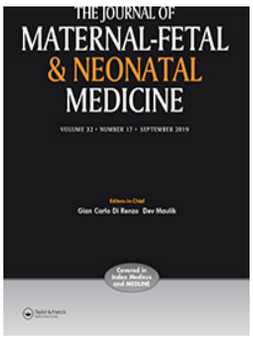

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REVIEW ARTICLE

Which criteria should be used for starting pharmacologic therapy for management of gestational diabetes in pregnancy? Evidence from randomized controlled trials

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ABSTRACT

Introduction: There is inconclusive evidence to support any specific criteria for starting pharmacologic therapy after diet in women with gestational diabetes mellitus (GDM). We aimed to analyze the most used criteria for starting pharmacologic treatment for patients with GDM.

Material and methods: Electronic databases were searched from their inception to September 2017. We included all the randomized controlled trials (RCTs) of GDM managed initially by diet and exercise reporting criteria for starting pharmacologic therapy. RCTs in women with pregestational diabetes were excluded. Data regarding glucose values used for starting pharmacologic therapy were extracted and carefully reviewed.

Results: We included 15 RCTs (4307 women) in the meta-analysis. For fasting glucose target, 8/14 (57%) used a value lower or equal to 90 mg/dL and the remainder used values <99 mg/dL. Of the 10 RCTs targeting 2-h postprandial values, the majority (9/10, 90%) used 120 mg/dL. The majority of RCTs (13/15, 87%) recommended pharmacologic therapy if either 1 or 2 values per 1- or 2-week period were higher than the target values: 7/13 (54%) used 1 value and 6/13 (46%) used 2 values higher than target values. One RCT (7%) used >50% of the values higher than the target values and another one (7%) used >30%.

Conclusion: The majority of RCTs (87%) used very tight criteria of either 1 or 2 values over the target values in the 1 or 2-week period for starting pharmacologic treatment for patients with GDM; more than 50% used 2 values.

KEY MESSAGE

- Pharmacologic therapy should be considered in women with gestational diabetes when, despite an adequate diet and exercise, 1 or 2 blood glucose values are over the target values of 90mg/dL fasting or 120mg/dL 2-hour postprandial over 1 or 2 weeks.

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KEYWORDS
Diabetes; diet; exercise; pregnancy; therapy

Introduction

Gestational diabetes mellitus (GDM) is a common disorder complicating pregnancy, with short- and long-term consequences for the mother, fetus and newborn. It has been estimated that about 6–18% or more of all the pregnancies are complicated by GDM in pregnancy, depending on the country, on the characteristics of the study population and on the GDM screening method used [1–65]. The latest reports from the International Diabetes Federation (IDF) estimate that worldwide, approximately one in seven births in 2015 were complicated by some form of hyperglycemia during pregnancy [53].

The aim of the treatment of GDM is to prevent maternal and neonatal morbidity and mortality by achieving glucose levels similar to those in nondiabetic women, while avoiding hypoglycemia.

Management for women with GDM includes diet [64], physical activity [60], and oral hypoglycemic agents and/or insulin [66] as needed. Nutrition counseling and physical activity should be the primary initial interventions in the management of GDM. Women with GDM must receive practical nutritional education and counseling that will empower them to choose the right quantity and quality of food and level of physical activity. If lifestyle modification with diet and exercise

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fails to achieve glucose control, metformin, glyburide, or insulin should be considered as safe and effective treatment options for GDM [54]. However, the criteria for starting pharmacologic therapy after initial diet and exercise therapy for GDM remain controversial.

Objective

The aim of this review was to conduct a systematic review of randomized controlled trials (RCTs) to analyze the criteria for starting pharmacologic therapy for GDM after initial diet and exercise treatment was introduced.

Materials and methods

Search strategy

This review was performed according to the PRISMA statement recommended for systematic review [55–57]. The review protocol was designed *a priori* to define methods for collecting, extracting and analyzing the data. The research was conducted with the use of Medline, Ovid, and Cochrane Library as electronic databases. The trials were identified with the use of a combination of the following text words: "gestational diabetes", "GDM", "diabetes in pregnancy", "therapy", "treatment", "diet", "exercise", "trial" and "randomized" from the inception of each database through September 2017. Review of articles also included the abstracts of all references that were retrieved from the search. No restrictions for language or geographic location were applied.

Study selection

We included all RCTs studying women with GDM that started with nonpharmacologic treatment such as diet and exercise, and proceeded to pharmacologic therapy only after initial nonpharmacologic treatments had failed. RCTs in women with pregestational diabetes (DM) were excluded. Studies in women with impaired glucose tolerance, and studies not reporting criteria for starting pharmacologic therapy for GDM were also excluded.

Data extraction and risk of bias assessment

The risk of bias in each included study was assessed using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*. Seven domains related to risk of bias were assessed in each included trial since there is evidence that these issues are associated with biased estimates of treatment effect: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting; and (7) other bias. Review authors' judgments were categorized as "low risk", "high risk" or "unclear risk" of bias [55].

Data extraction

For each trial, data regarding our primary objective, criteria for starting pharmacologic therapy for GDM, were extracted and carefully reviewed. We also reviewed the type of glucose screening, frequency of glucose monitoring, and target glucose values, as they are closely associated with our primary objective. The types of GDM screening were defined as one-step, i.e. 75 g 2-h glucose load, and two-step, i.e. 50 g 1-h glucose load, followed if abnormal by a 100 g 3-h glucose load test.

Results

We identified 51 RCTs on therapy for diabetes in pregnancy, and these were assessed for eligibility (Figure 1) [1–51]; 36 were excluded; we included 15 trials of 4307 women in our review [1–15]. Figure 2 shows the risk of bias of each of these trials. Most of them had high risk of performance bias and detection bias, and low risk of attrition bias and reporting bias.

Table 1 shows the characteristics of the included trials. No RCT compared differing criteria for starting pharmacologic therapy after the diagnosis of GDM and initial diet therapy. Eight out of the 15 included RCTs (53%) used the one-step diagnostic test [1,4–6,8–10,12]; six (40%) trials used the two-step test [2,3,7,11,13,15]; and Spaulonci et al. used either the one- or two-step test [14]. Sample size ranged from 23 [6] to 1000 women [5]. For each RCT we reported inclusion and exclusion criteria of the enrolled patients when described in the RCT.

Table 2 shows the methods of management of women included in trials. In most of them (10 RCTs, 67%) glucose monitoring was assessed four times daily (fasting and either 1, 1.5 or 2 h after each of the three main meals – breakfast, lunch, and dinner) [1,5,7–9,11–15]; 2 (13%) trials used seven times daily approach (i.e. fasting, preprandial before lunch and dinner, 2 h after each main meal) [2,10]; 1 (7%) trial checked nine times daily monitoring, (fasting and 1 and 2 h after each main meal); (3) 1 (7%) trial monitored six times daily (fasting, preprandial before lunch and dinner, 1 h after each main meal); (4) and 1 (8%) trial did not describe the monitoring approach [6].

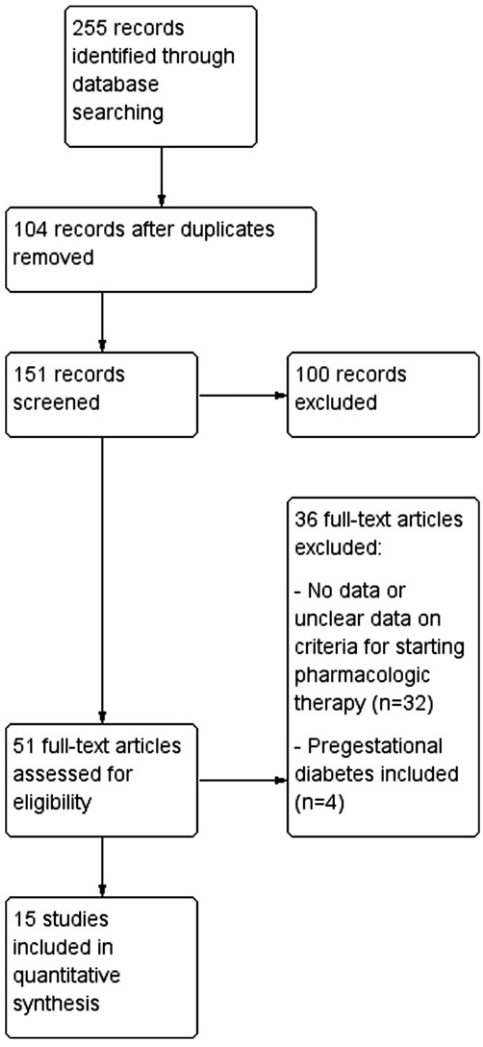

Figure 1. Flow diagram of studies identified in the systematic review. (Prisma template [Preferred Reporting Item for Systematic Reviews and Meta-analyses]).

Fourteen out of 15 (93%) RCTs used fasting glucose as a target [1–5,7–15], the higher fasting value allowed was 99 mg/dL: 8/14 (57%) used a value lower or equal to 90 mg/dL as target [1–4,9,10,12,15], 5 (36%) used 95 mg/dL [7,8,11,13,14], and 1 (7%) used 99 mg/dL [5]. Of the 10 RCTs using the 2-h postprandial value as target, 9 (90%) had 120 mg/dL as cutoff [2,6,9–15], and 1 used 126 mg/dL as the cutoff [5]. Of the four RCTs using 1-h postprandial value as target, three (75%) had 120 mg/dL as cutoff [3,4,7], and one 140 mg/dL [1]. One RCT used the 1.5-h postprandial value of 120 mg/dL as a target[8]. One RCT used the 2-hour postprandial target of 120 mg/dL only [6]. One RCT considered also the Hb1Ac value of 6.0 g/dL [9].

Regarding the type of initial nonpharmacologic treatment, 15 RCTs (100%) reported a new diet was recommended, while 4 RCTs (27%) reported that exercise was also recommended.

Regarding the glucose values used for starting pharmacologic therapy after diet and exercise, there were seven different criteria that the included studies applied:

- Thirteen trials (87%) used 1 or 2 values higher than the target values [1,2,4–13,15]; of these, 7/13 (54%) used 1 value higher than target values [2,6,7,9,10,13,15], and 6/13 (46%) used 2 values higher than target values [1,4,5,8,11,12]. Of these 13 trials, 5 (38%) assessed 1 week of glucose values [2,11–13,15], 7 (54%) assessed 2 weeks [1,4–7,9,10], 1 assessed either 2 or 4 weeks [8], and in 1 trial the finding of 1 fasting value higher than the target value was enough to start pharmacologic therapy [7].
- One trial (7%) used >50% of the values higher than the target values in 1 week [3].
- One trial (7%) used >30% of the values higher than the target values in 1 week [14].

Discussion

Main findings

This systematic review of 15 RCTs, including 4307 women, evaluated the criteria for starting pharmacologic therapy in women with GDM. We did not find any RCT comparing different criteria for starting pharmacologic therapy. All 15 RCTs included women with GDM. The most common features for these RCTs were that they used the one-step test (with 75-g glucose load) for GDM diagnosis (8/15; 53%); 67% (10/15 RCTs) monitored glucose values four times per day; and 50% (7/14) used a fasting target of 90 mg/dL and 90% (9/10) a 2-h target of 120 mg/dL.

Regarding our main aim, we found seven different criteria for starting pharmacologic therapy after diet in women with GDM. The most commonly used criterion was either 1 or 2 values per 1 or 2-week period higher than the target values (7 RCTs, 47%), of which four used only 1 value (27% of total), and three (20% of total) used two values.

There were several limitations in our study. No trials comparing a policy of very tight versus tight glycemic control and assessing the criteria for starting pharmacologic therapy in diabetes in pregnancy could be identified. Therefore, a standard meta-analysis was not feasible. The clinical heterogeneity within the trials was very high. The included trials used different protocol management, diagnostic test, initial medication therapy, glucose monitoring, and target glucose values. Moreover, not all RCTs considered the same

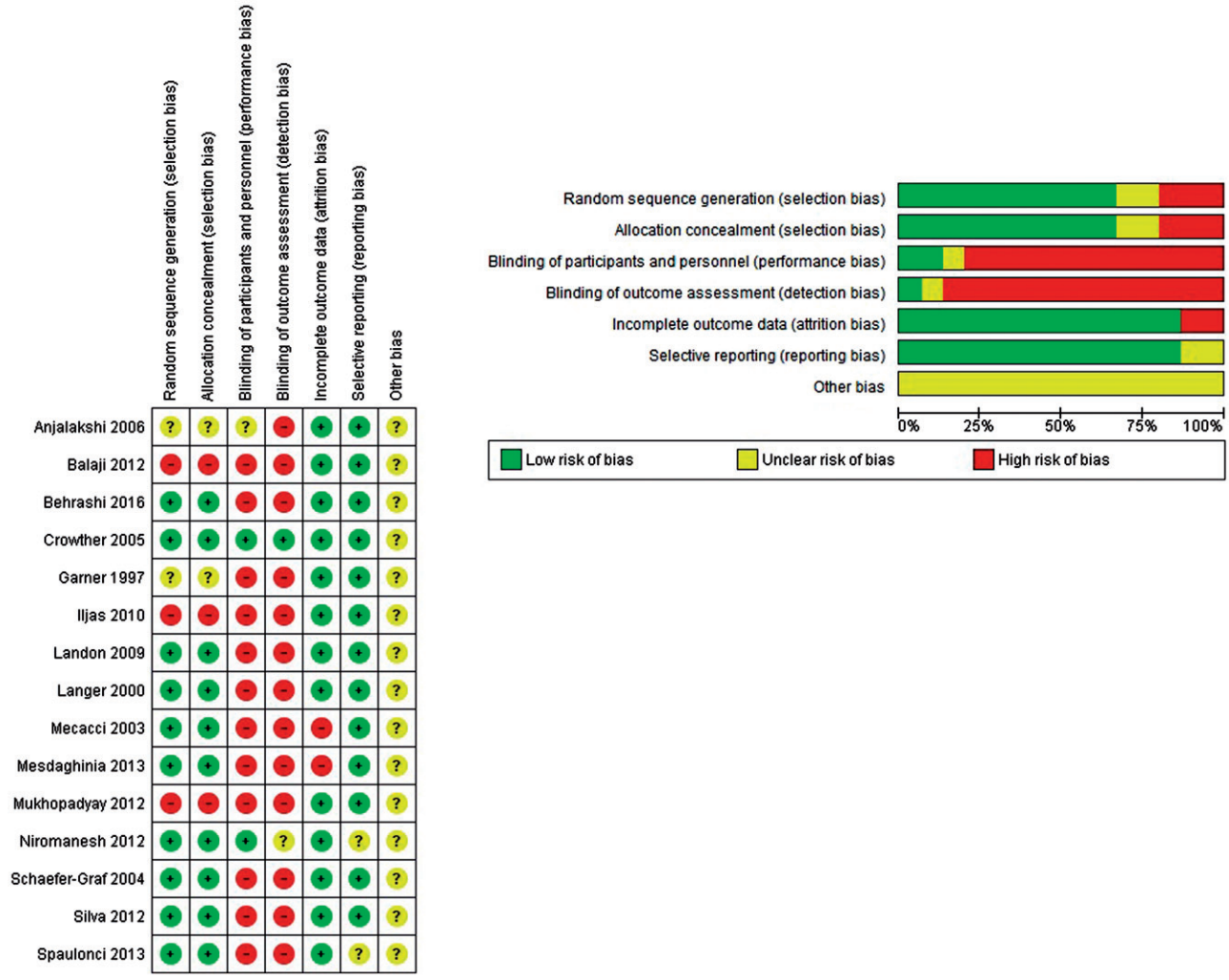

Figure 2. Assessment of risk of bias. (A) Summary of risk of bias for each trial; Plus sign: low risk of bias; minus sign: high risk of bias; question mark: unclear risk of bias. (B) Risk of bias graph about each risk of bias item presented as percentages across all included studies.

outcomes. The impossibility to compare the studies was the major shortcoming of our review.

Interpretation and conclusions

When evaluating RCTs that included criteria for starting pharmacologic therapy in women with GDM, the most common criteria for GDM diagnosis was the one-step test. The most common frequency for glucose monitoring was four times per day, i.e. fasting and after each main meal, using a fasting of 90 mg/dL and a 2 h of 120 mg/dL as targets. Importantly, we found seven different criteria for starting pharmacologic therapy after diet. Most studies used very tight criteria of either 1 or 2 values in one- or 2-week period higher than the target values, of which 7 studies used only 1 value (47% of total), and 6 used 2 values (40% of total). While very tight (1 or 2 abnormal target values in 1 or 2 weeks) versus tight (> 30% or >50% abnormal target values in 1 week) criteria for starting pharmacologic therapy did not seem to affect outcomes, it is impossible to really assess this comparison given the absence of head-to-head RCTs with this study design. Furthermore, the outcomes are in part the effect of the pharmacologic therapy used after the initial nonpharmacologic treatment.

Our study underlines the unmet need to standardize worldwide GDM screening and management. Regarding screening, recent RCTs and a meta-analysis demonstrate that one-step approach seems to be the best screening method [65]. Additionally, regarding GDM management, international societies do not agree on the criteria to switch from diet to pharmacological therapy and which is the first medication to adopt (e.g. insulin versus oral hypoglycemic agents).

Therefore, future well-designed and properly powered RCTs are needed to answer many questions regarding GDM diagnosis and management, including

Table 1. Characteristics of the included trials.

	Origin	Sample size	Diagnostic test used[a]	Inclusion criteria	Exclusion criteria
Garner et al. [1]	Canada	299	One step	All pregnant women between 24 and 32 weeks otherwise low-risk pregnancy	Multiple gestation; maternal–fetal blood group incompatibility; known congenital anomaly; prior evidence of placenta previa or abruptio placentae; significant maternal disease including chronic hypertension, connective tissue disease, endocrine disorders, and chronic hepatic disease; long-term medical therapy affecting glucose metabolism such as steroids and beta-mimetic tocolytic agents; and imminent delivery
Langer et al. [2]	USA	404	Two step	Singleton pregnancies, between 11 and 33 weeks	Not stated
Mecacci et al. [3]	Italy	49	Two step	Caucasian race, singleton pregnancy, pregestational BMI between 19 and 25 kg/m^2	Not stated
Schaefer-Graf et al. [4]	Germany	187	One step	(1) All F $<$ 120 mg/dL (6.6 mmol/l) and 2 h $<$ 200 mg/dL (11.1 mmol/l); (2) Singleton pregnancy 16–34 weeks confirmed by US before 20 weeks; (3) No maternal medical conditions known to affect fetal growth; (4) No abuse of tobacco, alcohol, or illicit drugs during pregnancy	Not stated
Crowther et al. [5]	Australia	1000	One step	Singleton or twin pregnancies	Previously treated GDM or active chronic systemic disease (except essential hypertension)
Anjalakshi et al. [6]	India	23	One step	Singleton pregnancies	–
Landon et al. [7]	USA	958	Two step	Pregnancies between 24 and 31 weeks, F $<$ 95 mg/dL at 100 g OGTT	PDM, an abnormal result on a glucose screening test before 24 weeks, history of stillbirth, multifetal gestation, asthma, or chronic hypertension; if taking corticosteroids; known fetal anomaly; imminent or preterm delivery was likely because of maternal disease or fetal conditions
Ijäs et al. [8]	Finland	97	One step	Pregnancies between 12 and 34 weeks	Preeclampsia, essential hypertension requiring antihypertensive medication or fetal growth restriction ($<$5p for GA)
Balaji et al. [9]	India	320	One step	Age 20–30 years, between 12 and 28 weeks, BMI $\leq$35 kg/m^2 at 1st visit	PDM, ketoacidosis, severe kidney disease, cardiovascular disease, stroke, cancer, severe psychological disorders, hypothyroidism, anemia, antibiotic treatments or currently taking insulin
Mukhopadhyay et al. [10]	India	60	One step	Singleton	PDM, severe anemia, heart disease, renal disorder, in treatment with steroids
Niromanesh et al. [11]	Iran	160	Two step	18–40 years, between 20 and 34 weeks	History of systemic underlying diseases (cardiovascular, renal, liver and autoimmune), substance abuse, overt diabetes mellitus (except previous history of GDM) and major fetal malformation
Silva et al. [12]	Brazil	200	One step	$>$ 18 years, singleton, between 11 and 33 weeks, AC 10–75%, no maternal or fetal conditions likely to affect treatment or neonatal outcome	Intolerance of the drugs or unwillingness to participate, fetal risk (AC $>$97% or $<$5%), lack of follow-up or fetal malformation diagnosed upon delivery, other pathologies that might interfere with perinatal results or hypoglycemic therapy
Mesdaghinia et al. [13]	Iran	200	Two step	18–45 years, singleton, between 24 and 34 weeks	PDM
Spaulonci et al. [14]	Brazil	92	One or two step	Singleton	Risk factors for lactic acidosis (renal failure, heart failure, chronic liver disease, severe chronic pulmonary disease, coronary insufficiency, history of thromboembolic phenomena), anatomic and/or chromosome anomalies of the conceptus detected by ultrasonography
Behrashi et al. [15]	Iran	258	Two step	18–45 years, singleton pregnancy, between 1 and 33 weeks	PDM, premature rupture of membranes, severe bleeding, or known kidney, and hepatic, hematological, and/or cardiovascular disease
Total		4307	–	–	–

GDM: gestational diabetes mellitus; PDM: pregestational diabetes mellitus; IBW: ideal body weight; tr: trimester; US: ultrasound.
[a]One step, i.e. 75 g 2-h glucose load; two step, i.e. 50 g 1-h glucose load, followed if abnormal by a 100 g 3-h glucose load test.

Table 2. Management of women included in the trials.

	Glucose monitoring	Target value for glycemic control	Type of diet	Recommendations about exercise	Glucose values used for starting pharmacologic therapy based on target values
Garner et al. [1]	Four times daily[a]	F: < 4.4 mmol/l (80 mg/dL); 1 h: < 7.8 mmol/l (140 mg/dL)	• 35 kilocalories/kg IBW/day	Not stated	2 or more values higher in 2 weeks
Langer et al. [2]	Seven times daily[b]	F: < 5.0 mmol/l (90 mg/dL); Preprandial: < 5.3 mmol/l (95 mg/dL) 2 h: < 6.7 mmol/l (120 mg/dL)	• 25 kilocalories/kg BW/day for obese women; • 35 kilocalories/kg BW/day for nonobese women; • Three meals and 4 snacks; • 40 to 45% calories from carbohydrates	Not stated	1 or more preprandial or 2 h values higher in 1 week
Mecacci et al. [3]	Nine times daily[c]	F: < 5.0 mmol/l (90 mg/dL); 1 h: < 6.7 mmol/l (120 mg/dL)	ADA recommendations[d]	Not stated	More than 50% values higher after 1 week
Schaefer-Graf et al. [4]	Six times daily[e]	Intervention group: F: < 4.5 mmol/l (80 mg/dL); 1 h: < 6.1 mmol/l (110 mg/dL) Control group: F: < 5.0 mmol/l (90 mg/dL); 1 h: < 6.7 mmol/l (120 mg/dL)	• 25 kilocalories/kg BW/day for overweight women; • 30 kilocalories/kg BW/day for normal weight women	Exercise after meals	Intervention group: • AC >75th p < 36 weeks or • F ≥ 120 mg/dL and/or • 2 h ≥ 200 mg/dL Control group: • Two or more values or • Four profiles with at least 1 value higher in 2 weeks
Crowther et al. [5]	Four times daily[f]	F: < 5.5 mmol/l (99 mg/dL); 2 h: < 7.0 mmol/l (126 mg/dL)	Dietary advice from qualified dietician	Not stated	• Two values higher in 2 < 35 weeks; • 2 h > 8.0 mmol/l (144 mg/dL) in 2 > 35 weeks; • One value >9.0 mmol/l (162 mg/dL) in 2 weeks
Anjalakshi et al. [6]	Not specified	2 h: < 6.7 mmol/l (120 mg/dL)	MNT	Not stated	1 value 2 h higher in 2 weeks
Landon et al. [7]	Four times daily[f]	F: < 5.3 mmol/l (95 mg/dL); 2 h: < 6.7 mmol/l (120 mg/dL)	ADA recommendations[g]	Not stated	• > 50% values higher between 2 study visits; • One random value >160 mg/dL (8.9 mmol/l) • 1 F > 95 mg/dL, the patient's caregiver initiated treatment (more or less seven visits)
Ijäs et al. [8]	Four times daily[h]	F: < 5.3 mmol/l (95 mg/dL); 1.5 h: < 6.7 mmol/l (120 mg/dL)	Dietary and lifestyle counseling	Not stated	2 values higher in 2–4 weeks
Balaji et al. [9]	Four times daily[f]	F: < 5.0 mmol/l (90 mg/dL); 2 h: < 6.7 mmol/l (120 mg/dL); Hb1Ac: < 6.0 g/dL	MNT	Not stated	1 value higher in 2 weeks
Mukhopadhyay et al. [10]	Seven times daily[b]	F: < 5.0 mmol/l (90 mg/dL); 2 h: < 6.7 mmol/l (120 mg/dL)	• 25 kilocalories/kg BW for obese women; • 35 kilocalories/kg BW for nonobese women; • Three daily meals; 40–45% of calories from carbohydrates	Not stated	1 value higher in 2 weeks

(*continued*)

Table 2. Continued

	Glucose monitoring	Target value for glycemic control	Type of diet	Recommendations about exercise	Glucose values used for starting pharmacologic therapy based on target values
Niromanesh et al. [11]	Four times daily[f]	F: < 5.3 mmol/l (95 mg/dL); 2 h: < 6.7 mmol/l (120 mg/dL)	• 15 kilocalories/kg BW for obese women; • 22 kilocalories/kg BW for overweight women; • thirty-kcal/kg BW normal weight women; • 40 kilocalories/kg BW for underweight women; • 45% of calories from carbohydrates, 20% from protein and 35% from fat; • Three meals and 3 snacks; • Calories: 10% breakfast, 30% each lunch and dinner, 30% as snacks	30 min of walking per day	2 values higher in 1 week
Silva et al. [12]	Four times daily[a]	F: < 5.0 mmol/l (90 mg/dL); 1 h: < 6.7 mmol/l (120 mg/dL)	• 25 kilocalories/kg BW/day for overweight women; • 35 kilocalories/kg BW/day for normal weight women • Three full meals and 4 light meals; • 35 to 45% calories from carbohydrates	Not stated	2 values higher after 1 week
Mesdaghinia et al. [13]	Four times daily[f]	F: < 5.3 mmol/l (95 mg/dL); 2 h: < 6.7 mmol/l (120 mg/dL)	Dietary changes[i]	Not stated	1 value higher in 1 week
Spaulonci et al. [14]	Four times daily[f]	F: < 5.3 mmol/l (95 mg/dL); 2 h: < 6.7 mmol/l (120 mg/dL)	• 25 to 35 kcal/kg IBW based on pregestational BMI • fifty-five% carbohydrates, 15% proteins, 30% fat	30-min walk 3 times a week	> 30% values higher in 1 week
Behrashi et al. [15]	Four times daily[f]	F: < 5.0 mmol/l (90 mg/dL); 2 h: < 6.7 mmol/l (120 mg/dL)	Education for lifestyle change (exercise and diet)	Education for lifestyle change (exercise and diet)	1 value higher in 1 week

F: fasting; GA: gestational age; IBW: ideal body weight; BW: body weight; BMI: body mass index.
[a]Fasting and 1 h after each main meal – breakfast, lunch, and dinner.
[b]Fasting, before lunch and dinner, 2 h after main meals – breakfast, lunch, and dinner, and at bedtime.
[c]Fasting, preprandial before lunch and dinner, 1 and 2 h after each main meal – breakfast, lunch, and dinner.
[d]American Diabetes Association [67].
[e]Fasting, preprandial before lunch and dinner, 1 h after each main meal – breakfast, lunch, and dinner.
[f]Fasting and 2 h after each main meal – breakfast, lunch, and dinner.
[g]American Diabetes Association [68].
[h]Fasting and 1.5 h after each main meal – breakfast, lunch, and dinner.
[i]Cheung [69].

which criteria should be used to recommend pharmacologic therapy because of failed diet therapy.

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Disclosure statement

The authors report no conflict of interest.

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