50–60 years MetS	12 m	Hypocaloric diet + MI 4000 mg	40	55.6	31.5	6.2	9.4	–	No	
				Hypocaloric diet + placebo	40	55	30.7	6.39	10.6	–		
Artini	2013 (Italy)	PCOS Overweight	12 wk	Folic acid 400 μg + MI 2000 mg	25	34.9	26.5	–	2.5	–	No	
				Folic acid 400 μg	25	36.2	31.6	–	2.5	–		
D'Anna	2013 (Italy)	Pregnant women: RF for T2DM Prepregnancy BMI < 30 kg/m^2 FPG < 126 mg/dl Random plasma glucose < 200 mg/dl Singleton pregnancy	aprox 26 wk	Folic acid 400 μg + MI 4000 mg	99	31	22.8	–	1.36	–	Yes	Analysis defined as intention-to-treat, but results given per protocol
				Folic acid 400 μg	98	31.6	23.6	–	1.38	–		

Matarrelli	2013 (Italy)	GDM FPG ≥ 5.1–7 mmol/l	aprox 27.3 wk	D + E + Folic acid 400 μg + MI 4000 mg	36	33.0	23.5	5.4	–	–	No		
			aprox 23.5 wk	D + E + Folic acid 400 μg	39	33.8	24.7	5.4	–	–			
D'Anna	2015 (Italy)	Prepregnancy BMI > 30 kg/m^2 Singleton pregnancy	Until delivery, aprox 25–26 wk	Folic acid 400 μg + MI 4000 mg Folic acid 400 μg	110 110	30.9[a] 31.7[a]	33.8[a] 33.8[a]	4.6 4.6	3.0 3.4	– –	Yes		Analysis defined as intention-to-treat but performed per protocol for perinatal outcomes
Hernández Mijares	2015 (Spain)	DM 40–73 years BMI 20–40 kg/m^2	12 wk	4 g Pinitol + 0.45 g MI + DCI + 0.13 g others Sweetened beverage	19 19	58.8 61.2	32.2 31.5	6.7 7.0	4.31 4.48	6.52 6.19	No		

DM, diabetes mellitus; T2DM, type 2 diabetes mellitus; GDM, gestational diabetes mellitus; PCOS, polycystic ovarian syndrome; RF, risk factor; MetS, metabolic syndrome; FPG, fasting plasma glucose, IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OAD, oral antidiabetic drug; MI, myoinositol; DCI, D-chiroinositol.

[a] Median.

2.7. Additional analyses

The information concerning the risk of bias was used to perform a sensitivity analysis, excluding trials with relevant weaknesses in their design or execution.

Separate analyses were performed for studies conducted in pregnant subjects, patients with PCOS, patients with abnormal glucose homeostasis (prediabetes/diabetes/GDM) and patients receiving an intervention lasting for at least 3 months. The last analysis was not prespecified in the protocol.

3. Results

3.1. Search results

The search retrieved 476 abstracts. As depicted in the flow chart (Fig. 1), 20 studies including 1239 patients fulfilled the inclusion criteria [6–10,12–26].

3.2. Overall studies characteristics

Six studies were conducted in patients with PCOS (202 subjects), seven in patients with abnormal glucose homeostasis or type 2 diabetes (285 subjects), four in pregnant patients with or without GDM (576 subjects), two in postmenopausal women with metabolic syndrome (160 subjects) and one in senior subjects (16 subjects). Treatment time ranged from 28 days to 12 months. Ten studies were conducted in Italy, five in Korea, and the rest in US, Venezuela, and Spain. Additional characteristics of included studies are described in Table 1.

3.3. Risk of bias of individual studies

Quality assessment that made studies qualify for inclusion in the sensitivity analysis is reported in Table 1. In summary, three studies were excluded after sensitivity analysis; two because they were planned as intention to treat and some outcomes were only analyzed per protocol [9,14] and one because of substantial differences between the published protocol and the article [21].

3.4. Effects of inositol on glucose-related parameters

Baseline characteristics were well balanced among treatment arms in the different trials. As can be seen in Table 2, significant differences were observed in 5 out of the 8 outcomes measured, namely FPG (MD −0.44 mmol/l, 95% CI −0.65, −0.23), 2 h PG after 75 g OGTT (MD −0.69 mmol/l, 95% CI −1.14, −0.23), abnormal glucose tolerance (AGT, RR 0.28, 95% CI 0.12, 0.66), fasting insulin (MD −38.49 pmol/l, 95% CI −52.63, −24.36), and HOMA-IR (MD −1.96 mmol × mUI/l, CI −2.62, −1.30). No differences were observed in BMI, HbA1c and rate of patients requiring insulin treatment. I^2 figures were high, ranging from 0% for insulin treatment to 97% for fasting insulin.

Subgroup analyses in women with PCOS, pregnant women, patients with or at risk of hyperglycemia and treatment duration ≥3 months are depicted in Table 3. Estimates of treatment effect were not significantly modified in the four subgroup analyses and I^2 figures continued to be high.

3.5. Adverse events of the intervention

Mention to adverse events was present in 13 articles with no sign of seriousness. Authors used expressions such as “None of the women reported an adverse reaction to therapy”.

Table 2
Glucose outcomes after inositol supplementation.

Outcome (units/%)	N studies	N subjects		I^2	Mean difference or RR (CI 95%)	P
		Inositol	Control			
Fasting plasma glucose (mmol/l)	16	524	532	94%	−0.44 (−0.65, −0.23)	<0.0001
2 h PG after 75 gr OGTT (mmol/l)	5	282	283	51%	−0.69 (−1.14, −0.23)	0.003
Abnormal glucose tolerance (%)	3	241	243	63%	0.28 (0.12, 0.66)	0.003
Insulin treatment (%)	3	162	192	0%	0.42 (0.16, 1.15)	0.09
HbA1c (%)	6	122	117	91%	−0.31 (−0.70, 0.09)	0.13
Fasting insulin (pmol/l)	15	318	324	97%	−38.49 (−52.63, −24.36)	<0.00001
HOMA-IR (mUI/l*mmol/l)	10	244	255	96%	−1.96 (−2.62, −1.30)	<0.00001
BMI (kg/m^2)	10	240	226	77%	0.04 (−0.30, 0.38)	0.83

3.6. Publication bias

Funnel plots displayed symmetrical distributions for all the outcomes with exception of fasting insulin and HOMA-IR, where a relative lack of medium sized studies with an unfavorable influence was noted (data not shown).

3.7. Sensitivity analysis

The sensitivity analysis did not affect treatment estimates in any substantial way (data not shown).

4. Discussion

Results from the present meta-analysis confirm that supplementation with inositol has glucose lowering effects that are driven by an improvement in insulin sensitivity independent of weight loss.

Our observations are concordant with the postulated mechanism of action of inositol as part of a phosphoglycan that acts as a messenger of insulin action in peripheral tissues [27]. Early animal models of NIDDM revealed an increased urinary inositol excretion attributed to glycosuria. D-chiro-inositol content in urine and muscle was reduced and attributed in turn to a reduced synthesis of D-chiro-inositol due to the decrease in the precursor myo-inositol [28–31]. However, glycosuria is probably not the single culprit in human studies, since decreased urinary D-chiro-inositol is observed in subjects with insulin resistance [32]. Intriguingly, the altered inositol profile in urine seems much more related to the degree of insulin resistance than to the presence of type 2 diabetes per se [4]. Inositol supplementation has been widely studied in patients with PCOS, a condition where insulin resistance plays a pivotal role. Prior meta-analyses conducted in this population indicate a positive effect of inositol administration in hormonal and reproductive disturbances [33,34].

Table 3
Subgroup analysis.

Outcome (units)	N studies	N subjects		I^2	Mean difference or RR (95% IC)	P
		Inositol	Control			
Hyperglycemic subjects (DM, preDM and GDM)						
Fasting plasma glucose (mmol/l)	9	238	260	97%	−0.6 (−0.98, −0.22)	0.002
2 h PG after 75 gr OGTT (mmol/l)	2	66	68	0%	−0.67 (−1.39, 0.04)	0.07
Abnormal glucose tolerance (%)	1	35	38	NA	0.08 (0.02, 0.31)	0.0003
Insulin treatment (%)	2	63	94	45%	0.37 (0.08, 1.73)	0.21
HbA1c (%)	6	122	117	91%	−0.31 (−0.7, 0.09)	0.13
Insulinemia (pmol/l)	8	203	222	97%	−39 (−61.9, −16.09)	0.0008
HOMA-IR (mUI/l*mmol/l)	7	191	212	97%	−2.41 (−3.44, −1.39)	<0.00001
BMI (kg/m^2)	4	132	132	0%	−0.27 (−0.62, 0.08)	0.13
PCOS						
Fasting plasma glucose (mmol/l)	4	73	59	0%	−0.33 (−0.43, −0.23)	<0.00001
2 h PG after 75 gr OGTT (mmol/l)	1	10	10	NA	−1.58 (−3.28, 0.12)	0.07
Insulinemia (pmol/l)	6	108	94	79%	−36.69 (−47.96, −25.42)	<0.00001
HOMA-IR (mUI/l*mmol/l)	3	53	43	79%	−1 (−1.45, −0.54)	<0.0001
BMI (kg/m^2)	1	10	10	NA	−1.58 (−3.28, 0.12)	0.07
Treatment duration ≥3 months						
Fasting plasma glucose (mmol/l)	9	396	384	96%	−0.56 (−0.88, −0.24)	0.0007
2 h PG after 75 gr OGTT (mmol/l)	5	282	283	51%	−0.69 (−1.14, −0.23)	0.003
Abnormal glucose tolerance (%)	3	241	243	63%	0.28 (0.12, 0.66)	0.003
Insulin treatment (%)	2	134	136	0%	0.18 (0.03, 0.97)	0.05
HbA1c (%)	4	77	74	92%	−0.41 (−1.1, 0.29)	0.25
Insulinemia (pmol/l)	8	190	176	96%	−53.04 (−70.81, −35.28)	<0.00001
HOMA-IR (mUI/l*mmol/l)	7	167	157	96%	−2.13 (−3.07, −1.19)	<0.00001
BMI (kg/m^2)	7	175	161	74%	−0.19 (−0.75, 0.37)	0.51
Pregnancy (GDM prevention and treatment)						
Fasting plasma glucose (mmol/l)	4	265	288	77%	−0.31 (−0.47, −0.16)	<0.0001
2 h PG after 75 gr OGTT (mmol/l)	3	241	243	71%	−0.64 (−1.16, −0.11)	0.02
Abnormal glucose tolerance (%)	3	241	243	63%	0.28 (0.12, 0.66)	0.003
Insulin treatment (%)	3	162	192	0%	0.42 (0.16, 1.15)	0.09
Insulinemia (pmol/l)	1	24	45	NA	−48.6 (−69.82, −27.38)	<0.00001
HOMA-IR (mUI/l*mmol/l)	1	24	45	NA	−1.8 (−2.4, −1.2)	<0.00001

We found a very relevant effect of inositol supplementation on AGT (RR 0.28, CI 0.12–0.66) that is driven by studies conducted in pregnant women as illustrated in subgroup analysis. To date, three meta-analyses have addressed the effects of inositol on glucose outcomes during pregnancy [35–37]. They have analyzed whether supplementation with myo-inositol is safe and effective for prevention of GDM [36], its treatment [35] or both of them [37]. The main difference with this meta-analysis is that we only included published RCTs and our conclusion is similar. Of note, Farren et al. [38] have recently published a randomized controlled trial of inositol supplementation in women with family history of DM (N = 240) with a nonsignificant increase in FPG and GDM incidence. Even when these results are intriguing, their addition to the meta-analysis would not overrule the beneficial effects on GDM prevention (data not shown).

Subgroup analysis in patients with hyperglycemia, showed that the effect of inositol supplementation on FPG and HOMA index was nominally higher in this subgroup. MD in FPG in the overall analysis was −0.44 mmol/l (CI −0.65, −0.23) while in the subgroup of patients with hyperglycemia (diabetes, prediabetes and patients at risk for GDM) was −0.6 mmol/l (−0.98, −0.22). This reduction is similar to that observed with low potency antihyperglycemic drugs, such as alpha-glucosidase inhibitors [39]. These results ask for further and larger studies on hyperglycemic subjects. The lack of effect of inositol on HbA1c may be explained by the presence of only 4 four studies (77 patients) in which inositol supplementation lasted more than 3 months and where HbA1c was assessed. Mean HbA1c reduction observed in this subgroup was −0.41% (−1.1, 0.29), and was likely not significant due to a lack of statistical power but consistent with the observed reduction in FPG achieved with inositol. This figure of HbA1c reduction is also consistent with the one obtained with low potency antihyperglycaemic drugs such as acarbose (−0.77% in HbA1c in subjects with diabetes, non-significant effects in subjects with impaired glucose tolerance) [39,40].

The present meta-analysis, extends available information about the effects of inositol in glucose-related outcomes, being the single study addressing all reported clinical situations (pregnant patients, hyperglycemic subjects, women with PCOS and patients receiving an intervention lasting at least 3 months). Limitations include the presence of high heterogeneity across the different outcomes which are not minimized in the subgroup analyses, so we do not have real clues about its roots. We speculate that dietary intake of inositol (225–1500 mg/day) [41,42] could have an impact especially in studies using supplementation doses in the lower range, which is quite wide (1200–4000 mg/day).

Information concerning potential side effects with inositol treatment is very relevant. Apparently, no serious side effects were observed but only 13 of 20 of the studies mentioned adverse events in their reports, usually without much detail. These results are in line with the review of Carlomagno in 2011 [43] which stated that despite its wide clinical use, there was still scarce information of myo-inositol safety and/or side effects. The main side effect in their review was that the highest dose of myo-inositol (12 g/day) induced mild gastrointestinal side effects such as nausea, flatus and diarrhea. Of special interest are adverse effects during pregnancy, as they can affect both, the mother and the fetus. There is transplacental transfer of inositol [44] and even when it explains less than 10% of fetal inositol content, the situation could differ with the use of pharmacological doses. Although current literature has not reported any adverse effect of inositol on serious outcomes such as perinatal mortality, some trials have reported neutral effects on particular outcomes such as maternal hypertension, caesarean section, macrosomia or neonatal hypoglycaemia [35,36]. In an animal model of GDM, supplementation with myo-inositol at large doses (10 g/kg) had favorable effects on insulin sensitivity and glucose tissue uptake. No side effects were described although apparently not specifically sought [45].

In conclusion, inositol supplementation decreases blood glucose through an improvement in insulin sensitivity that is independent of weight. Taking into account these positive effects on glucose homeostasis, inositol could be considered as a therapeutic agent in conditions of insulin resistance and non-severe hyperglycemia.

However, before using inositol as a therapeutic agent for hyperglycemia two points need clarification. The first one is a thorough assessment of adverse effects described with the use of pharmacological doses of inositol. The second one derives from the high heterogeneity observed across the studies and is the need to characterize the optimal formulation and the target population. Both questions require future randomized controlled trials to be answered.

Funding sources

None.

Conflict of interest

None.

References

[1] Celentano C, Matarrelli B, Mattei PA, Pavone G, Vitacolonna E, Liberati M. Myo-inositol supplementation to prevent gestational diabetes mellitus. Curr Diabetes Rep 2016;16(3):30.
[2] Muscogiuri G, Palomba S, Lagana AS, Orio F. Inositols in the treatment of insulin-mediated diseases. Int J Endocrinol 2016;2016:3058393.
[3] Ortmeyer HK. Dietary myoinositol results in lower urine glucose and in lower postprandial plasma glucose in obese insulin resistant rhesus monkeys. Obes Res 1996;4(6):569–75.
[4] Ortmeyer HK, Huang LC, Zhang L, Hansen BC, Larner J. Chiroinositol deficiency and insulin resistance. II. Acute effects of D-chiroinositol administration in streptozotocin-diabetic rats, normal rats given a glucose load, and spontaneously insulin-resistant rhesus monkeys. Endocrinology 1993;132(2):646–51.
[5] Ortmeyer HK, Larner J, Hansen BC. Effects of D-chiroinositol added to a meal on plasma glucose and insulin in hyperinsulinemic rhesus monkeys. Obes Res 1995;3(Suppl 4):605S–8S.
[6] Nestler JE, Jakubowicz DJ, Reamer P, Gunn RD, Allan G. Ovulatory and metabolic effects of D-chiro-inositol in the polycystic ovary syndrome. N Engl J Med 1999;340(17):1314–20.
[7] Costantino D, Minozzi G, Minozzi E, Guaraldi C. Metabolic and hormonal effects of myo-inositol in women with polycystic ovary syndrome: a double-blind trial. Eur Rev Med Pharmacol Sci 2009;13(2):105–10.
[8] Genazzani AD, Lanzoni C, Ricchieri F, Jasonni VM. Myo-inositol administration positively affects hyperinsulinemia and hormonal parameters in overweight patients with polycystic ovary syndrome. Gynecol Endocrinol 2008;24(3):139–44.
[9] D'Anna R, Di Benedetto A, Scilipoti A, Santamaria A, Interdonato ML, Petrella E, et al. Myo-inositol supplementation for prevention of gestational diabetes in obese pregnant women: a randomized controlled trial. Obstet Gynecol 2015;126(2):310–5.
[10] Kim HJ, Park KS, Lee SK, Min KW, Han KA, Kim YK, et al. Effects of pinitol on glycemic control, insulin resistance and adipocytokine levels in patients with type 2 diabetes mellitus. Ann Nutr Metab 2012;60(1):1–5.
[11] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol 2009;62(10):e1–34.
[12] Matarrelli B, Vitacolonna E, D'Angelo M, Pavone G, Mattei PA, Liberati M, et al. Effect of dietary myo-inositol supplementation in pregnancy on the incidence of maternal gestational diabetes mellitus and fetal outcomes: a randomized controlled trial. J Matern Fetal Neonatal Med 2013;26(10):967–72.
[13] Artini PG, Di Berardino OM, Papini F, Genazzani AD, Simi G, Ruggiero M, et al. Endocrine and clinical effects of myo-inositol administration in polycystic ovary syndrome. A randomized study. Gynecol Endocrinol 2013;29(4):375–9.
[14] D'Anna R, Scilipoti A, Giordano D, Caruso C, Cannata ML, Interdonato ML, et al. myo-Inositol supplementation and onset of gestational diabetes mellitus in pregnant women with a family history of type 2 diabetes: a prospective, randomized, placebo-controlled study. Diabetes Care 2013;36(4):854–7.

[15] Hernández-Mijares ABC, Rovira-Llopis S, Álvarez A, Orden S, Rubio-Puchol O, Víctor V, et al. Chronic consumption of an inositol-enriched beverage ameriolates endothelial dysfunction and oxidative stress in type 2 diabetes. J Functional Foods 2015;18:598–607.
[16] Santamaria A, Giordano D, Corrado F, Pintaudi B, Interdonato ML, Vieste GD, et al. One-year effects of myo-inositol supplementation in postmenopausal women with metabolic syndrome. Climacteric 2012;15(5):490–5.
[17] Dona G, Sabbadin C, Fiore C, Bragadin M, Giorgino FL, Ragazzi E, et al. Inositol administration reduces oxidative stress in erythrocytes of patients with polycystic ovary syndrome. Eur J Endocrinol 2012;166(4):703–10.
[18] Kim H, Lee IS, Kim JM, Hung H, Kang YE, Kim TK, et al. Pinitol does not affect glucose levels, insulin resistance and the adipocytokine in prediabetic individuals – a preliminary study. Curr Top Nutraceutical Res 2012;10(2):111–6.
[19] Cho YBN, Chung H, Jeong T, Lee KT, Jeon S, Kim H, et al. Randomized controlled trial of sajabalssuk (Artemisia Princeps Pampanini) to treat prediabetes. Eur J Integrat Med 2012;4:299–308.
[20] Corrado F, D'Anna R, Di Vieste G, Giordano D, Pintaudi B, Santamaria A, et al. The effect of myoinositol supplementation on insulin resistance in patients with gestational diabetes. Diabet Med 2011;28(8):972–5.
[21] Giordano D, Corrado F, Santamaria A, Quattrone S, Pintaudi B, Di Benedetto A, et al. Effects of myo-inositol supplementation in postmenopausal women with metabolic syndrome: a perspective, randomized, placebo-controlled study. Menopause 2011;18(1):102–4.
[22] Choi JY, Shin SK, Jeon SM, Baek NI, Chung HG, Jeong TS, et al. Dose-response study of sajabalssuk ethanol extract from Artemisia princeps Pampanini on blood glucose in subjects with impaired fasting glucose or mild type 2 diabetes. J Med Food 2011;14(1–2):101–7.
[23] Kim JI, Kim JC, Kang MJ, Lee MS, Kim JJ, Cha IJ. Effects of pinitol isolated from soybeans on glycaemic control and cardiovascular risk factors in Korean patients with type II diabetes mellitus: a randomized controlled study. Eur J Clin Nutr 2005;59(3):456–8.
[24] Campbell WW, Haub MD, Fluckey JD, Ostlund Jr RE, Thyfault JP, Morse-Carrithers H, et al. Pinitol supplementation does not affect insulin-mediated glucose metabolism and muscle insulin receptor content and phosphorylation in older humans. J Nutr 2004;134(11):2998–3003.
[25] Iuorno MJ, Jakubowicz DJ, Baillargeon JP, Dillon P, Gunn RD, Allan G, et al. Effects of d-chiro-inositol in lean women with the polycystic ovary syndrome. Endocr Pract 2002;8(6):417–23.
[26] Davis A, Christiansen M, Horowitz JF, Klein S, Hellerstein MK, Ostlund Jr RE. Effect of pinitol treatment on insulin action in subjects with insulin resistance. Diabetes Care 2000;23(7):1000–5.
[27] Croze ML, Soulage CO. Potential role and therapeutic interests of myo-inositol in metabolic diseases. Biochimie 2013;95(10):1811–27.
[28] Kennington AS, Hill CR, Craig J, Bogardus C, Raz I, Ortmeyer HK, et al. Low urinary chiro-inositol excretion in non-insulin-dependent diabetes mellitus. N Engl J Med 1990;323(6):373–8.
[29] Asplin I, Galasko G, Larner J. Chiro-inositol deficiency and insulin resistance: a comparison of the chiro-inositol- and the myo-inositol-containing insulin mediators isolated from urine, hemodialysate, and muscle of control and type II diabetic subjects. Proc Natl Acad Sci U S A 1993;90(13):5924–8.
[30] Larner J, Huang LC, Schwartz CF, Oswald AS, Shen TY, Kinter M, et al. Rat liver insulin mediator which stimulates pyruvate dehydrogenase phosphate contains galactosamine and D-chiroinositol. Biochem Biophys Res Commun 1988;151(3):1416–26.
[31] Huang LC, Fonteles MC, Houston DB, Zhang C, Larner J. Chiroinositol deficiency and insulin resistance. III. Acute glycogenic and hypoglycemic effects of two inositol phosphoglycan insulin mediators in normal and streptozotocin-diabetic rats in vivo. Endocrinology 1993;132(2):652–7.
[32] Suzuki S, Kawasaki H, Satoh Y, Ohtomo M, Hirai M, Hirai A, et al. Urinary chiro-inositol excretion is an index marker of insulin sensitivity in Japanese type II diabetes. Diabetes Care 1994;17(12):1465–8.
[33] Unfer V, Nestler JE, Kamenov ZA, Prapas N, Facchinetti F. Effects of inositol(s) in women with PCOS: a systematic review of randomized controlled trials. Int J Endocrinol 2016;2016:1849162.
[34] Pundir J, Psaroudakis D, Savnur P, Bhide P, Sabatini L, Teede H, et al. Inositol treatment of anovulation in women with polycystic ovary syndrome: a meta-analysis of randomised trials. BJOG 2018 Feb;125(3):299–308.
[35] Brown J, Crawford TJ, Alsweiler J, Crowther CA. Dietary supplementation with myo-inositol in women during pregnancy for treating gestational diabetes. Cochrane Database Syst Rev 2016;9:CD012048.
[36] Crawford TJ, Crowther CA, Alsweiler J, Brown J. Antenatal dietary supplementation with myo-inositol in women during pregnancy for preventing gestational diabetes. Cochrane Database Syst Rev 2015;(12):CD011507.
[37] Zheng X, Liu Z, Zhang Y, Lin Y, Song J, Zheng L, et al. Relationship between myo-inositol supplementary and gestational diabetes mellitus: a meta-analysis. Medicine (Baltimore) 2015;94(42):e1604.
[38] Farren M, Daly N, McKeating A, Kinsley B, Turner MJ, Daly S. The prevention of gestational diabetes mellitus with antenatal oral inositol supplementation: a randomized controlled trial. Diabetes Care 2017;40(6):759–63.
[39] van de Laar FA, Lucassen PL, Akkermans RP, van de Lisdonk EH, Rutten GE, van Weel C. Alpha-glucosidase inhibitors for patients with type 2 diabetes: results from a Cochrane systematic review and meta-analysis. Diabetes Care 2005;28(1):154–63.
[40] Van de Laar FA, Lucassen PL, Akkermans RP, Van de Lisdonk EH, De Grauw WJ. Alpha-glucosidase inhibitors for people with impaired glucose tolerance or impaired fasting blood glucose. Cochrane Database Syst Rev 2006;(4):CD005061.
[41] Clements Jr RS, Darnell B. Myo-inositol content of common foods: development of a high-myo-inositol diet. Am J Clin Nutr 1980;33(9):1954–67.
[42] Dinicola S, Minini M, Unfer V, Verna R, Cucina A, Bizzarri M. Nutritional and acquired deficiencies in inositol bioavailability. Correlations with metabolic disorders. Int J Mol Sci 2017;18(10).
[43] Carlomagno G, Unfer V. Inositol safety: clinical evidences. Eur Rev Med Pharmacol Sci 2011;15(8):931–6.
[44] Staat BC, Galan HL, Harwood JE, Lee G, Marconi AM, Paolini CL, et al. Transplacental supply of mannose and inositol in uncomplicated pregnancies using stable isotopes. J Clin Endocrinol Metab 2012;97(7):2497–502.
[45] Plows JF, Budin F, Andersson RA, Mills VJ, Mace K, Davidge ST, et al. The effects of myo-inositol and B and D vitamin supplementation in the db/+ mouse model of gestational diabetes mellitus. Nutrients 2017;9(2).