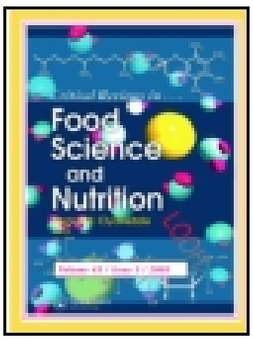

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Effect of Inositol and its Derivatives on Diabetes: A Systematic Review

Ayçıl Özturan[a], Sabriye Arslan[a], Betül Kocaadam[a], Emine Elibol[b*], İdil İmamoğlu[c], Makbule Gezmen Karadağ[a]

[a]Gazi University, Faculty of Health Sciences, Nutrition and Dietetics Department, Emniyet Mah. Muammer Yaşar Bostancı Cad. No:16 06560 Beşevler/Ankara, Turkey

[b]Ankara Yıldırım Beyazıt University, Faculty of Health Sciences, Nutrition and Dietetics Department, 06010, Ankara, Turkey

[c]Nutrition Counseling Center, Çukurambar Mahallesi Muhsin Yazıcıoğlu Cad. No: 8/31 Çankaya/Ankara, Turkey

***Address correspondence to Emine ELİBOL, MSc**

Ankara Yıldırım Beyazıt University, Faculty of Health Sciences, Nutrition and Dietetics Department, Ayvalı Mahallesi, Gazze Caddesi, Milli İrade Kampüsü, 06010 Ankara, Turkey

E-mail: semilay.5252@gmail.com

Phone: +90312 906 1946 Fax: +90 312 906 2967

Ayçıl Özturan, MSc

E-mail: ayciloزturan@gmail.com

Phone: +90312 2162648 Fax: +90 312 2162636

Sabriye Arslan, MSc

E-mail: sabriyebolluk@hotmail.com

Phone: +90312 2162949 Fax: +90 312 2162636

Betül Kocaadam, MSc

E-mail: betulkocaadam@gmail.com

Phone: +90312 2162968 Fax: +90 312 2162636

İdil D. İmamoğlu, MSc, Dietitian

E-mail: info@idilimamoglu.com

Phone: +90 312 287 4345 | Fax: +90 312 287 4340

Assoc. Prof. Makbule Gezmen Karadağ

E-mail: mgezmen@gazi.edu.tr

Phone: +90312 2162638 Fax: +90 312 2162636

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Abstract:

A growing body of research has investigated the association between inositol and diabetes. The purpose of this review is to report through a systematic way the current scientific evidence relating potential benefits of inositol isomers on diabetes/gestational diabetes. The screening of the studies published last decade was performed in 4 databases (Pubmed-Web of Science-The Cochrane Library-Lilacs). Among the 1640 studies identified in the search, only 26 studies had sufficient data to be included in the systematic review. The available literature suggests that inositol seems to be provide improvements in fasting blood glucose and other biochemical results, which are among the most important parameters in diabetic individuals. Although there are some studies demonstrating that inositol may be effective in prevention and treatment of diabetes/ gestational diabetes, conduction of studies with larger sample and longer follow-up duration is required for it to be represented as an effective strategy in management of diabetes.

Keywords: Diabetes, Gestational diabetes, inositol, myo-inositol, D-chiro-inositol

Introduction

Inositol, which is thought to be an essential vitamin that belongs to vitamin group B family, is known as cyclohexane-1,2,3,4,5,6-hexol (Şat and Keleş, 2004; Croze and Soulage, 2013; Muscogiuri et al., 2016). In plants, hexaphosphate form of inositol exists as phytic acid or salts, in other words as phytates. Phytic acid exists in composition of cereals, oilseeds, and legumes, and is the way of phosphorus deposition in many plant cells (Şat and Keleş, 2004; Lee et al., 2012). 99% of inositol is in its myo-inositol form in nature and mammalian cells. 1%, however, exists in its D-chiro-inositol form. Nowadays, inositol has been excluded from being essential after discovery that human body can synthesize myo-inositol to a sufficient extent (Croze and Soulage, 2013).

Abnormalities in metabolism of myo-inositol and D-chiro-inositol, of which inositol is the precursor, lead to insulin resistance and development of diabetic conditions. It has been observed in the studies that, development of diabetic complications is accompanied by intracellular myo-inositol depletion, increased myo-inositol in urine, described as inosituria, and decreased D-chiro-inositol excretion, as well as intracellular sorbitol accumulation (Şat and Keleş, 2004). In studies conducted on insulin sensitivity, a linear relationship was determined between decreased urinary D-chiro-inositol excretion ratio and decreased insulin sensitivity (Şat and Keleş, 2004; Adams et al., 2014; Scioscia et al., 2007a), this situation may be evaluated as a measure of insulin resistance (Suzuki et al., 1994).

Insulin-mimetic effects of Myo-inositol or its isomers is thought to result from that inositol phosphoglycans (IPG), which contain myo-inositol or D-chiro-inositol, act like an insulin mediator. Many studies have investigated glucose use of P-type IPG (P-IPG) in diseases

characterized by insulin resistance (Scioscia et al., 2007b). Inositol phosphoglycans are secondary messengers of insulin (Govindarajan et al., 2015; Unfer et al., 2016). Insulin hormone that binds to its receptor on the cell membrane forms the Insulin-Receptor Substrate (IRS). IRS stimulates a messenger called P13kinase, activating GLUT4. Myo-inositol supports production and activation of P13kinase (Govindarajan et al., 2015). Secondary messengers that develop due to myo-inositol regulate glucose intake by increasing activity of glucose transport proteins, whereas secondary messengers that develop due to D-chiro-inositol, however, support glycogen synthesis (Larner, 2002; Pintaudi et al., 2016).

The objective of this study is to discuss potential benefits of myo-inositol and D-chiro-inositol supplementation on diabetes and gestational diabetes by compiling randomized controlled studies.

Methods

This systematic compilation was written in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria.

This systematic review has made a backward screening of the appropriate publications without any limitations concerning dates. Screening was performed in ‘Pubmed’, ‘Web of Science’, ‘The Cochrane Library’, ‘Lilacs’ databases via 4 databases via access network of Gazi University, and by manual search, articles that were thought to be incompletely screened were examined.

As keywords, ‘inositol OR chiro inositol OR myo inositol’ and ‘diabetes OR insulin resistance OR metformin OR diabetes mellitus OR type 2 diabetes mellitus OR NIDDM OR non insulin

dependent diabetes' were used. The search was performed by using appropriate search method and keywords, as well as conjunctions "and" and "or".

Studies whose full text could be reached with appropriate keywords for search database, which were written in English language between 2007 and 2017, human and animal studies, clinical, randomized controlled, cross-sectional and prospective studies were included in this systematic compilation. *İn vitro* studies, cell studies, gene studies, compilations, meta-analyses, verbal and poster reports represented in congresses, case reports, theses, and articles written in different languages were excluded from the study. During the process of article evaluation, 1640 articles were obtained. Firstly, the titles were examined and were subjected to initial exclusion. After that, 26 investigations which were examined in details in terms of specific expediency were evaluated (Refer to Figure 1: Flow Diagram).

Required data from the studies included in the compilation were evaluated by researchers. Study's design, objective, sample size and age range, study plan/treatment, duration, evaluation criteria and result were compiled normatively. For human studies, Down's and Black Checklist was used, whereas for animal studies, SYRCLE checklist was used and appropriate articles were included in the study.

Results

Researches addressed in the study were performed on humans and animals, researches on diabetes and gestational diabetes were examined separately (Table 1-2). Sample sizes and study groups of the studies vary. When their methods were examined, it was observed that situation determination, case-control, and interventional studies were conducted and when their results were examined, it was determined that obtained data generally resulted in the same way.

When the studies were examined, it was observed that researches were planned and conducted by administration of two forms of inositol, myo-inositol and D-chiro-inositol, for evaluation of effectiveness of inositol. It was observed that biochemical results and anthropometric measures were obtained in groups for evaluation of effectiveness of inositol. When the researches included in the context of the study were examined, inositol was determined to provide improvements in fasting blood glucose and other biochemical results, which are among the most important parameters in diabetic individuals.

Studies in which relationship of diabetes and inositol was examined

Human studies

Considering potential beneficial effects of inositol in diabetic patients, its effectiveness in the patients was evaluated by administering inositol with different doses and for different durations. When the human studies in which relationship of diabetes and inositol was examined, it was determined that the study with the longest duration lasted 3 years and in this study which was performed with diabetic patients with depression, myo-inositol concentration in right dorsolateral prefrontal region was related with the visuospatial injury, and this relationship may be related with gradual weight loss and progressive changes in neural activity that form the basis of visuospatial functions in diabetic patients (Haroon et al., 2009).

When effect of inositol on fasting blood glucose and HbA1c, which is among the most important control markers in diabetes, was examined it was found that in individuals that took inositol derivatives as supplement for 3 months, fasting blood glucose and HbA1c levels were lower (Pintaudi et al., 2016); in obese T1DM patients, when HbA1c, insulin resistance, and BMI were examined after co-administration of folic acid with D-chiro-inositol for 24 weeks, metabolic

control was ensured in the patients (Maurizi et al., 2017). Furthermore, inositol-related concentrations of diabetic individuals were examined by performing urinary tests, urinary chiro- and myo-inositol concentrations were determined to be high in Type-2 DM patients (Hong et al., 2012). When effect of inositol on insulin resistance which is an important diabetes-related condition was examined, it was expressed that myo-inositol and D-chiro-inositol decreased insulin increase after glucose intake in children with high basal insulin levels (Mancini et al., 2016).

In a study examining relationship of inositol with brain in diabetic individuals, hyperglycemia in type 1 DM was determined to be related with glucose and myo-inositol accumulation in cortex and white mater (Heikkilä et al., 2009). In a study in which anti-diabetic properties of inositol on glycemic control and how inflammatory condition and/or endothelial function and/or intracellular redox condition of type 2 DM individuals were affected were investigated, it was reported that inositol supplementation may provide improvement in glycemic control by improving endothelial function and intracellular redox condition in diabetic patients and may provide a positive effect in prevention of atherosclerosis and cardiovascular complications independently from anti-diabetic treatment in diabetic patients (Hernández-Mijares et al., 2015).

Animal Studies

Among animal studies in which relationship of inositol with diabetes was examined, also in studies in which inositol derivatives with different doses and durations were administered as supplement, the study with the longest duration was conducted for 4 months and it was aimed to evaluate the ability of myo-inositol in preventing or delaying development of insulin resistance and of fatty tissue, and to test its capacity in preventing intracellular inositol depletion that was

related with hyperglycemia and/or insulin resistance; and it was determined that myo-inositol supplementation markedly decreased epididymal white fatty tissue and fatty acid synthase activity, it was effective in preventing tissue inositol depletion but could not prevent insulin resistance or obesity (Croze et al., 2015). In another study, birth weight and plasma inositol levels, which are potential indicators for fetal programming, were evaluated and plasma inositol concentrations of pigs with low birth weight were determined to be higher (Nissen et al., 2010). When effect of inositol on some biochemical parameters, which are among the most important control markers in diabetes, was examined, it was demonstrated that it may reduce plasma glucose, C-peptide, glucagon, triglyceride, and BUN in Type 2 DM mice, may improve glucose tolerance, and may enhance insulin immunoreactivity (Yao et al., 2008). Due to positive metabolic effects produced by myo-inositol administered to mice for 15 days, it was expressed that it may be used in treatment of type 2 DM (Marine et al., 2013). It was determined that IG-1, one of the acylated inositol glycans, had insulin-mimetic bioactivity and improved glucose tolerance in obese and non-obese diabetic mice (Suzuki et al., 2014) and it was proposed that myo-inositol may be effective in removal of glucose from adipose tissue via insulin-dependent signaling mechanism and may play a positive role in treatment of obesity-related type 2 diabetes (Antony et al., 2017). Additionally, it has been shown that DCI has a positive role in regulating insulin-mediated glucose intake via P13K/act signal pathway in type 2 diabetic rats (Gao et al., 2016) and it has been reported that concomitant use of inositol and inositol hexakisphosphate (IP6) as supplement may be effective in treatment of type 2 DM and related metabolic disorders by having some effects on lipid and carbohydrate metabolism (Foster et al., 2016). In addition to

this, in another study, D-chiro-inositol was reported to be effective in neuropathies, which are among complications of diabetes (Farias et al., 2011).

Studies in which relationship between gestational diabetes and inositol was examined

It has been reported that synthesis, metabolism and/or renal excretion of MI and DCI are altered in early pregnancy period in pregnant women with GDM (Murphy et al., 2016). In situation determination reports performed for relationship of inositol with diabetes in individuals with gestational diabetes, the relationship of urinary inositol derivatives with blood glucose, HbA1c and birth weight, and it was reported that inositol phosphoglycan type-A had a potential role in maternal metabolism control and fetal growth in individuals with GDM (Scioscia et al., 2007b), and a positive correlation between increased urinary and inositol phosphoglycan type-P (P-IPG) excretion (Scioscia et al., 2007a).

In interventional studies conducted, however, myo-inositol was determined to be effective in improving insulin resistance (Corrado et al., 2011) and reducing GDM incidence and fetal microsomy in individuals with GDM (D'Anna et al., 2013). In a controlled study conducted, it was reported that GDM development incidence was lower, insulin need was lower and birth occurred at later gestational ages. Furthermore, infants' birth weights were determined to be lower and incidence of hypoglycemia was determined to be lower (Matarrelli et al., 2013). In another study, compared to the control group, myo-inositol concentrations in amniotic fluids of the women developed GDM were determined to be significantly higher (Santamaria et al., 2016a).

When effect of inositol on GDM incidence was examined, myo-inositol supplementation began to be administered in first trimester in obese pregnant women was determined to be reduce GDM

incidence via reduction of insulin resistance (D'Anna et al., 2015). In addition to this, it was expressed that inositol supplementation administered from early pregnancy period might reduce GDM incidence in overweight women (Santamaria et al., 2016b).

When animal studies evaluating relationship between gestational diabetes and inositol were examined, only one study was determined in the literature and it was proposed that vitamins B1 and B2 supplementations may be beneficial for treatment/prophhylaxis of GDM (Plows et al., 2017).

Discussion

Inositol in the body is obtained from foods or can be synthesized by insulin in the body. After that, myo-inositol is converted into inositol by insulin in insulin-sensitive tissues such as muscular, hepatic and fat tissues (Hong et al., 2012). Diabetes is a metabolic disorder that causes functional disorders also in brain. Circulatory alterations that may lead to hypo- and hyperperfusion occur in brain in Type 1 diabetic patients (Heikkilä et al., 2009). In a study based on the hypothesis that hyperglycemia is related with alterations in glucose and myo-inositol concentrations in brain, amount of glucose and myo-inositol in brain of diabetic individuals was determined to be higher. In another previous study, similarly, the amount of inositol in dorsolateral regions of diabetic individuals was determined to be higher in diabetic individuals (Haroon et al., 2009). The reason for this has been thought to be that inositol increases together with increasing glucose during hyperglycemia, as myo-inositol is formed of glucose (Heikkilä et al., 2009).

In cases of type II diabetes, insulin resistance, gestational diabetes (GDM) and metabolic syndrome, reduction and extreme urinary excretion of intracellular myo-inositol (MI) and low chiro-inositol (DCI) level and lower urinary excretion are observed (Mancini et al., 2016). In a previous study, it was determined that urinary myo-inositol excretion of diabetic patients was significantly higher compared to healthy individuals and there was no difference in terms of chiro-inositol excretion (Hong et al., 2012). In another previous study, however, in contrary to this, urinary myo- and chiro-inositol excretion was found to be increased in case of insulin resistance (Suzuki et al., 1994; Larner, 2002). These different results were thought to result from difference in methods in researches. An increase in urinary excretions of MI and DCI was determined both in late and early periods of pregnancy (Murphy, 2016; Santamaria et al., 2016b). Marked inositoluria in early periods in GDM may be as a result of a pregnancy-related increase in maternal glomerular filtration rate and of other physiological alterations occurring during pregnancy such as reduction in proximal renal tubular reabsorption. Sodium-dependent myo-inositol transporter 2 (SMIT2), a member of sodium/glucose co-transporter family, actively promotes reabsorption of myo-inositol and D-chiro-inositol in proximal renal tubules and other tissues. SMIT1 transporter, however, is also involved in cellular uptake of MI, and not in cellular uptake of DCI. D-glucose prevents this active inositol transport. Thus, inositoluria occurring at early phase of pregnancy may result from transport of inositols via SMIT2 due to increased glycosuria and/or pregnancy-induced renal tubular impairment. Furthermore, at late pregnancy periods, increased urinary excretion of inositols may also result directly or indirectly from affection of active reabsorption of MI and DCI by increasing of pregnancy hormones. This alteration observed in inositol metabolism in GDM is similarly determined also in pregnant

women with pregnancy-induced hypertension (PIH) (Santamaria et al., 2016b). Increased inositoluria has been thought to be result of increased MI in the amniotic fluid (Santamaria et al., 2016b).

In a previous study, myo-inositol (550 mg) and D-chiro-inositol (13.8 mg) treatment were applied twice daily for 3 months for type 2 diabetic patients. At the end of 3 months, a significant reduction occurred in fasting blood glucose and HbA1c values (Pintaudi et al., 2016). In a study conducted on children, however, inositol uptake and insulin release prior to OGTT were determined to be lower compared to those not received insulin. In the study, it was emphasized that inositol application may be beneficial for patients with high fasting insulin levels (Mancini et al., 2016). In a rat study, however, it was determined that bread enriched with inositol reduced blood glucose (Yao et al., 2008), however, in another study, it was determined that inositol supplementation was effective in preventing tissue inositol depletion, but not in insulin resistance (Croze et al., 2015). In a study in which concomitant inositol and inositol hexakiphosphate supplementation was given, it was emphasized that it may be effective in treatment of type 2 DM (Foster et al., 2016), and in a rat study conducted, similarly, with myo-inositol supplementation, it was emphasized that MI may play a positive role in Type 2 DM (Antony et al., 2017). These results suggest that myo-inositol produces an effect enhancing insulin sensitivity by increasing insulin-mediated glucose uptake and glucose use in peripheral tissues and lowering beta-cell functional disorder-related insulin resistance (Antony et al., 2017).

In addition to this, it has been thought to behave like a PPARγ agonist and to stimulate GLUT translocation and activation via an insulin-mediated pathway in fat tissue (Antony et al., 2017). In another rat study, however, MI supplementation was shown to be beneficial for

treatment/prophylaxis of GDM (Plows et al., 2017). Myo-inositol supplementation (2 or 4 g/day) given to slightly overweight, overweight pregnant women or those with tendency for GDM was reported to reduce GDM incidence (D'Anna et al., 2014; Matarrelli et al., 2013; D'Anna et al., 2015; Santamaria et al., 2016b). Furthermore, myo-inositol supplementation was shown to be effective in improving insulin resistance and reducing need for insulin treatment in individuals with GDM (Corrado et al., 2011; Matarrelli et al., 2013; D'Anna et al., 2015). Although the biochemical mechanisms for benefits of myo-inositol supplementation in patients with GDM or insulin resistance are not still clearly understood, it is likely to have a direct intracellular effect on the enzyme Acetyl CoA carboxylase, which stimulates lipogenesis, and to be used as the precursor of inositol phosphoglycan-containing D-chiro-inositol. It has been suggested that binding of insulin to its specific receptors stimulates intracellular transport of inositol phosphoglycan-containing D-chiro-inositol and explains its role as a mediator in insulin signalization cascade (Matarrelli et al., 2013).

One of the objectives of treatment of diabetic patients is to provide adequate amount of insulin and short-acting insulin in order to provide optimal glycemic control (Maurizi et al., 2017). In some previous studies, it was found that HbA1c (%) values of diabetic patients taking inositol exhibited reduction compared to the healthy group (Pintaudi et al., 2016; Hernández-Mijares et al., 2015; Maurizi et al., 2017). The reason for this was thought to result from that inositol provided improvement in insulin resistance due to its metabolic effect. D-chiro inositol (DCI) may play a role as an insulin sensitizator, as a default tool for intracellular insulin transport (Maurizi et al., 2017). Among rat studies, in a study demonstrating that DCI had a positive effect on hypoglycemic effectiveness, it was emphasized that DCI may promote glycogen synthesis

and may play an important role in metabolic function of insulin via PI3K/Act pathway (Gao et al., 2016).

Oxidative stress has been defined as an important mechanism in development of atherosclerosis, and it is a risk factor for hyperglycemia, hyperlipidemia, and endothelial impairment and may trigger development of endothelial dysfunction (Brownlee, 2001; Steinberg, 1997). In a research, a beverage enriched with inositol was administered to diabetic patients and healthy individuals for 12 weeks. At the end of the research, it was emphasized that its use improved intracellular redox condition and endothelial function in diabetic patients and, hence, may provide an improvement in glycemic control (Hernández-Mijares et al., 2015). In a rat study, however, it was demonstrated that inositol had a neuroprotective effect through reducing reactive oxygen species by its antioxidant property (Hernández-Mijares et al., 2015).

It is well-known that slowing down of growth during fetal development, intrauterine growth retardation (IUGR) and, hence, low birth weight have a vital effect on health in later periods of life. Poor fetal growth has been thought to be increased in adults carrying the risk for a metabolic disorder such as type 2 diabetes (Nissen et al., 2010). In a previous study, plasma myo- and D-inositol concentrations of low birth weight piglets were determined to be higher than other piglets (Nissen et al., 2010). The reason for this has been thought to result from synthesis of myo-inositol from glucose together with increasing glucose in the body and D-chiro-inositol is synthesized from myo-inositol via epimerization in diabetic individuals.

In case of insulin resistance and GDM, abnormalities occur in metabolism of inositol phosphoglycan type-P (P-IPG) (Mancini et al., 2016). It has been thought that in women suffering from GDM, urinary excretion of inositol phosphoglycan is increased and exhibits a

positive correlation with blood glucose levels, also inositol phosphoglycan may play a role not only in glycemic control, but also in fetal growth in women with GDM (Scioscia et al., 2007b). Similarly, it has also been thought that increased urinary excretion of P-IPG in GDM exhibit a positive correlation with insulin resistance and it may play a role also in fetal growth (Scioscia et al., 2007a). In a previous study it was demonstrated that MI supplementation is effective in reducing fetal macrosomia (D'Anna et al., 2013), in another study MI supplementation was reported to be effective both in leading to lower birth weight and delivery at later gestational weeks (Matarrelli et al., 2013). Hypothetical role of P-IPG in insulin resistance is related with enhancement of insulin resistance during pregnancy, the fact that fetal-placental unit is a potential resource of this molecule, with its increased production in case of pre-eclampsia which is strongly related with insulin resistance during normal pregnancy (Scioscia et al., 2007a). It has been suggested that fetus increases production of P-IPG as a response to hyperinsulinism in order to allow glucose to remove in mothers with poorly-controlled diabetes (Scioscia et al., 2007a). Inositol glycans, which are produced upon stimulation of glycosylphosphadytilinositols by insulin, can control activity of large number of insulin effector enzymes. In a study, it was demonstrated that IGs reduced plasma glucose, increased glycogen contents in liver and skeletal muscles and reduced glucose intolerance (Suzuki et al., 2014).

Conclusion and recommendations

Previous human and animal studies support that inositol may reduce blood glucose and increase insulin sensitivity by exhibiting insulin-mimetic activity. The fact that abnormalities in metabolism of inositol may be related with insulin resistance and positive effect of myo-inositol especially in case of intracellular myo-inositol deficiency has been mentioned. However, it is

early for representing inositol as a treatment option for prophylaxis or treatment of type 2 diabetes or gestational diabetes in individuals included in the risk group. Additionally, in relevant studies, effectiveness of inositol's supplementary intake has been evaluated, not via dietary intake. In the future, studies including amount of inositol taken via foods are required. In conclusion, although there are some studies demonstrating that inositol may be effective in prophylaxis and treatment of diabetes/GDM, conduction of studies with larger sample size and longer follow-up duration are required for representation as an effective strategy in management of diabetes.

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Table 1: Studies evaluating relationship between diabetes and inositol

Author-year	Study design	Study objective	Sample size and age range	Study plan/treatment	Duration (scope/intervention observation)	Evaluation criteria	Conclusion
Human studies							
Haroon et al. (2009)	Case control	To investigate whether high myo-inositol level in dorsolateral region is related with visuospatial injury in diabetic patients with depression	DM + depressive (n:18) DM + non-depressive (n:20) Control (n:19) Adult individuals	Both recall and recognition duties of Rey-Osterreith Complex Figure Test (ROCF) were scored. Myo-inositol concentrations in bilateral prefrontal white mater voxels were measured by using proton magnetic spectroscopy spectrum.	3 years (scope)	A1C (Hgb A1C), creatine, Rey-Osterreith Complex Figure Test	Potential relationship pattern between myo-inositol concentration and visuospatial injury in right dorsolateral prefrontal region was observed among health controls and it was reported that this relationship might be related with losing weight and progressive changes in neural activity, which forms the basis of visuospatial

Author-year	Study design	Study objective	Sample size and age range	Study plan/treatment	Duration (scope/intervention observation)	Evaluation criteria	Conclusion
							functions, in diabetic individuals.
Heikkila et al. (2009)	Case control	To evaluate effect of hyperglycemia on regional glucose and other substrate concentrations in non-diabetic and type 1 DM patients.	T1DM (n:17) Non-DM control (n:12) Type 1 diabetic 17 and non-diabetic 12 male control individual (22-43 years old)	Type 1 DM male individuals and non-diabetic controls were compared.	Not Available	N-Acetylaspartate (NAA), creatine, choline, myo-inositol (mI) and glucose levels in frontal cortex, frontal white mater, and thalamus	Hyperglycemia in type 1 diabetes is in relation with glucose and myo-inositol accumulation in cortex and white mater.
Hong et al. (2012)	Case control	To investigate role of urinary chiro and myo-inositol levels as the biological markers of T2 DM.	T2DM (n:101) (27-83 years old) Control (n:212) (21-69 years old)	Urinary chiro and myo-inositol levels of Type 2 DM individuals and healthy controls were compared.	Not Available	Urinary chiro and myo-inositol concentrations, fasting plasma glucose, HDL, LDL, triglycerides, total cholesterol, BUN, creatinine, and HbA1c	Urinary chiro and myo-inositol levels were determined to be high in Type 2 diabetic patients and urinary myo-inositol was suggested

Author-year	Study design	Study objective	Sample size and age range	Study plan/treatment	Duration (scope/intervention observation)	Evaluation criteria	Conclusion
						were measured.	to be a decent marker for prediction of T2 DM.
Hernandez et al. (2015)	Double-blind randomized controlled study	To investigate anti-diabetic properties of a product enriched with inositol derivatives on glycemic control and how inflammatory condition and/or endothelial function and/or intracellular redox condition were affected in type 2 DM individuals.	Type 2 DM individuals: those took beverage enriched with inositol (n:19) those took beverage enriched with sucrose (n:19)	Normocaloric diet for initial 1 month (n:38) All attendants: 2 beverages per day (250 ml + 250 ml) IEB: Includes inositol derivatives and carbohydrate resources SB: Includes sucrose and other carbohydrate resources.	Normocaloric diet for 1 month + intervention - observation for 12 weeks.	BMI, blood pressure, blood glucose, HbA1c, insülin, HOMA-IR, total cholesterol, triacylglycerols, HDL, LDL, apolipoprotein (Apo) AI and B, hsCRP, total ROS and GSH, PMNs IL-6 and TNF-α VCAM-1, ICAM-1 and P-selectin, PMN, glutathione CMFDA	It was reported that IEB supply may provide improvement in glycemic control by improving endothelial function and intracellular redox condition in diabetic patient, and this diet intervention may be effective in prevention of atherosclerosis and cardiovascular complications in diabetic

Author-year	Study design	Study objective	Sample size and age range	Study plan/treatment	Duration (scope/intervention observation)	Evaluation criteria	Conclusion
							patients, independently from anti-diabetic treatment.
Mancini et al. (2016)	Prospective cohort	It was aimed that inositol may be effective in enhancing insulin sensitivity in children with insulin resistance.	23 obese individuals 11.5 ± 2.3 years old	6 months: normocaloric diet. OGTT was performed twice and in the 2nd one, myo-inositol 1100mg + D-chiro-inositol 27.6 mg + folic acid 400 g were administered.	6 months (intervention-observation)	Waist-hip ratio, body fat percentage, blood pressure and total cholesterol, LDL, HDL and triglyceride, glucose, insulin. .	Myo-inositol and D-chiro inositol reduces insulin increase after glucose intake in children with high basal insulin levels.
Pintaudi et al. (2016)	Pilot study	It was aimed to evaluate effectiveness and safety of myo-inositol and D-chiro-inositol treatment	Type 2 DM (n:20) individuals (60.8 ± 11.7 years old)	Myo-inositol (550mg) and d-chiro-inositol (13.8mg) were administered per oral twice per day.	3 months (intervention-observation)	Fasting blood glucose and HbA1c	Blood glucose and HbA1c levels were found to be lower after 3-month treatment.

Author-year	Study design	Study objective	Sample size and age range	Study plan/treatment	Duration (scope/intervention observation)	Evaluation criteria	Conclusion
		in T2 DM.					
Maurizi et al. (2016)	Randomized controlled study	It was aimed to demonstrate that DCI and folic acid may reduce insulin resistance by improving glucose control in extremely overweight or obese T1 DM patients.	Extremely overweight or obese T1 DM patients (n:26) (17–50 years old)	Treatment group: 1 g DCI + 400 mcg folic acid once per day Control group: 400 mcg folic acid Once per day.	24 weeks	BMI, HbA1c, Insulin resistance (IR)	Concomitant administration of DCI and folic acid may provide metabolic control in extremely overweight or obese T1 DM patients.
Animal studies							
Yao et al. (2008)	Animal study	To examine effect of tartary buckwheat bran extract (TBBE) enriched with DCI on blood glucose, lipid profile and insulin immunoreactivity in diabetic mice.	T2 DM Male KK-Ay mice (n:40) Control C57BL/6 mice (n:10)	Different doses to DM mice; 182 mg of TBBE/kg 91 mg of TBBE/kg 45 mg of TBBE/kg	5 weeks (intervention-observation)	blood glucose, plasma C-peptide, glucagon, total cholesterol, triglyceride, and blood urea nitrogen (BUN) levels, insülin immunoreactivity	It was demonstrated that administration of TBBE enriched with DCI may lower plasma glucose, C-peptide, glucagon, triglycerides, and BUN, may improve glucose tolerance

Author-year	Study design	Study objective	Sample size and age range	Study plan/treatment	Duration (scope/intervention observation)	Evaluation criteria	Conclusion
							and may enhance insulin immunoreactivity in Type 2 DM mice.
Farias et al. (2011)	Controlled animal study	To investigate whether D-chiro-inositol has a protective effect on diabetic neuropathy in diabetes-induced experimental animals.	DM+DCI (n:10), DM+non DCI (n:10), euglysemic+non-DCI (n:10)	Diabetic DCI group: 20 mg/kg/12 h Diabetic and normal non-intervention group: NaCl 0.9%; 0.1 ml/10 g/12 h	60 days (intervention-observation)	peak-to-peak amplitude (PPA), nerve conduction velocity (NCV), chronaxy, blood glucose, nerve analyzes	DCI is effective in preventing diabetic neuropathies in STZ-induced diabetes.
Nissen et al. (2011)	Animal study	To evaluate the relationship of type 2 diabetes with birth weight and plasma inositol, potential indicators for fetal programming.	Piglets (n:24)	Plasma inositol levels and type 2 DM relationship of 12 low birth weight 12 normal birth weight piglets	110 days (intervention-observation)	Birth weight, inositol	Plasma myo- and D-inositol concentrations of low birth weight (LBW) piglets were found to be higher compared to other piglets.
Croze	Animal	To	80 mice	intraperit	15 days	Blood	Mice that

Author-year	Study design	Study objective	Sample size and age range	Study plan/treatment	Duration (scope/intervention observation)	Evaluation criteria	Conclusion
et al. (2013)	study	examine metabolic effects of chronic myo-inositol treatment in mice	6g/L myoinositol to drinking water (n:20) Randomly intraperitoneal salt solution or myo-inositol 1,2 mg/gr body weight (n:60)	oneal salt solution: NaCl 0.9%, w/v intraperitoneal myo-inositol: 1,2mg/g drinking water myoinositol: 6g/L	(intervention-observation)	glucose, plasma insulin HOMA-IR T-cholesterol Triacylglycerol Nonesterified fatty acid Plasma adiponectin and leptin Adipocyte count and size insulin secretion test insulin tolerance test	took myo-inositol exhibited an enhancement in glucose tolerance due to enhanced insulin sensitivity. Adipose tissue enlargement of mice that took myo-inositol was reduced and this reduction was found to be related with reduction of cellular volume. No change occurred in adipocyte count. Protein kinase B/act phosphory

Author-year	Study design	Study objective	Sample size and age range	Study plan/treatment	Duration (scope/intervention observation)	Evaluation criteria	Conclusion
							lation was increased in skeletal muscle with myo-inositol treatment. It was reported that myo-inositol treatment may be used in T2 DM treatment.
Suzuki et al. (2014)	Animal study	To evaluate insulin-like bioactivities of acylated inositol glycans.	6 C57B/6N mice	IG-1: 40 mg/g body weight	28 days (intervention-observation)	Plasma glucose, plasma insulin, total cholesterol, triglycerides, NEFA, adiponectin, TNF-alpha, leptin, body weight, food intake, glycogen content in liver and skeletal muscles	IG-1, one of AIGs, has an insulin-mimetic bioactivity and has improved glucose tolerance in obese and non-obese diabetic mice.
Croze	Animal	To	Control	Control	4 months	Insulin	High-fat

Author-year	Study design	Study objective	Sample size and age range	Study plan/treatment	Duration (scope/intervention observation)	Evaluation criteria	Conclusion
et al. (2015)	study	evaluate ability of dietary myo-inositol supplementation in preventing or delaying insulin resistance and fatty tissue enlargement, and to test its capacity for preventing hyperglycemia and/or insulin resistance-related intracellular inositol depletion in diet-induced obesity in mice.	(n:10) High-fat diet (n:10) High-Fat + myoinositol (n:10)	group: standard diet High-fat diet: 60% fat High-fat + myoinositol (HF-MI): 0,58mg/g drinking water myoinositol + 60% fat	(intervention-observation)	tolerance test, urine, hepatic histopathological evaluation, urinary and tissue myo-inositol blood glucose, plasma insulin	diet was determined to be related with inosituria and intra-tissue inositol depletion in liver and kidneys Myoinositol supplementation significantly decreased epididymal white fat tissue and fatty acid synthase activity and was effective in preventing tissue inositol depletion. However, it could not prevent insulin resistance

Author-year	Study design	Study objective	Sample size and age range	Study plan/treatment	Duration (scope/intervention observation)	Evaluation criteria	Conclusion
							or obesity.
Gao et al. (2016)	Controlled animal study	To investigate hypoglycemic effect of D-chiro inositol (DCI) in type 2 diabetes	50 Sprague-Dawley (SD) rats 5 groups: Normal control (NC)(n:10), Normal high dose (NH) (n:10), Diabetic control (DC) (n:10), Diabetic low dose (LD) (n:10), Diabetic high dose (HD) (n:10)	High dose group: 60 mg/kg.bw/day DCI Low dose group: 30 mg/kg.bw/day DCI Control group	5 weeks (1 week duration for orientation + 4 weeks intervention) (intervention-observation)	Fasting blood glucose Serum insulin GLUT4 BS Beta-actin Hepatic tissue analysis OGTT	DCI has a positive effect on hypoglycemic effectiveness and has increased glycogen synthesis. DCI has been shown to have a positive role in insulin-mediated glucose uptake via PI3K/Act signal pathway in type 2 diabetic rats.
Foster et al. (2016)	Controlled animal study	To investigate whether concomitant use of Inositol hexakisphosphate (IP6) and inositol as supplement is	Total 30 rats; First 4 weeks: Normal diet (n:6) 45% high fat diet (n:24) Second 4 weeks: non-	IP6 and inositol treatment : 650 mg/kg bw Glibenclamide treatment : 10 mg/kg bw	8 weeks (intervention-observation)	Body weight, blood glucose, glycated hemoglobin, insulin, serum leptin, HOMA-insulin resistance	It was reported that concomitant use of inositol and inositol hexakisphosphate (IP6) as supplemen

Author-year	Study design	Study objective	Sample size and age range	Study plan/treatment	Duration (scope/intervention observation)	Evaluation criteria	Conclusion
		effective in treatment of type 2 DM and some related metabolic disorders.	diabetic control (n:6), non-diabetic high-fat diet control (n:6), diabetic untreated (n:6), diabetic rats treated with the combination of IP6 and inositol (n:6) and diabetic rats treated with glibenclamide (n:6)			scores, intestinal amylase activity, serum and fecal lipids and food and fluid consumption	t may be effective in treatment of type 2 DM and related metabolic disorders by having some effects on lipid and carbohydrate metabolism.
Antony et al. (2017)	Controlled animal study	To investigate anti-hyperlipidemic and anti-diabetic effects of myo-inositol in obese type 2 diabetic	Total 30 5 week –old male Wistar rats. 5 groups: Normal control (n:6) Diabetic control (n:6)	High dose group: 50 mg/kg myoinositol Low dose group: 25 mg/kg miyoinositol Control	30 days (intervention-observation)	Lipid biomarkers, fasting blood glucose (FBG), changes in body weight, food and water	It was suggested that myo-inositol may be effective in removal of glucose from adipose tissue via insulin-

Author-year	Study design	Study objective	Sample size and age range	Study plan/treatment	Duration (scope/intervention observation)	Evaluation criteria	Conclusion
		rats.	Diabetic rats low dose myoinositol (n:6) Diabetic rats high dose myoinositol (n:6) Diabetic rats which received pioglitazone 10 mg/kg (n:6)	group		intakes, plasma insulin, HOMA-IR, oral glucose tolerance, intraperitoneal insulin tolerance, urea, creatinine, marker enzymes of liver function, b-cell function and the expression levels of insulin receptor-induced signaling molecules, histology of liver, pancreas, kidney, heart and adipose tissues.	dependant signaling mechanism and may play a positive role in treatment of obesity-related type 2 diabetes.

Table 2: Studies which evaluated relationship between gestational diabetes and inositol

Authors-year	Study design	Study objective	Sample size and age range	Study plan/treatment	Duration (scope/intervention observation)
Human studies					
Scioscia et al. (2007)	Cross-sectional	To examine the relationship of urinary excretion of inositol phosphoglycan type A with glycemic control and birth weight in women with GDM.	Women with GDM (n:48) and healthy pregnant women (n:23)	Situation determination was performed. There was no treatment or intervention.	Not available
Scioscia et al. (2007a)	Cross-sectional	To demonstrate correlation of inositol phosphoglycan type-P with insulin resistance in women with GDM.	48 women with GDM 23 healthy pregnant women	Situation determination was performed. There was no treatment or intervention.	Not available
Corrado et al. (2011)	Randomized, prospective, controlled study	To examine effect of myo-inositol supplementation on effectiveness of endogenous insulin in individuals with GDM.	69 patients; Study group (n:24) Control group (n:45)	Control group: 400 mcg/d folic acid Study group: 400 mcg/d folic acid + 4 g/d myoinositol	8 weeks (intervention-observation)
Danna et al. (2013)	randomized prospective open- label placebo - controlled	To check the hypothesis that myo-inositol supplementation reduces initiation of gestational diabetes in pregnant women with family history of type 2 DM.	Supplementation group (n:110) Placebo (n:110)	Study group myo-inositol + 200mcg X2/d folic acid Placebo: 200mcg X2/d folic acid	2 years (intervention-observation)

Authors-year	Study design	Study objective	Sample size and age range	Study plan/treatment	Duration (scope/intervention observation)
Matarreli et al. (2013)	Prospective Randomized, Double blind Placebo controlled Pilot study	To check the hypothesis that myo-inositol improves insulin resistance and GDM incidence in women with risk for GDM	Pregnant women with finding of increased FBG during first trimester or early second trimester Myo-inositol group (n:35) Control group (n:39)	Control group: 400mcg/d Study group: 4000mg /d inositol+ 400mcg/d folic acid (as divided into 2, 2 sachets per day)	During pregnancy
Danna et al. (2015)	Open-label, randomized study	To evaluate whether myo-inositol supplementation is effective in reducing GDM and insulin resistance in obese pregnant women.	Obese pregnant women (pregestational BMI ≥30 kg/m2) at 12^{th}-13^{th} gestational age (n:220)	Myo-inositol twice daily (2 g myo-inositol +200 mcg folic acid) or placebo (200 mcg folic acid)	From first trimester till delivery
Murphy et al. (2016)	A nested case–control study	To determine whether urinary excretion of myo-inositol (MI) and D-chiro-inositol (DCI) due to alteration of insulin sensitivity in early and late pregnancy periods and whether urinary excretion of inositol	Pregnant women (n:375)	Situation determination was performed. There was no treatment or intervention. Random urinary excretion analysis at 6th-14^{th} gestational	From November 2009 to April 2011 (scope)

Authors-year	Study design	Study objective	Sample size and age range	Study plan/treatment	Duration (scope/intervention observation)
		is higher in GDM patients compared to normal gravidas (NG).		weeks, 22nd-32nd gestational weeks and postpartum 6th week.	
Santamaria et al. (2016a)	A retrospective study	To evaluate myo-inositol levels in amniotic fluids of women with Gestational diabetes and Pregnancy Induced Hypertension (PIH)	GDM (n:30), gestational HT (n:30) and normal pregnant women (n:30)	Situation determination was performed. There was no treatment or intervention. Amniotic fluid was obtained at 15th-18th gestational weeks.	Retrospective 3 years (scope)
Santamaria et al. (2016)	open-label, randomized study	To evaluate whether myo-inositol supplementation reduces GDM in slightly overweight women.	220 overweight pregnant women (pregestational BMI ≥25 and <30 kg/m^2)	From first trimester till delivery, 110 pregnant women were administered myo-inositol (2 g myoinositol + 200 mg folic acid), 110 pregnant women, however, were administered placebo (200 mg folic acid) twice daily.	From first trimester till delivery
Animal studies					
Plows et al. (2017)	Animal study	Determination of whether myo-inositol (MI) and vitamins B2, B6, B12, and D supplementation will be beneficial for prophylaxis/treatment	143 mice	4 week-old mice were divided into 8 distinct groups. Suboptimal B2, Suboptimal B2 + MI,	They were fed with diet for 8 weeks and pregnancy without breeding.

Authors-year	Study design	Study objective	Sample size and age range	Study plan/treatment	Duration (scope/intervention observation)
		of GDM.		AIN-93G, MI only, B2 only, B2 + MI, Vitamin Mix, MI + vitamin mix	

Figure 1. Flow Diagram