Simple lifestyle recommendations and the outcomes of gestational diabetes. A 2×2 factorial randomized trial

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Abbreviations: body mass index (BMI), C reactive protein (CRP), gestational diabetes mellitus (GDM), glycated haemoglobin (HbA1c), homeostasis model assessment of insulin resistance (HOMA-IR), large-for-gestational age (LGA), metabolic equivalent of activity (MET)

Abstract

The benefits of exercise and behavioural recommendations in gestational diabetes mellitus (GDM) are controversial. In a randomized trial with a 2x2 factorial design, we examined the effect of exercise and behavioural recommendations on metabolic variables, and maternal/neonatal outcomes in 200 GDM patients.

All women were given the same diet: group D received dietary recommendations only; group E was advised to briskly walk 20-minutes/day; group B received behavioural dietary recommendations; group BE was prescribed the same as B+E.

Dietary habits improved in all groups. In a multivariable regression model, fasting glucose did not change. Exercise, but not behavioural recommendations, was associated with the reduction of postprandial glucose (p<0001), glycated haemoglobin (HbA1c) (p<0.001), triglycerides (p=0.02), and C-reactive protein (CRP) (p<0.001) and reduced any maternal/neonatal complications (OR=0.50; 95%CI 0.28 0.89;p=0.02).

In GDM patients a simple exercise program reduced maternal postprandial glucose, Hba1c, CRP, triglycerides and any maternal/neonatal complications, but not fasting glucose values.

Registered at ClinicalTrials.gov (Identifier: NCT01506310)

Key words: behavioural recommendations, exercise, gestational diabetes mellitus

Introduction

A few randomized trials have examined the effect of exercise in patients with gestational diabetes (GDM), with discordant results [1-5]. Most researchers [2-4] performed complex interventions, usually not available in clinical setting, and the compliance with exercise was low [6].

The objective of the present randomized trial, with a 2x2 factorial design, was to test whether four different lifestyle programs containing simple exercise and behavioural recommendations, associated or alone (diet only, group D; diet+behavioural recommendations, group B; diet+exercise, group E; diet+behavioural recommendations+exercise, group BE) could help GDM patients in improving fasting glucose values (primary outcome) and reducing values of HDL-cholesterol, triglycerides, insulin, Homeostasis-Model-Assessment-Insulin Resistance (HOMA-IR), high-sensitivity C-reactive protein (CRP), HbA1c, postprandial glucose, and the incidence of any maternal/neonatal complications (secondary outcomes).

Methods

All pregnant women attending the Sant'Anna Hospital (Torino) from July 2009 to February 2012 were enrolled. The inclusion criteria were: age 18-50; 24-26th weeks of gestational age; GDM diagnosis based on a 75g-oral glucose tolerance test; singleton pregnancy. The exclusion criteria were: BMI>40kg/m^2; any known diseases, medications, or obstetrical absolute/relative contraindications to exercise [7]. The approval of the local Ethical Committee and the written informed consent of the participants were obtained.

An individually prescribed diet was given to each woman (carbohydrates 48-50%, proteins 18-20%, fats 30-35%, fibre 20-25 g/day, no alcohol). The group E was advised to briskly walk at least 20-minutes/day every day (140-minutes/week; Borg's scale target rating 12-14). Group B received individually oral/written recommendations for helping with healthy dietary choices (i.e. lowering carbohydrate intake, strategies for out-of-home eating, healthy cooking and food shopping and related behavioural suggestions) and debunking false myths about diet in pregnancy. Group BE was prescribed brisk walking at least 20-min/day along with the same recommendations of group B.

Evaluations were performed at 24-26th gestational weeks at baseline, and at 38th week or before delivery (if delivery was preterm) at end-of-study. At baseline and end-of-study, participants completed a validated semi-quantitative food-frequency questionnaire, blindly checked by two dieticians, and the Minnesota-Leisure-Time-Physical-Activity questionnaire [8] to evaluate exercise levels of the previous month, expressed as metabolic equivalent of the activity (METs; hours/week). Patients were monitored by weekly phone calls and visited every 2-weeks to monitor adverse events and protocol adherence (for groups B/BE: consuming at least 18% proteins, 20g/day fibre, abolishing alcohol; for groups E/BE: performing at least 20-minutes/day brisk walking every day). Patients self-monitored capillary blood glucose 4-6 times/day (pre-prandial and 2-h postprandial) by the Accu-Chek® glucometer (Roche Diagnostics, USA). Insulin treatment was prescribed in the presence of foetal abdominal circumference >70th percentile at ultrasound and/or hyperglycaemia.

A sample of 200 patients had a 95% statistical power to detect at least a 10% reduction in fasting glucose by exercise, corresponding to an effect size of 0.50 [4], with a 2-tailed α-value=0.05. Randomization was stratified by baseline BMI and METs, and was implemented through a website (www.epiclin.it). The dieticians, the obstetricians who reported maternal/neonatal complications, and the laboratory personnel were blinded to the group assignment.

Maternal complications included pregnancy-induced hypertension, infectious diseases, cholestasis during pregnancy and peri- and post-partum complications. Newborn complications included: LGA (birthweight>90th percentile), pre-term birth (gestational age at delivery <37weeks), and any neonatal conditions requiring a specific treatment or a prolonged in-hospital stay.

METs, triglycerides, insulin, HOMA-IR, and CRP values were log-transformed to approximate normality. Within- and between-group analyses were used to evaluate differences within and among groups (D/E/B/BE). Continuous variables were analyzed by a linear regression model, after adjusting for the baseline value of each variable. The secondary dichotomous outcomes were analyzed by a multivariable logistic regression model. All analyses were adjusted for age, pre-pregnancy BMI, and baseline METs.

Results

All participants completed the study, and no adverse events were reported (Fig.1-Appendix). Baseline and end-of-study characteristics of participants are summarised in Tables 1A-2A (Appendix). Groups D/B reduced exercise levels, while exercise recommendations adherence was 68.6% and 64.0% in groups E and BE, respectively. Weight, BMI, and fasting insulin significantly ameliorated in all groups, while postprandial glucose ($p<0.001$), HbA1c ($p<0.001$), triglycerides ($p=0.01$), and CRP ($p<0.001$) concentrations reduced in E/BE groups. The dietary pattern improved in all groups: total energy intake, total fat, saturated fat, and sodium decreased, alcohol was abolished, and protein and fibre intake increased (all p-values<0.01). Adherence to nutritional recommendations did not differ among groups.

Groups E+BE and B+BE were combined in accordance with the factorial design (Tables 1-2).

In an adjusted regression model (Tab.1), fasting glucose did not significantly change; exercise was associated with the reduction of postprandial glucose, triglycerides and CRP concentrations, while behavioural recommendations were not. The interaction exercise-behavioural recommendations did not reach significance in any models ($p>0.3$).

Group D showed a higher incidence of maternal/neonatal complications (Tab.2). In an adjusted logistic regression model, exercise reduced the risk of any maternal/neonatal complications while behavioural recommendations or the interaction exercise-behavioural recommendations did not (OR=0.92;95%CI 0.29-2.90; $p=0.89$).

Conclusions

Exercise reduced maternal postprandial glucose, HbA1c, CRP and triglycerides values and the incidence of any maternal/neonatal complications, but not fasting glucose in GDM women. Behavioural recommendations failed to significantly affect any outcomes.

Different exercise programs have been tested in GDM: a decline [1,4,9] or no variations [2,4,10] in blood glucose values, and a reduction in insulin-resistance, lipoproteins, blood pressure values, inflammation and oxidative stress have been reported [11-12]. In our patients, fasting glucose values did not change, probably because mean fasting values were already within normal ranges [1,5]; alternatively, home exercise may have been less intense than supervised sessions performed in laboratory [13]. However, we found a significant reduction in postprandial glucose and HbA1c levels,

with health implications on GDM outcomes, as reported [1,4,9]. The significant reduction in triglycerides, but not in other lipid variables, of our exercising women was in line with literature [14]. Additionally, CRP values were reduced by exercise. This is interesting because GDM women are characterized by a low-grade systemic inflammation state [15], that could be implicated in the pathogenesis of maternal/foetal complications [12]. Accordingly, our women in the exercise groups showed a reduced incidence of any maternal/neonatal complications (Tab.2).

In our women, neither exercise nor behavioural recommendations when added to diet conferred benefits in decreasing gestational weight or insulin-resistance. Their improved dietary habits might have influenced insulin-resistance; otherwise, exercise in early pregnancy or more intensive programs would be more effective [6,12]. Finally, behavioural recommendations failed to add benefits to diet in our patients, probably because only simple recommendations were given, instead of a multiple-sessions structured approach.

Our intervention was conducted with little resources; no drop-outs or adverse events occurred. Our patients reported a good adherence to recommendations, probably because walking can be done at any time and is simple and inexpensive.

We did not perform supervised lifestyle programs. Recall errors might have occurred during questionnaires compilation; women in the intervention groups could have over-reported exercise or declared healthier nutritional habits. However, all the outcomes, which were blindly measured, were consistent with the declared lifestyle changes. This study was underpowered to find small differences in the incidence of adverse maternal/neonatal outcomes.

The best way of treating GDM is not known; a 20-min walk every day appears to be safe and effective and may be associated with better maternal/neonatal outcomes.

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Table 1. Association between exercise, behavioural recommendations, and all the variables listed at the end of the trial, by a linear regression model adjusted for age, pre-pregnancy BMI, METs and the values of the variables at baseline.

	Exercise			Behavioural recommendations		
	No (n=99)	**Yes (n=101)**	**Adjusted difference (95%CI); p**	**No (n=101)**	**Yes (n=99)**	**Adjusted difference (95%CI); p**
Weight (kg)	74.0±12.2*	73.1±11.2	-0.6 (-1.5, 0.2); 0.16	73.6 ±11.4	73.6 ±11.4	-0.1 (-0.9, 0.7); 0.79
BMI (kg/m^2)	27.5±4.4	27.6 ±4.1	-0.2 (-0.5, 0.1); 0.22	27.6 ±4.4	27.5 ±4.2	0.04 (-0.4, 0.3); 0.81
Fasting glucose (mg/dl)	74.1±10.7	72.4±10.3	-2.0 (-4.5, 0.6); 0.13	73.3±10.1	73.2±11.0	-0.3 (-2.8, 2.2); 0.81
Postprandial glucose (mg/dl)	117.2±16.5	106.1±19.0	-11.1 (-16.1 -6.1); <0.001	113.0±20.0	110.2±17.1	-2.8 (-7.8 2.2); 0.27
HbA1c (%)	4.9±0.4	4.6±0.5	-0.3 (-0.4 -0.2); <0.001	4.8±0.5	4.8±0.4	-0.02 (-0.1 0.09); 0.71
Total cholesterol (mg/dl)	257.4±42.8	253.6±43.9	-3.6 (-12.5, 5.3); 0.42	254.0±44.3	257.0±42.4	1.1 (-7.7, 9.9); 0.80
HDL cholesterol (mg/dl)	71.9 ±13.2	71.4±13.0	0.06 (-1.4, 1.5); 0.74	71.8±15.1	71.6 ±10.7	0.3 (-1.1, 1.7); 0.68
Log-triglycerides (mg/dl)	5.1±0.4	5.0±0.3	-0.08 (-0.2, -0.01); 0.02	5.1±0.3	5.1±0.3	-0.01 (-0.08, 0.06); 0.72
Log-fasting insulin (μU/ml)	2.3±0.5	2.3±0.5	0.01 (-0.10, 0.12); 0.86	2.3±0.4	2.3±0.4	-0.09 (-0.20, 0.02); 0.12
Log-HOMA-IR (mmol/l×μU/ml)	0.6±0.5	0.6±0.5	-0.02 (-0.14; 0.11); 0.79	0.6±0.5	0.5±0.5	-0.10 (-0.22, 0.03); 0.06
Log-CRP (mg/l)	1.2±0.9	1.0±0.8	-0.3 (-0.4, -0.2); <0.001	1.1±0.9	1.1±0.8	0.05 (-0.08, 0.17); 0.46

*Mean±SD

Table 2. Maternal and neonatal outcomes by intervention arm in a logistic regression model, after adjustments for age, pre-pregnancy BMI, and METs at baseline

					Exercise				Behavioural recommendations			
	D	**E**	**B**	**BE**	**No**	**Yes**			**No**	**Yes**		
					***N*=99**	***N*=101**			***N*=101**	***N*=99**		
	%	**%**	**%**	**%**	**%**	**%**	**OR; 95%CI**	**P**	**%**	**%**	**OR;95%CI**	**P**
Insulin treatment	10.0	5.9	6.1	6.0	8.1	5.9	0.84; 0.26, 2.70	0.77	7.9	6.1	0.71; 0.25, 2.25	0.56
Maternal complications	12.0	5.9	10.2	6.0	11.1	5.9	0.48; 0.17, 1.39	0.18	8.9	8.1	0.86; 0.31, 2.35	0.76
Caesarean sections	26.0	17.7	20.4	16.0	23.2	16.8	0.60; 0.29, 1.23	0.16	21.8	18.2	0.77; 0.38, 1.56	0.47
Preterm newborns	8.0	3.9	4.1	2.0	6.1	3.0	0.45; 0.11, 1.91	0.28	5.9	3.0	0.47; 0.11, 1.96	0.30
Large-for-gestational age newborns	14.0	9.8	10.2	10.0	12.1	9.9	0.82; 0.33, 2.03	0.67	11.9	10.1	0.85; 0.35, 2.08	0.72
Neonatal complications	10.0	3.9	4.1	2.0	7.1	3.0	0.50; 0.12, 2.12	0.35	6.9	3.0	0.43; 0.10, 1.81	0.25
Hospital stay > 4days	26.0	17.7	34.7	24.0	30.3	20.8	0.60; 0.31, 1.15	0.12	21.8	29.3	1.48; 0.78, 2.83	0.23
Any complications*	60.0	47.1	57.1	40.0	58.6	43.6	0.50; 0.28, 0.89	0.02	53.5	48.5	0.79; 0.44, 1.39	0.41

D=diet only E= exercise B=behavioural recommendations BE= exercise plus behavioural recommendations

OR= odd ratio

*1 or >1 of all the conditions listed