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PCOS

D-Chiro-inositol and its significance in polycystic ovary syndrome: a systematic review

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Abstract

Background. The pathogenesis of polycystic ovary syndrome (PCOS) has been linked to the development of insulin resistance and hyperinsulinemia. The objective of this study is to investigate the effects of insulin sensitising agents such as D-chiro-inositol (DCI) on ovulation and insulin resistance in women with PCOS.

Methods. This was a systematic review done in an Academic Department of Obstetrics and Gynaecology in the UK of all studies published on PCOS and DCI up till May 2010. Patients were women with PCOS receiving DCI or where the relationship between insulin resistance and DCI had been investigated. Ovulation rates and changes in insulin sensitivity were the main outcome measures.

Results. Less DCI-IPG was released in PCOS women compared to controls and this seems to correlate positively with insulin resistance and hyperinsulinemia evident in these patients. DCI administration had beneficial effects on ovulation, anthropometric and metabolic markers in PCOS women by enhancing insulin. The effects of metformin in improving insulin action in PCOS women was achieved though the release of DCI-IPG mediators.

Conclusions. Heterogeneity observed in the methodologies of each study, the scarcity of relevant studies and the small sample sizes used prohibit reliable conclusions to be drawn. Therefore, more studies must be conducted in the future to evaluate accurately the effects of DCI in PCOS.

Keywords: *D-chiro-inositol, DCI, PCOS, polycystic, ovary, syndrome, review*

Introduction

Polycystic ovary syndrome (PCOS) affects 5–10% of women between the age of 12 and 45 years old [1–3]. The current definition requires two or more of the following requirements: chronic ovulatory disorder (oligo-ovulation to anovulation and amenorrhea), presence of hyperandrogenism either manifested in laboratory tests or in clinical symptoms and ultrasound evidence of polycystic ovaries where other causes of anovulation and hyperandrogenism have been ruled out [4–6].

The pathogenesis of PCOS has been linked to the development of insulin resistance and hyperinsulinemia [7–9]. Hence, treatment regimens include insulin-sensitizing agents like metformin, rosiglitazone, pioglitazone, and D-chiro-inositol (DCI). There have been many published reviews concerning the effects of these agents, but none concentrating on DCI [10–12]. This is of particular interest as metformin has a high incidence of gastrointestinal side effects and has not been shown to be as effective as clomiphene for increasing live birth rates, while DCI has been documented of having a good adverse effect profile [10].

DCI is present in small amounts in human tissue and is synthesised via the metabolism of myoinositol (MYO) [13]. Numerous studies have identified that low levels of urine DCI and high levels of urine myoinositol in patients increase the chances of developing insulin resistance [14,15]. DCI is a vital component of inositol phosphoglycan (IPG), a key mediator of insulin action [16].

This review aimed to gather all the relevant information concerning the link between DCI and PCOS and specifically to investigate the effects of DCI on ovulation and insulin resistance in PCOS. It is further aimed to identify fields to which research should be directed in the future.

Materials and methods

Studies eligible for review

Because of the low number of relevant studies, the selection criteria were nonrestrictive and included non-randomised-controlled trials (non-RCTs). Hence, screening the title and abstract of the candidate articles was enough to determine their eligibility for this review.

Finding relevant studies

The MEDLINE (1966–July 2010), EMBASE (1980–2010), and ISI web of knowledge databases were searched using the

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terms ''polycystic ovary syndrome'' and ''D-chiro-inositol'' without any limits/restrictions. All studies obtained were reviewed. The original PDFs of studies obtained from the search were located through direct online links to the files from the search results, for example through ''Science Direct'' or through indirect links provided by the electronic library resource gateway of the University of Nottingham. A manual search of references from all the studies was also conducted to identify any other potentially relevant studies. The Cochrane database was also used to identify any relevant reviews or meta-analyses. The search criterion ended in July 2010. The search findings were independently double-checked by the second author (MG).

Methodological quality assessment

The methodological quality of the studies was determined by their internal validity which depended on the following five factors: randomization, allocation concealment, blinding, relevant outcome measures and description of an acceptable withdrawal/drop-out rate (Figure 2).

Results

Selecting the relevant studies

Figure 1 demonstrates the selection process of the relevant papers. The initial literature search done through MEDLINE via PubMed yielded 19 relevant papers. From these, nine were reviews of the literature which mainly concentrated on the effects of insulin sensitizers for the treatment of PCOS (predominantly metformin). There was no review exploring specifically the effects of DCI in PCOS. Two articles were further excluded because they did not aim to explore the association between DCI and PCOS. Searching through the Cochrane, EMBASE, ISI web of knowledge databases and hand searching of the references of relevant manuscripts did not yield additional papers.

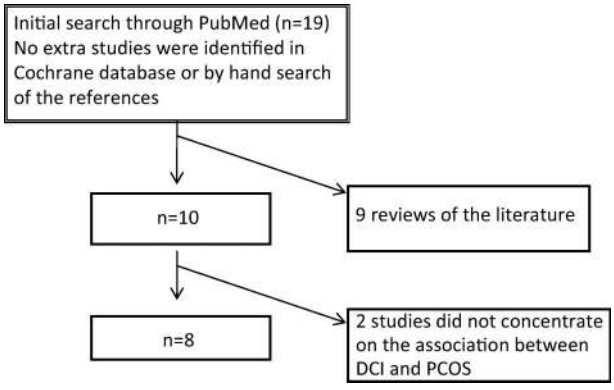

Figure 1. A flow chart summarising the selection process.

General characteristics of studies included

Eight articles identified from the literature were relevant (involving 479 participants) [17–24]. Four of these directly described the effects of administration of DCI on ovulation as well as endocrine and metabolic variables in PCOS [18,20,22,23]. The remaining four articles explored the relationship between insulin and release of DCI-containing IPG and did not look at the effects on ovulation [17,19,21,24]. Table I summarizes the main characteristics of the aforementioned articles.

Table II illustrates the main characteristics of each study. Four of eight studies had scored less than 4/5 for internal validity and were hence classified as LQ [17,20,21,24]. The remaining four studies scored 4/5 or more and were classified as HQ [18,19,22,23]. All of the studies scored 4/5 for descriptive validity, except Baillargeon et al. [19], which scored 3/5. Seven of eight had significant results and proved their hypotheses except Cheang et al. [20], which had a small sample size ($n = 11$) and was prematurely terminated.

The four studies describing the effects of DCI administration were double-blinded, RCTs involving a placebo [18,20,22,23]. Iuorno et al. [22] included 20 lean women (BMI, 20–24.4 kg/m^2) diagnosed with PCOS, whereas Gerli et al., Nestler et al., and Cheang et al., included 283, 44, and 11 obese, PCOS women respectively (BMI $>$ 28 kg/m^2). The mean age of the participants in the four studies was similar (late 20s) [18,20,22,23]. Inclusion criteria common to these studies were oligo-amenorrhea (defined as less than eight menstrual cycles per year) and hyperandrogenism. Women with other endocrine pathologies like thyroid dysfunction, hyperprolactinemia, or diabetes mellitus were excluded [18,20,22,23].

The intervention varied in the four studies: Gerli et al. involved administration of 100 mg of DCI twice daily, Iuorno et al. and Nestler et al. used 600 mg and 1200 mg of

Methodological Quality Assessment

A study was classified as high quality (HQ) if it scored 4/5 or more for the internal validity. Studies scoring less than 4/5 were classified as low quality (LQ). Descriptive validity of each study was determined by checking if the groups were similar at baseline and that description of any adverse effects, duration of the trial, index and control interventions and selection criteria was adequate. Furthermore, statistical validity was assessed by checking that the sample size was described and that point estimates and measures of variability were included in the results. Finally, and most importantly, the results of the studies were assessed in order to determine whether the authors have fulfilled their study objectives and hypotheses. As with searching for the relevant studies, methodological quality assessment was also carried out independently by the second author (MG).

Figure 2. Methodological quality assessment.

Table I. The main characteristics of the studies included in the review.

Study	Number of participants (*n*)	Inclusion criteria	Study design	Main outcome measure	Main findings
Baillargeon et al. [17]	16	Inclusion: oligomenorrhea, hyperandrogenism Exclusion: hyperprolactinemia, thyroid dysfunction, late-onset adrenal hyperplasia.	Case–control study	WHR, BMI, total testosterone, fasting insulin, plasma DCI, uCL of DCI, $AUC_{insulin}$, AUC_{DCI}, SBP, DBP	The coupling between insulin action and release of DCI-IPG mediator is impaired in obese PCOS women.
Nestler et al. [18]	44	Inclusion: oligomenorrhea and hyperandrogenemia or hirsuitism, BMI > 28. Exclusion: diabetes mellitus, thyroid dysfunction, hyperprolactinemia, on any medication for previous 2 months.	RCT	Ovulation (serum progesterone), BMI, WHR, Reproductive hormones (total and free testosterone, DHEAS etc), Metabolic Markers (Fasting glucose and insulin, SBP, DBP, cholesterol, LDL, HDL,TG)	DCI enhances insulin action in PCOS women and hence improves ovulation and levels of metabolic markers.
Baillargeon et al.,(2004) [19]	19	Inclusion: women 18–35 years of age, chronic oligomenorrhea, hyperandrogenemia. Exclusion: hyperprolactinemia, thyroid dysfunction, late-onset adrenal hyperplasia, diabetes mellitus, on any medication in the previous 2 months.	RCT	WHR, BMI, total and free testosterone, fasting insulin, $AUC_{insulin}$, $AUC_{DCI-IPG}$, SBP, DBP	Metformin may improve insulin action in PCOS women by improving release of DCI-IPG mediators
Cheang et al. [20]	11	Inclusion: women 18–40 years of age, chronic oligomenorrhea, hyperandrogenemia. Exclusion: hyperprolactinemia, thyroid dysfunction, late-onset adrenal hyperplasia, diabetes mellitus, oral contraceptives.	RCT	BMI, WHR, total and free testosterone, fasting insulin and glucose, Plasma DCI, S_i, $AUC_{insulin}$, $AUC_{glucose}$, $AUC_{DCI-IPG}$	Increase in DCI-IPG may improve insulin sensitivity in PCOS women
Baillargeon et al. [21]	37	Inclusion: oligomenorrhea, hyperandrogenism. Exclusion: hyperprolactinemia, thyroid dysfunction, late-onset adrenal hyperplasia.	Case–control study	BMI, WHR, free testosterone, fasting insulin, plasma DCI and MYO, uCL of DCI, S_i, $AUC_{insulin}$, $AUC_{DCI-IPG}$, SBP, DBP	Increased urinary clearance of inositols might decrease the release of DCI-IPG mediator contributing to insulin resistance and hyperinsulinemia.
Iuorno et al. [22]	20	Inclusion: oligomenorrhea, hyperandrogenemia, BMI <24.5. Exclusion: hyperprolactinemia, thyroid dysfunction.	RCT	Ovulation (serum progresterone), BMI, WHR, total and free testosterone, TG, LDL, SBP, DBP, $AUC_{insulin}$	DCI improves serum insulin and androgen concentrations and blood pressure in lean PCOS women.
Gerli et al. [23]	283	Inclusion: PCO on ultrasound, oligomenorrhea, amenorrhea, age less than 35, clinical and biochemical hyperandrogenism. Exclusion: Congenital adrenal hyperplasia, thyroid dysfunction, hyperprolactinemia.	RCT	Ovulation (serum progesterone), BMI, WHR, Metabolic Markers (insulin, glucose, cholesterol, VLDL, LDL, HDL), pregnancy	Inositol produces beneficial effects in ovarian function in PCOS women
Baillargeon et al. [24]	49	Inclusion: Oligomenorrhea and hyperandrogenemia or hirsuitism. Exclusion: diabetes mellitus, thyroid dysfunction, hyperprolactinemia, on any medication in the previous 2 months.	Case–control study	BMI, WHR, total and free testosterone, fasting insulin, plasma MYO and DCI, uCL of DCI, $AUC_{insulin}$, $AUC_{DCI-IPG}$, S_i, SBP, DBP	Increase in urinary clearance of DCI and impaired release of DCI-IPG in response to insulin are key features in PCOS.
TOTAL	479				

BMI, body mass index; WHR, waist hip ratio; uCL, urinary clearance; AUC, area under the curve; SBP, systolic blood pressure; DBP, diastolic blood pressure; DHEAS, dehydroepiandrosterone sulfate; VLDL, very-low-density lipoprotein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglyceride.

Table II. The assessment of methodological quality of the selected studies.

N	Study	Internal validity						Descriptive validity					Statistical validity		Positive results*
		A	B	C	D	E	Score	F	G	H	I	J	K	L	
1	Baillargeon et al. [17]	N	N	N	Y	Y	2/5, LQ	N	N	Y	Y	Y	Y	Y	Y
2	Nestler et al. [18]	Y	Y	Y	Y	Y	5/5, HQ	Y	N	Y	Y	Y	Y	Y	Y
3	Baillargeon et al. [19]	Y	N	Y	Y	Y	4/5, HQ	N	N	Y	Y	Y	y	Y	Y
4	Cheang et al. [20]	Y	N	N	Y	Y	3/5, HQ	Y	N	Y	Y	Y	Y	Y	N
5	Baillargeon et al. [21]	N	N	N	Y	Y	2/5, LQ	Y	N	Y	Y	Y	Y	Y	Y
6	Iuorno et al. [22]	Y	Y	Y	Y	Y	5/5, HQ	Y	N	Y	Y	Y	Y	Y	Y
7	Gerli et al. [23]	Y	N	Y	Y	Y	4/5, HQ	Y	N	Y	Y	Y	Y	Y	Y
8	Baillargeon et al. [24]	N	N	N	Y	Y	2/5, HQ	N	N	Y	Y	Y	Y	Y	Y

A, adequate randomization; B, allocation concealment; C, blinding; D, relevant outcome measures; E, withdrawal/drop-out rate described and acceptable; F, groups similar at baseline. G, adverse effects described? H, duration of trial described? I, index and control interventions explicitly described; J, selection criteria described? K, was the sample size in each group described?; L, were point estimates and measures of variability and presented for primary outcome measures? N, No; or not applicable. Y, Yes. HQ, high quality; LQ, low quality.
*Y or N if the objectives/ hypotheses of the study have been achieved/proven.

DCI once daily respectively, whereas Cheang et al. used 1500 mg of DCI twice daily as the main intervention. Duration of treatment also varied in the four trials ranging from 6 to 8 weeks in Nestler et al., Iuorno et al., and Cheang et al. to 16 weeks in Gerli et al. [18,20,22,23]. The above are all presented in Table I.

Ovulation

The main outcome measure in the studies investigating the effects of DCI supplementation was ovulation [18,22,23]. This was determined by measuring serum progesterone levels weekly. Nestler et al. [18] found that 19 of 22 women with PCOS ovulated compared to 6 of 22 in the placebo group ($P < 0.001$). In another study, 6 of 10 lean PCOS women in the DCI group ovulated in comparison with 2 of 10 in the placebo group ($P = 0.17$) [22]. Finally, Gerli et al. [23] found that the DCI group had both significantly greater ovulation frequency and shorter time to first ovulation.

Insulin resistance/sensitivity

Studies on the relationship between insulin sensitivity and DCI revealed variable results although the majority demonstrated that the DCI-IPG system was linked to insulin sensitivity and that appeared to be a defect in PCOS.

Cheang et al. [20] did not reveal any significant improvement in insulin sensitivity (S_i) in women treated with DCI. Some women who received DCI did not have an increase in DCI-containing IPG (DCI-IPG), whereas some women who received a placebo demonstrated an increase in the release of DCI-IPG. Finally, a significant positive correlation was observed between DCI-IPG release and S_i in PCOS women (regardless of DCI or placebo treatment) [20].

On the other hand, four studies compared the release of DCI-IPG between PCOS women and healthy controls at different concentrations of insulin. These either showed that the DCI-IPG system was linked to insulin sensitivity or that there appeared to be a defect in PCOS [17,19,21,24]. One cross-sectional case–control study involved 16 participants who were exposed at two different concentrations of insulin [17]. In this study, patients with PCOS were significantly more obese and insulin resistant than the controls, at baseline [17]. At low and high insulin levels, DCI-IPG release increased significantly in healthy subjects initially before it returned to baseline levels. On the other hand, DCI-IPG release in patients with PCOS was unchanged regardless the increase in insulin levels [17]. Therefore, DCI-IPG release was significantly lower in PCOS women compared to those in healthy subjects, hence suggesting reduced insulin sensitivity secondary to defects in DCI-IPG mediating effects on insulin action [17].

Two case–control studies investigated the relationship between urinary clearance of DCI (uCL_{DCI}), DCI-IPG levels ($AUC_{DCI\text{-}IPG}$), and S_i [21,24]. Baillargeon et al. [21] involved 37 participants (27 women suffering from PCOS and 10 participants that had mild thyroid problems as controls), whereas Baillargeon et al. [24] involved 49 participants (23 patients with PCOS and 26 healthy controls). Both studies had significant positive correlation between $AUC_{insulin}$ (serum concentration of insulin) and uCL_{DCI} after an oral glucose tolerance test (OGTT) in PCOS women. Also, uCL_{DCI} was significantly higher in PCOS than the control group in both studies [21,24]. Furthermore, Baillargeon et al. [21] found that $AUC_{insulin}$ was increased by 65% and $AUC_{DCI\text{-}IPG}$ was reduced by 60% in PCOS women compared to the control group and these findings were statistically significant. Similar significant observations were also observed in Baillargeon et al. [24], where $AUC_{DCI\text{-}IPG}$ was reduced while $AUC_{insulin}$ was increased in PCOS women hence $AUC_{DCI\text{-}IPG}$: $AUC_{insulin}$ ratio was decreased in PCOS. Thus, insulin resistance and the subsequent hyperinsulinemia (high $AUC_{insulin}$) are associated with a decreased release of serum DCI-IPG mediator of insulin action (low $AUC_{DCI\text{-}IPG}$). Both experimental and control groups in Baillargeon et al. [24] had a similar MYO concentration and uCL_{MYO} indicating that the defect in PCOS involves DCI and not MYO. Finally, there was a significant negative correlation between total testosterone levels and S_i in women with high uCL_{DCI} (regardless PCOS or not) [24]. From that, one can speculate that total testosterone is significantly associated with S_i only in high uCL_{DCI}. Indeed Baillargeon et al. [24] indicated that the interaction between uCL_{DCI} and total testosterone was one of the best independent predictors of insulin resistance.

Baillargeon et al. [19] hypothesized that the positive effects of metformin on insulin action are partly brought about by an increase in DCI-IPG. Of the 19 obese PCOS

Table III. Studies primarily reporting key clinical outcomes of interest in PCOS.

Study	Number of participants (*n*)	Study design	Ovulation	Anthropometric measurements (BMI, WHR)	Cycle regularity
Nestler et al. [18]	44	RCT	DCI Group: 86.3% ovulated, Placebo Group: 27.3% ovulated, Statistical significance ($P < 0.001$)	BMI (kg/m^2): DCI Group: at baseline = 31.3 ± 2.4, after DCI = 31.5 ± 2.4 ($P > 0.05$). Placebo Group: baseline = 31.0 ± 2.2, after placebo = 31.0 ± 2.2 ($P > 0.05$) WHR: DCI Group: at baseline = 0.86 ± 0.05, after DCI = 0.84 ± 0.06 ($P < 0.001$), Placebo Group: at baseline = 0.84 ± 0.08, after placebo = 0.85 ± 0.08 (P > 0.05)	No data
Iuorno et al. [22]	20	RCT	DCI Group: 60% ovulated, Placebo Group: 20% ovulated, No statistical difference (p = 0.17)	BMI (kg/m^2): DCI Group; at baseline = 34.1 ± 1.8, after DCI = 33.1 ± 1.7 ($P<0.05$), Placebo Group: at baseline = 34.1 ± 1.2, after placebo = 33.6 ± 1.0 (P > 0.05) WHR: DCI Group: at baseline = 0.87 ± 0.12, after DCI = 0.78 ± 0.006 ($P < 0.05$), Placebo Group: at baseline = 0.88 ± 0.001, after placebo = 0.88 ± 0.002 (P > 0.05)	No data
Gerli et al. [23]	283	RCT	DCI Group: 23% ovulated; Placebo Group: 13% ovulated; Statistically significant ($P < 0.01$)	BMI (kg/m^2): DCI Group: at baseline = 35.2, after DCI = 34.6 ($P = 0.03$); Placebo Group: at baseline = 35.3, after placebo = 35.6 ($P = 0.04$) WHR: DCI Group: at baseline = 0.88, after DCI = 0.88 ($P > 0.05$), Placebo Group; at baseline = 0.88, after placebo = 0.88 ($P > 0.05$)	No data
TOTAL	347				

women involved in this RCT, 10 received 500 mg metformin thrice daily while 9 received a placebo treatment. After the treatment, waist hip ratio (WHR), free testosterone, and systolic and diastolic BP decreased significantly in the metformin compared to the placebo group [19]. $AUC_{insulin}$ during an OGTT decreased significantly in the metformin group. Thus, $AUC_{DCI\text{-}IPG}$: $AUC_{insulin}$ ratio after metformin therapy increased significantly compared to the placebo group. In other words, the percentage release of DCI-IPG per unit of insulin, increased by a factor of 3 in the metformin, compared to the placebo group [19].

The results in the above-mentioned studies have thus demonstrated a link between DCI-IPG mediator of insulin action and insulin resistance. Serum DCI-IPG levels are lower in PCOS women leading to insulin resistance and hyperinsulinemia which is strongly associated with the pathophysiology of PCOS. As anovulation in women with PCOS is linked with insulin resistance, these experimental data support a role for DCI in the treatment of anovulatory infertility in PCOS.

Other variables (reproductive steroids and anthropometric measures)

The levels of reproductive steroids (e.g. testosterone) and other metabolic markers (e.g. blood pressure, cholesterol, etc.) were recorded in the four primary studies investigating the effects of DCI administration [18,20,22,23].

Three studies demonstrated a significant reduction in circulating androgens, serum insulin, systolic and diastolic BP, and serum triglyceride concentrations after administration of DCI in PCOS women [18,22,23]. In addition, Gerli et al. [23] found that HDL concentration was increased significantly in the DCI group.

On the other hand, Cheang et al. [20] did not reveal any statistically significant difference in these variables in the DCI group compared to the placebo group.

Key clinical outcomes of interest in PCOS

In order to arrive at a useful summary on the effectiveness in PCOS population on the main clinical outcomes of interest such as resumption of ovulation and weight reduction, we further limited the analysis to only the studies where these clinical outcomes had been reported [18,22,23]. The mean dose of DCI used in these studies was 600 mg but ranged from 100 to 1200 mg. The total number of women in these studies was 347. Cycle regularity was another important outcome measure that we sought to identify. Unfortunately, the studies currently available to us failed to provide that data [18,22,23]. In the three studies isolated, more women with PCOS ovulated after administration of DCI compared to those on the placebo. In two of these three

studies these differences were statistically significant [18,23].

BMI was overall improved after administration of DCI with two of three studies reporting significant decrease [22,23]. Similarly, WHR was significantly improved in two of the three studies [18,22].

Discussion

It has been demonstrated that PCOS women who received DCI enjoyed lower free and total cholesterol levels, lower blood pressure, increased insulin sensitivity, and a higher frequency of ovulation [18,22,23]. Furthermore, DCI administration in PCOS women seems to improve BMI, WHR and both systolic and diastolic blood pressure, hence improving the overall physical health of the patient [18,22,23].

In general, the trials selected demonstrated that ucL_{DCI} increases in PCOS and obese women and is associated with a decrease in DCI-IPG release and hyperinsulinemia (increase in AUC_{DCI}). Also, an inverse correlation between ucL_{DCI} and S_i is evident in the trials [17,21,24]. In brief, women suffering from PCOS have low serum DCI concentration which is a key component of DCI-IPG, a mediator of insulin action. This ultimately leads to a decrease in insulin action hence insulin resistance and hyperinsulinemia. Having established a strong association between insulin resistance and PCOS, restoring insulin sensitivity (in this case by administration of DCI) can lead to improved ovulatory function and decreased serum androgen concentration [25,26].

The main strength of this review is that it is the first one focusing on the effects of inositol and, more specifically, DCI administration in PCOS women. To minimize any potential bias, the selection of the relevant articles as well as methodological quality assessment were carried out independently by two authors. This ensured that the literature concerning the relationship between DCI (whether as a supplement or as a naturally occurring metabolite) and PCOS was selected and screened efficiently. Furthermore, the methodological assessment allowed us to evaluate the validity of the information obtained from each study.

On the other hand, this review has a few weaknesses, mainly arising because of the small amount of studies currently available. Some trials comparing the release of DCI-IPG between PCOS women and healthy controls at different concentrations of insulin were cross-sectional case–control studies and according to the methodological quality criteria used for this review, were of LQ [17,21,24]. Furthermore, the controls used in Baillargeon et al. had mild thyroid problems and might not be representative of the community. Thus, more HQ (RCTs) studies involving larger and more representative samples must be conducted in the future in order to be able to draw reliable conclusions.

There were only four clinical trials in the literature and these investigated the effects of DCI in PCOS women in the short term (6–16 weeks) [18,20,22,23]. Three of these studies were conducted by the same group of researchers who were advocates for DCI as a drug for women with PCOS, thus conflict of interest might have been introduced in these studies [18,20,22]. Only Gerli et al. had a relatively large number of participants ($n = 283$), whereas the sample size in the remaining three clinical trials was small. We therefore suggest that more clinical trials must be carried out in the future, by many different research groups, involving larger samples and extending for a longer period of time so that long-term effects (and potentially complications) can be assessed.

Heterogeneity in these studies may be a problem since three trials examined the effects of DCI in obese PCOS women [18,20,23], while one trial involved lean PCOS women. Heterogeneity was also introduced in the dosing regimens used, the duration of follow up as well as the selection criteria of each primary study.

Conclusion

This was the first review of the literature focusing on the relationship between DCI and PCOS. In summary, it showed that DCI was an effective intervention on the key clinical parameters of interest to women with PCOS such as resumption of ovulation and weight reduction. Although the connection between DCI and PCOS has been well established for more than a decade, a surprisingly small number of studies have been published. Therefore, more large-scale and long-term RCTs must be conducted to fully appreciate the effects of DCI in women suffering from PCOS. Lastly, we believe that research concerning the effects of DCI in PCOS has not been conducted properly for a drug that could potentially be an important alternative to metformin in overweight women and those who cannot tolerate it.

DCI was however discontinued from development by the company that conducted Phase I and Phase II studies in both women with PCOS and women with diabetes (Insmed Virginia, USA) in 2002 and it is available as a nutriceutical of varying potency and quality in a number of countries. In a press release from Insmed in 2002 a statement on the company's website (http://investor.insmed.com/releasedetail.cfm?ReleaseID = 125212) reads as follows: ''In recently completed clinical trials in patients with PCOS, INS-1 was safe and well tolerated but did not achieve statistical significance on its primary efficacy measures. Although an overall increase in ovulation rates was not achieved, an increased number of pregnancies occurred in the INS-1 (proprietary name for DCI) treated patients. The company is currently evaluating the clinical relevance of this observation and whether it warrants further investigation'' [27]. The results of this systematic review however, suggest that this further investigation is now warranted.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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