The Effect of a Single Mega dose Injection of Vitamin D on serum Adiponectin concentration at First Gestational Diabetes Mellitus: A Randomized Controlled Clinical Trial

Mahdieh Hosseinzadeh
Shahid Sadoughi University of Medical Sciences and Health Services Yazd Research and Clinical Centre for Infertility

Elham Razmpush
Shahid Sadoughi University of Medical Sciences and Health Services Yazd Research and Clinical Centre for Infertility

Elham Shareghfarid
Shahid Sadoughi University of Medical Sciences and Health Services Yazd Research and Clinical Centre for Infertility

Elham Hosseinzadeh
Islamic Azad University of Yazd

Hossein Hadinedoushan
Shahid Sadoughi University of Medical Sciences and Health Services Yazd Research and Clinical Centre for Infertility

Maryam Salami
Shahid Sadoughi University of Medical Sciences and Health Services Yazd Research and Clinical Centre for Infertility

Maryam Khosravi
Mashhad University of Medical Sciences

Maryam Amini (maramin2002@gmail.com)
Tehran University of Medical Sciences https://orcid.org/0000-0002-5279-213X

Hassan Mozaffari-Khosravi
Shahid Sadoughi University of Medical Sciences and Health Services Yazd Research and Clinical Centre for Infertility

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Abstract

Background: vitamin D is being increasingly recognized for its important non-skeletal functions including endocrine actions. This study investigated if a single, large, intramuscular post-artum injection of vitamin D improve adiponectin levels among women with gestational diabetes mellitus (GDM). Methods: A total of 45 pregnant women with GDM participated in this randomized clinical trial. They were randomly divided into intervention and control group. The intervention group received an intramuscular injection of 300,000 IU of vitamin D during 3 to 10 days after their child delivery, but controls did not. Serum 25-hydroxyvitamin D, fasting blood glucose, HbA1c and serum adiponectin were measured at baseline and after 3 months of intervention. Results: Serum 25 OH vitamin D increase significantly in the intervention but not in the control group from 24.25 to 62.10 (nmol/l) (p-value< 0.01). Comparison in within group showed that adiponectin level increased significantly only among intervention group after the vitamin D injection from 7.45 to 8.98 (ngr/dl) (P-value=0.01), while between group comparisons showed no significant differences in adiponectin concentration after the intervention (P-value<0.05). Between and within group comparisons reported no significant alterations in the levels of glycated hemoglobin (HbA1c) and FPG (fasting plasma glucose), as well. Conclusions: The 300,000 IU single dose of intramuscular injection of vitamin D is regarded as an effective procedure to improve vitamin D status which significantly increased the adiponectin levels among mothers with gestational diabetes after delivery. Trial registration: The trial was registered in Iranian Registry of Clinical Trials available at http://www.irct.ir. The reference number is IRCT138902113840N1.

Background

Vitamin D has been widely confirmed to improve the bone mineralization and calcium homeostasis [1]; Though, apart from this traditional role, vitamin D is being increasingly recognized for its important non-skeletal functions including endocrine and physiological actions (2) since it is mediated through vitamin D receptor (VDR) which is widely expressed in many related tissues, such as adipocytes, smooth muscles, skin, immune system, colon, pancreatic β-cells, keratinocytes, osteoblasts and vasculature tissues (3). In a multinational study, the prevalence of vitamin D deficiency was estimated to be 64% among women in 2006 (4); regarding the prevalence in Iran in 2009, 86% of pregnant woman were reported to have vitamin D deficiency, likely due to the low intake of vitamin D containing foods rather than the duration of exposure to sunlight or the type of their clothing or even their body mass index (BMI) (5, 6). Many studies have shown that vitamin D levels are negatively associated with type 2 diabetes and insulin resistance in children and adults (7–10); vitamin D could play an important role in the pathogenesis of gestational diabetes mellitus (GDM) via affecting either insulin sensitivity or β-cell function or even both of them (11–13). GDM is defined as glucose intolerance with first recognition during pregnancy (14). Precisely, it has been proved that every 5 ng/ml decrease in serum vitamin D level is associated with a 1.29-fold increase in the risk of GDM (15); moreover, systematic review articles have highlighted the improvement in insulin sensitivity via greater serum vitamin D concentrations (11, 12, 16).

On the other hand, recent evidence indicated that low plasma adiponectin concentration is associated with GDM (17); Adiponectin is a specific polypeptide excreted from adipose tissue into the bloodstream and is inversely correlated with BMI and body fat percentage (18). In fact, it has been shown that the mRNA levels of adiponectin were reduced in the adipose tissue biopsies taken from GDM women (19). The anti-atherosclerotic, anti-inflammatory and anti-diabetic properties of adiponectin has been demonstrated in many studies (20–22); it has been found to have significant positive and negative relationships with insulin sensitivity (23) and insulin resistance (24). According to the recent findings, hypo-adiponectinemia is supposed to increase the risk of metabolic syndrome (25) and coronary artery disease (26); studies revealed that adiponectin concentrations as well as the related mRNA gene expression are decreased in type 2 diabetic patients with insulin resistance (18, 24, 27). Thus, it is obvious that the degree of hypo-adiponectinemia is closely related to the degree of insulin resistance (28). Concerning the adiponectin levels during pregnancy, it has been found to be more strongly correlated with insulin resistance compared to the total amounts of adipocytes (29); moreover, it has been suggested that the incidence of hypo-adiponectinemia during pregnancy could predict the postpartum insulin resistance, β-cell dysfunction as well as fasting hyper-glycaemia and hence, it might be relevant to the pathophysiology of the incidence of latter type 2 diabetes among women with prior GDM (30).

Belenchia et al assessed the effect of a daily dose of 4000IU vitamin D for 6 months among patients without diabetes and reported no significant changes in the levels of adiponectin(31). In another study by Gagnon C, who assessed the combined effect of calcium and vitamin D supplementation on insulin secretion, insulin sensitivity and β-cell function in participants with pre-diabetes for 6 months, reported that this intervention may not alter the adiponectin levels and β-cell function in multi-ethnic adults with low vitamin D status (32); whereas,interestingly, a placebo-controlled trial showed that a 1000 IU oral supplementation of vitamin D per day among patients with type 2 diabetes could lead to an increase in circulating adiponectin after 12 month (33). However, another trial was also conducted among patients with type 2 diabetes for 8 weeks which reported no significant changes in adiponectin levels after a 50000 IU vitamin D concentrations supplementation per week (34). Overall, a recent related systematic review and meta-analysis did not suggest a significant alteration in plasma adiponectin concentrations after the vitamin D supplementation either with different bolus or multiple daily doses of treatment (35).

To the best of our knowledge, this is the first study that aimed to investigate the effect of postpartum mega-dose of vitamin D injection on adiponectin levels among pregnant women with GDM to show that whether vitamin D supplementation could improve the plasma adiponectin concentrations.

Methods

Methods:

Study Design and Participation:

The present randomized clinical trial was registered in Iranian Registry of Clinical Trials with the following reference number IRCT138902113840N1, which is available at: http://www.irct.ir. The study adhereh to

CONSORT guidelines.

This study was conducted among 45 pregnant women with GDM, who referred to Yazd Diabetes Research Centre in Shahid Sadoughi University of Medical Sciences.

Inclusion criteria consisted of pregnant women aged 18 years and older, who were diagnosed with GDM for the first time, according to the criteria of Carpenter and Coustan in their 24–28 weeks of their gestation(36); patients who met one of the following criteria, after a one-step, 2h, 75-g oral glucose tolerance test (OGTT), were intended to have GDM: FPG≥ 92 mg/dl, 1-h OGTT≥180 mg/dl and 2-h OGTT≥153 mg/dl (37).

Exclusion criteria were thyroid, renal and hepatic diseases, the presence of mal-absorption and changing their routine treatment as well as taking vitamin D, calcium or multivitamin and mineral supplements.

Women were excluded if they were taking other Vitamin D products or during the study as well as taking antibiotics or glucocorticoids or other drug therapies.

The main researcher described the study protocol and procedure to the volunteered participants who intended to join the study and they were given adequate time to consult with their physicians and families.

Forty five pregnant women with GDM were randomly assigned into intervention and control group; during 3 to 10 days after their child delivery. Mothers were asked to refer to the clinic with their infants to record their anthropometric measurements and give them the vitamin D supplements; participants in intervention group received one intramuscular injection of 300,000 IU of 25 OH vitamin D in the morning and women in the control group, who were similar to intervention participants, were not given any supplements and were only asked not to change their routine diet.

Biochemical and Anthropometric Assessments:

A total of 6 ml of peripheral blood was taken from each of the participants after an 8–10 h of overnight fasting within 10 days during post-delivery; primary outcomes were serum adiponectin concentrations, serum 25-hydroxyvitamin D3 and parathyroid hormone (PTH) as well as serum calcium and phosphorus levels; the adiponectin test was carried out on 1.5 ml vials serum stored at –80˚C and was determined using a commercially available ELISA kit (BioVendor GmbH, Heidelberg, Germany). Aliquots of pre- and post-intervention serum samples were defrosted for final analysis; immunoassay of serum 25-hydroxyvitamin D3 was carried out using ELISA and an Immunodiagnostic Systems Ltd kit (IDSLtd, Boldon, UK) with a sensitivity of 2 nmol⁄ml; PTH was measured using ELISA and immunodiagnostic systems (Italy; IDS Ltd) with a sensitivity of 0.6 picomol/l. Serum calcium and phosphorus levels were measured using colorimetric method by Auto Analyzer (Echoplus Corporation, Italy) and Biosystems kit (Spain; Barcelona; Biosystems).

Secondary outcomes were serum fasting plasma glucose (FPG), oral glucose tolerance test (OGTT), fasting insulin level, glycated hemoglobin (HbA1c) as well as anthropometric parameters; 2 ml of the

whole blood was collected into separate tubes containing EDTA for the analysis of HbA1c levels; plasma and serum were separated and stored at –20˚C until final assay; FPG and OGTT were assessed using an enzymatic (glucose oxidize–peroxides) in-vitro test (Autoanalyser; Echo Plus Corporation, Roma, Italy) and serum insulin levels were assessed using enzyme-linked immunosorbent assay(ELISA) kits (Diametra Corporation, Milan, Italy);

Weight was measured using a digital scale (Seca, Germany) with an accuracy of 0.1 kg; height was measured without shoes and heavy clothing using a portable stadiometer with a precision of 0.1 cm; body mass index (BMI) was calculated by dividing weight (Kg) by the squared of height (m^2) based on the pre-pregnancy weights of participants; hip circumference was measured using a measuring tape to the nearest of 0.1 cm.

In addition, other necessary baseline information was obtained in a face to face interview via validated questionnaires such as age, literacy level and occupation, type of GDM treatment, type of delivery and type of feeding.

Dietary intake and nutrient intakes were estimated using a 3-day and 24-h dietary recall at the beginning and at the end of the study. Participants were asked not to change their usual diet.

Administration dose and Follow-up:

Calcitriol, as an active injection form of vitamin D was made by Iran Hormon Corp; ampoules were kept in refrigerator at 15–30 °C, away from light or frost; a single dose of 300000 IU of Calcitriol injection was given to every participant in the morning, who referred to Yazd Diabetes Research Center in Shahid Sadoughi University of Medical Sciences.

Statistical analysis:

Kolmogorov–Smirnov test was used to determine the normality of quantitative variables; paired t-test was used for comparing the means of variables with normal distribution between the beginning and the end of the study for each group; independent-test was applied to compare the means of variables between the two groups before and after the intervention. In addition, Wilcoxon test was carried out to compare the variables without normal distribution in each group between the beginning and the end of the intervention. Mann–Whitney U test was also used for comparing abnormal quantitative data between the two groups before and after the intervention. Chi-square and Fisher's exact test were conducted to compare qualitative variables between the two groups. The results of the quantitative data with normal distributions were reported as mean±SD. The significance level was set at P-value of ≤ 0.05.

Results

A total of 85 individuals were assessed for the study eligibility; 50 of eligible participants, who had their first gestational period, were randomly assigned into the intervention or control group; 3 of the participants were withdrawn during the study consisting of 1 participant in the control and 4 participants in the

experimental group due to incomplete supplement therapy in the expected time; finally, a total of 45 participants completed the study and remained for the final analysis (24 participants in the intervention and 21 individuals in the control group) (Fig 1). None of the participants have reported specific side-effects of Vitamin D supplementation.

Baseline characteristics of the participants are shown in table1; the average ages of participants in intervention and control groups were 30.7±6.2 and 29.5±4.0 years, respectively.

None of the baseline quantitative variables including BMI, the exact time of GDM diagnosis, the levels of HbA1c and adiponectin as well as qualitative variables such as literacy level, type of gestational diabetes therapy such as dietary manipulation, insulin therapy or both and type of delivery were not significant between the two groups (all $P \geq 0.05$).

Table 2 shows the mean differences of biochemical parameters before and after the study; between group comparisons showed that the mean difference of adiponectin concentration did not reach significant levels after the intervention (P = 0.2); however, within group comparison showed that adiponectin level increased significantly among intervention group after the vitamin D injection (P-value = 0.01). Between and within group comparisons reported no significant alterations in the levels of HbA1c and FPG.

Discussion

The association between mega-dose injection of vitamin D3 and adiponectin has been investigated for the first time in this study; within-group comparison showed that the levels of adiponectin increased significantly among intervention group after the vitamin D injection (*P*-value = 0.01); these results were in agreement with those published by some recent studies which suggested that adipokines and adipose tissue might be direct targets of vitamin D (3).The mechanism by which vitamin D could alter the adiponectin might be due to the up-regulation of CYP27B1gene expression; for instance, it has been proposed that 1,25-hydroxy vitamin D3 could regulate the secretion of adipocyte in visceral adipose tissue (10); Moreover, as abnormal oral glucose tolerance test observed in GDM is considered as a proinflammatory state, any reductions in the adiponectin levels among individuals would likely be due to these proinflammatory produced cytokines such as tumor necrotic factor alpha (TNF-α) and interleukin (IL)−1(38); Further, 1,25-hydroxy vitamin D3 might independently affect the expression of adiponectin via regulating the gene expression of TNF-α (10, 39, 40).

Although, there are no studies investigating the effect of vitamin D on adiponectin level, a cross-sectional study found that lower maternal 25-hydroxy vitamin D3 concentrations among overweight/obese pregnant women, who are at high-risk of GDM, might be mediated by adiponectin (41); A Turkish study conducted among 114 obese and healthy individuals showed that a positive relation exists between vitamin D and adiponectin concentrations (42); The aim of the mentioned study was to investigate the relation between vitamin D and metabolic syndrome in children and adolescents, which reported that the interaction between vitamin D and adiponectin levels may be an indicator of cardio-metabolic risk factors. In regard with our result, a randomized placebo controlled study among 47 patients with diabetes showed

that circulating adiponectin marginally increased via vitamin D3 supplementation at the end of 12 months of intervention in the treatment group (P = 0.065) while it did not alter in placebo group (33). A new meta-analysis, which assessed the relation between vitamin D and adiponectin in human clinical trials, reported that there could be a dose-response relationship between vitamin D supplementation and serum adiponectin levels(43). Shargorodsky et al in their cross-sectional study revealed that this existing positive association might be mediated by augmenting the gene expression of adiponectin as well as altering the activity of the renin-angiotensin-aldosterone system (44); in fact, vitamin D was found to be negatively correlated with the production of angiotensin via modifying the renin angiotensin-aldosterone system; it has been also reported that vitamin D might increase the serum adiponectin concentrations through decreasing the angiotensin generation (45). HbA1c and FPG levels did not significantly change after vitamin D3 intervention in our study. In contrast with our result, a study that assessed the effect of calcium and vitamin D co-supplementation which consisted of 50000 IU vitamin D per week and 1000 mg calcium per day among 51 women with GDM for 24 to28 weeks, showed significant reduction in FPG and serum insulin levels(46). We failed to find any reductions in HbA1c levels, which might be due to our 8-week intervention period that was too short for detecting any changes in the measures of HbA1c; in accordance with our result, a randomized controlled trial that was performed among 90 women with GDM, assessed the different effects between 5000 IU vitamin D and 400 IU vitamin D supplementation and showed that higher dose of vitamin D supplementation, commencing at a mean of 14 weeks of gestation, would not improve glucose levels in pregnancy (47). Another similar study conducted among 500 women with gestational age 12–16 weeks were randomly divided in two groups, one group received 400 IU vitamin D daily and group B 50,000 IU vitamin D every 2 weeks orally until delivery. This study concluded that 50000 IU vitamin D supplementation in every 2 weeks could decrease the incidence of GDM compared to the daily supplementation of 400 IU of vitamin D (48).

Adiponectin concentrations might strongly affect insulin resistance status, as lower level of adiponectin was observed to play an important role in the incidence of insulin resistance and type 2 diabetes (42). Regarding adipokine secretion, some recent studies have shown that vitamin D metabolites might increase the adipokine production (3); adipokines are associated with improved glycemic control and other metabolic indicators which might be the possible explanation for the significant impacts of vitamin D supplementation on the adipokine concentrations, especially among patients with type 2 diabetes or metabolic syndrome (35). Regulation of the adiponectin gene expression through 1,25-hydroxy vitamin D3, which is due to the related receptors located in preadipocytes, could be another possible mechanism for the positive association between vitamin D and adipokine (49); Further, VDR is expressed early in the adipogenesis in 3T3-L1 pre adipocytes cells, suggesting that VDR signaling pathway might play a role in adipocyte biology and function.

The present study did not show any significant impact on BMI; similarly, other studies with supplementation of 4000 IU to 50000IU of vitamin D 3 reported the same outcomes on BMI (50, 51); however, vitamin D could affect body weight and energy expenditure through calcium regulation in which calcium concentrations could modulate lipolytic activity in isolated human adipocytes (52).

Nevertheless, between group comparisons in the present study revealed that no significant alterations were observed in the levels of adiponectin after the mega dose injection of 25-hydroxy vitamin D3 (P = 0.2); in consistence with our results, an earlier study showed no significant association between serum levels of 25-hydroxy vitamin D3 and other adipocyte related hormones including resistin, IL–18 and adiponectin (53). On the other hand, although some studies have reported the protective effect of vitamin D on glycemic control, its beneficial effect on serum adiponectin level is controversial (33, 34, 54); One might say that, differences in the methods used for the adiponectin measurements as well as the related used dosages and durations of vitamin D supplementation, could be the reason for these discrepancies.

One advantage of the present study is that we used the mega dose of vitamin D 3, that has been never assessed before; we also used a parallel control group in which all measurements were performed similar to those in the intervention group. However, the limitations of the present study should be noted; we did not record the physical activity status of participants and the study was not blinded, neither; because we used injectional form of vitamin D, we could not include any supplementation as a placebo in our control group. It is highly recommended to investigate the effect of the vitamin D for longer duration and with higher sample size in future studies.

Conclusions

The 300,000 IU single dose of intramuscular injection of vitamin D is regarded as an effective and safe procedure to improve vitamin D status which significantly increased the adiponectin levels among treatment participants in within group comparison, while between group comparisons showed no significant differences in adiponectin concentration after the intervention.

Abbreviations

gestational diabetes mellitus:GDM

glycated hemoglobin: HbA1c

fasting plasma glucose:FPG

vitamin D receptor: VDR

oral glucose tolerance test: OGTT

parathyroid hormone: PTH

Immunodiagnostic Systems Ltd: IDSLtd

enzyme-linked immunosorbent assay: ELISA

body mass index: BMI

standard deviation: SD

tumor necrotic factor alph: TNF-α

interleukin: IL

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Research Committee of Ethics at Yazd University of Medical Sciences, Yazd, Iran. Written informed consent to participate in the study were obtained from all individuals.

Consent for publication

Not applicable

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interests.

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Authors' contributions

MH and HMK participated in the conception and design of the study, managing the project and drafting the manuscript. MH, ES and ER participated in the acquisition of data, data analysis, writing and drafting the manuscript. EH, HH, MS, MK gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. MA revised the manuscript, gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. All authors have read and approved the manuscript.

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Tables

Table 1: The comparison of means and percentage of the variables under the study in the IG and CG before intervention

Variables	Intervention Group (N=24)*	Control Group (N=21)	P-value
Age (year)	30.7±6.2	29.5±4	0.4
Pregnancy month for diagnosing GDM	5.1±2.3	4.7±2.2	0.6
Weight (kg)	70.2±12.5	69.9±11	0.9
Height (cm)	155.6±5	157.9±4.4	0.4
BMI (kg /m^2)	28.9±4.8	27.9±3.6	0.4
HA1C (%)	5.48±0.69	5.20±0.73	0.1
	Number (%)	Number (%)	
Literacy Level			
Illiterate	2(8.3)	3(14.4)	0.3**
Guidance school graduate	10(41.7)	11(52.4)	
High school graduate	7(29.2)	3(14.3)	
University graduate	5(20.8)	4(19)	
Type of treatment			
Insulin	11(45.8)	9(42.9)	0.9
Food therapy	10(41.7)	10(47.6)	
Insulin and diet therapy	2(9.5)	3(12.5)	
Type of delivery			
Natural	12(50)	14(66.7)	0.2
Cesarean section	12(50)	7(33.3)	
BMI*** (kg/m^2)	4(16.7)	4(19)	0.9
18.5-24.9	14(58.3)	12(57.1)	
25-29.9	6(25)	5(23.8)	
30<			

*IG: Intervention Group; CG: Control Group; ** Mann Whitney test ; ***Body Mass Index

Table 2: The comparison of means of the variables between the two groups before and after he intervention.

	intervention			**control**			***P*-Value (Between group)**	
	Before (Mean±SD)	**After (Mean±SD)**	*P*-Value (Within group)	**Before (Mean±SD)**	**After (Mean±SD)**	*P*-Value (Within group)	Befre	After
5(OH)D3 ımol/l)	25.30	24.10	0.02*	24.25	62.10	<0.001*	0.44	<0.001*
diponectin ng/dl)	7.45±2.63	8.98±2.66	0.01*	7.73±3.64	7.97±3.26	0.1	0.7	0. 21
bA1c ⅙) [b](mg/dl) †	36±7	37±13	0.77	33±7	34±6	0.63	0.1	0.81
PG (mg/dl) †	91.8±17.3	92.9±10.6	0.76	98.3±30.7	104.7±33.5	0.05	0.41	0.11

ıbbreviation: SD, Standard Deviation; HbA1c, hemoglobin A1c; FPG, Fasting Plasma Glucose

Significant difference ($p<0.05$)

Figures

Figure1: Flowchart of the study procedure

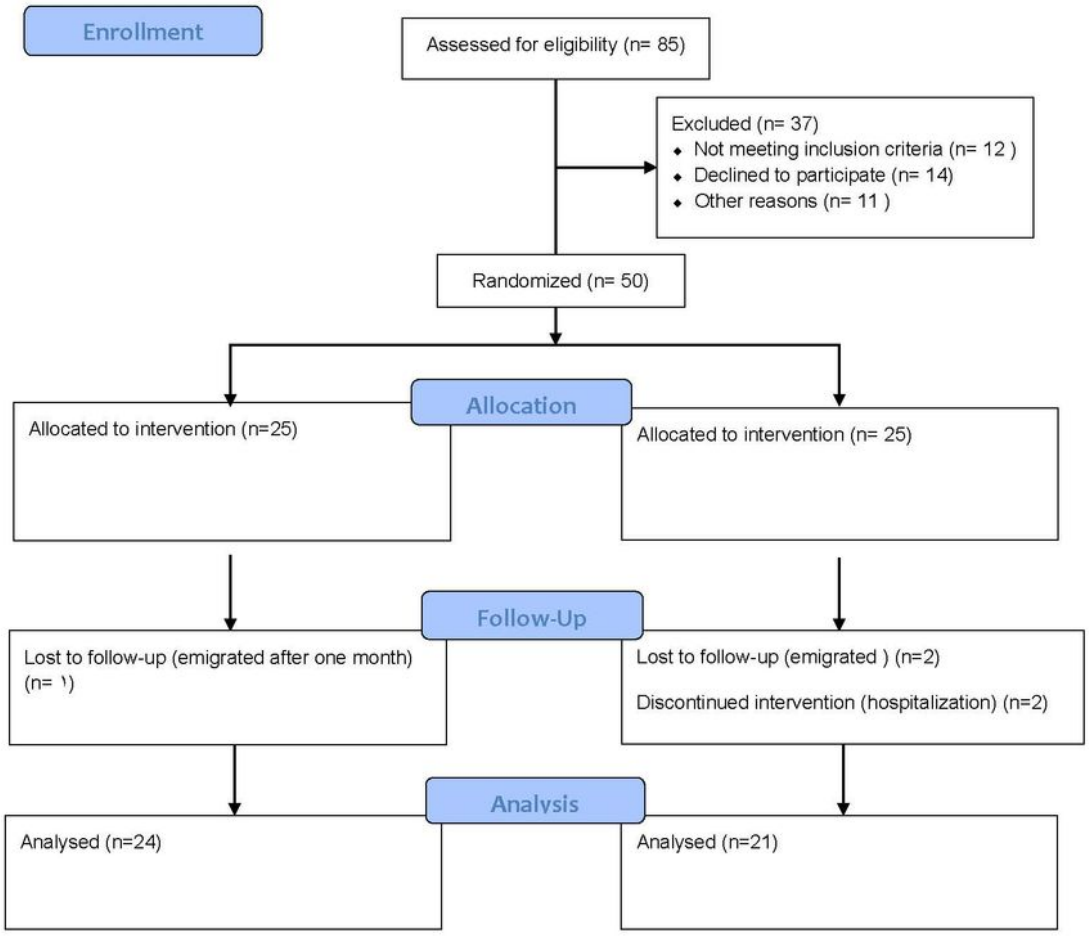

Figure 1

flowchart of the study procedure

Supplementary Files

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- CONSORT2010Checklist.doc