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ORIGINAL ARTICLE

METformin in DIastolic Dysfunction of MEtabolic Syndrome (MET-DIME) Trial: Rationale and Study Design

MET-DIME Trial

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Abstract
Purpose Insulin resistance plays a central role in the pathophysiology of metabolic syndrome (MS). Its cardiac deleterious effects are characterized by an increase in fibrous tissue that increases myocardial stiffness and contributes to subclinical left ventricular diastolic dysfunction (LVDD) and heart failure with preserved ejection fraction in patients with MS. In addition to lifestyle counseling (LC), metformin treatment may attenuate or even reverse diastolic dysfunction in these patients. This trial aims to evaluate if treating non-diabetic patients with MS and LVDD with metformin in addition to LC improves diastolic function and assess its impact in functional capacity and health-related quality of life (HRQoL).
Design MET-DIME is a phase II prospective, randomized, open-label, blinded-endpoint trial with a scheduled follow-up of 24 months. Fifty-four patients (adults 40–65 years old with AHA/NHLBI criteria of MS and rest LVDD) will be randomized by minimization to LC only or LC plus metformin (target dose of 1,000 mg twice daily). The primary endpoint will be change in mean of early diastolic mitral annular velocity, an echocardiographic parameter highly correlated with myocardial fibrosis (serial measurements will be performed at 6, 12 and 24 months). The secondary endpoints will include change in diastolic parameters at rest; metabolic, inflammatory and remodeling biomarkers; functional capacity; adipose tissue volumes and HRQoL.
Conclusion MET-DIME is a pragmatic trial designed to evaluate if adding metformin to the standard treatment of patients with MS improves diastolic dysfunction, assessing its impact in metabolic homeostasis, proinflammatory state, functional capacity and HRQoL.

Keywords Metabolic syndrome · Metformin · Diastolic Dysfunction · Insulin resistance

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Metabolic Syndrome and Diastolic Dysfunction

The metabolic syndrome (MS) is a constellation of cardiovascular risk factors that reached epidemic proportions during the last two decades. Although there are 6 sets of diagnostic criteria for MS, approximately 20 to 40 % of the adult population of United States and Europe have MS [1]. The prevalence of MS in Portugal also varies with the definition used but approximately 30 % of Portuguese adults fulfill the criteria for MS, with a clear association with cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM) [2]. The AHA/NHLBI modification of the NCEP-ATPIII criteria of MS [3] shows the strongest association with CVD in the Portuguese population [4]. Furthermore, although the association with cardiovascular disease and mortality is one of the major concerns on the approach to patients with MS, its harmful impact on global health with functional and psychological repercussions should also be considered [5, 6].

Insulin resistance is central to the pathophysiology of MS, associated with a proinflammatory, prothrombotic and oxidative state that increases the risk of cardiovascular disease, with its micro and macrovascular complications [7]. Moreover, MS is definitely associated with the obesity epidemic [7]. Abdominal obesity is one of the diagnostic criteria for MS, although waist circumference is not capable of distinguish between

visceral fat and subcutaneous adipose tissue, the former with a more ominous effect on cardiovascular function [8]. In the recent years other adipose tissues locations such as pericardial and epicardial fat were also shown to be associated with atherosclerotic burden and coronary disease, representing new cardiometabolic risk markers [9].

The metabolic dysfunctional status previously described is associated with deterioration of cardiac structure and function. Indeed, myocardial fibrosis plays a pivotal role in cardiac dysfunction in hypertensive and diabetic heart disease [10] and is also present in patients with MS [11]. Furthermore, cardiac remodeling with an important fibrotic response is exquisitely associated to left ventricle diastolic dysfunction (LVDD) and is present in older hearts, LV hypertrophy and T2DM [12]. LVDD is also present in patients with MS and there seems to be an association between the grade of LVDD and the number of coexisting MS criteria [13]. However, LVDD in MS patients is often subclinical [5, 14], representing a harder challenge to detect it and follow-up these patients adequately. Not only LVDD is central to the pathophysiology of heart failure with preserved ejection fraction (HF-PEF) [15] but insulin resistance, arterial hypertension, obesity and dyslipidemia are comorbidities of a large proportion of these patients which represent at least half of the heart failure patients [16, 17] The pathophysiological mechanisms of LVDD in HF-PEF are a topic of intense research, and our group has played an active role clarifying some issues regarding not only the modulation of diastolic function but also the mechanisms involved in LVDD [18].

Metformin and Metabolic Syndrome

Considering the dominant role of insulin resistance in the pathophysiology of the MS and its cardiac deleterious effects, it seems reasonable to consider that an increase in insulin sensitivity might be associated with a global improvement in the structure and function of the heart. Metformin is a biguanide approved for the treatment of T2DM known by its insulin-sensitizing effect. Furthermore, in the last years it was demonstrated in animal models of insulin resistance and arterial hypertension that metformin prevents cardiac remodeling and progression to heart failure with an evident benefit in time periods less than a year [19, 20]. The cardioprotection afforded by metformin treatment seems to result from interference with TGF-beta signaling pathway and activation of the AMP-kinase signaling cascade [21, 22].

Since insulin resistance is a dominant player in the MS in non-diabetic patients, improvement of the metabolic profile of these patients with metformin might be associated with favorable remodeling of myocardial structure and an improvement in myocardial function. According to the current recommendations for the management of non-diabetic patients with MS [3], lifestyle changes are mandatory and metformin is an option to these patients, but the demonstration of an unequivocal cardiovascular benefit would provide an inoffensive and widely available pharmacological weapon to improve the quality of life and delay the cardiovascular detrimental effects of MS.

Trial Objectives

1. Assess if treating non-diabetic patients with MS and rest LVDD with metformin, in addition to lifestyle counseling, improves diastolic function and assess its impact in functional capacity and health-related quality of life (HRQoL);
2. Evaluate if biomarkers of cardiac remodeling, inflammation, and glucose homeostasis are predictive factors of response to metformin treatment of non-diabetic patients with MS and LVDD.

Design

The study will include a screening phase and a prospective, randomized, open-label, blinded-endpoint (PROBE) trial to assess the effect of metformin administration in addition to lifestyle counseling to non-diabetic patients with MS during a scheduled duration of 24 months of follow-up.

During the screening phase patients will be recruited from the outpatient clinic of Gaia/Espinho Hospital Centre (tertiary care hospital with a reference population of 700,000 patients) dedicated to non-diabetic hypertensive patients with a total population of approximately 1,000 adult patients, the majority of whom have a clinical diagnosis of MS.

After the screening phase (with a maximum duration of 10 months), eligible subjects will be randomized to lifestyle counseling only or lifestyle counseling plus metformin treatment and followed-up for a 2-year period (Fig. 1). The lifestyle counseling will be provided in the form of written information and individualized during the interview in all clinic visits, emphasizing the importance of a healthy lifestyle, engage on regular moderate-intensity physical activity and healthy diet. Metformin treatment will start with 500 mg once daily (at breakfast) during the first week (Step 1); if well tolerated, the dose will be progressively increased to 500 mg twice daily (at breakfast and dinner) during 1 week (Step 2), to 1,000 mg at breakfast and 500 mg at dinner during 1 week (Step 3), in order to reach the target dose of 1,000 mg twice daily (at breakfast and dinner) during the rest of the follow-up.

Randomization will be performed using the minimization method [23]. Minimization criteria will be age (under 55 years

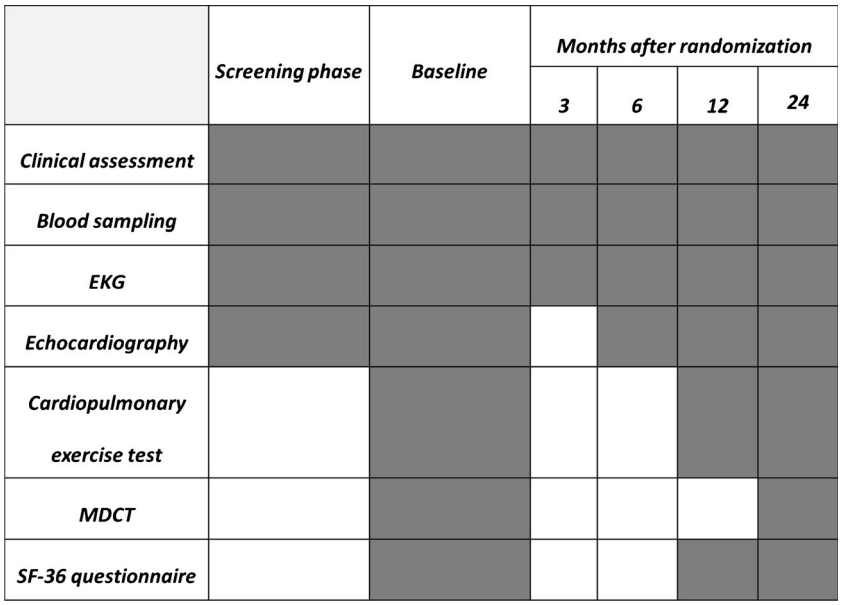

Fig. 1 Planned follow-up for all participants. *EKG* electrocardiography; *MDCT* multidetector computed tomography; *SF-36* Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36)

old or ≥55 years old), gender (male or female), baseline treatment with drugs that affect the renin-angiotensin-aldosterone axis (ACE inhibitors, angiotensin receptor blockers, mineralocorticoids antagonists or renin inhibitors), presence or absence of typical symptoms or most specific signs of heart failure [according to the European Society of Cardiology [24]] and degree of diastolic dysfunction [grades I, II and III, EAE/ASE echocardiographic criteria [25]].

Study Population

Eligible participants will be non-diabetic adults aged between 40 and 65 years fulfilling the AHA/NHLBI criteria for clinical diagnosis of MS [(at least 3 of the following: waist circumference ≥102 cm in males or ≥88 cm in females; fasting plasma triglycerides ≥150 mg/dL or on drug treatment for elevated triglycerides; fasting HDL cholesterol <40 mg/dL in males or <50 mg/dL in females or on drug treatment for reduced HDL; systolic blood pressure≥130 mmHg or diastolic blood pressure≥85 mmHg or on antihypertensive drug treatment in a patient with history of hypertension; fasting plasma glucose≥100 mg/dL) [3]] and with echocardiographic evidence of LVDD at rest, considering the mean of septal and lateral E′ as assessed by Tissue Doppler Imaging echocardiography (E'_{mean}<10.2 cm/s if 40–59 years old or E'_{mean}<7.2 cm/s if aged 60 to 65 years old) [25]. Patients should be in a stable dose of antihypertensive or antidislypidemic medication at least 1 month prior to recruitment, able to perform a cardiorespiratory fitness test and give a written informed consent.

Exclusion criteria are described in Table 1.

Endpoints

The primary endpoint will be the change in E'_{mean} during the 24 month follow-up period. Serial echocardiographic measurements will be performed at baseline, month 6, month 12 and month 24. The E′ is an echocardiographic parameter strongly correlated with myocardial fibrosis (r=−0.7) [25, 26].

The secondary endpoints will include diastolic echocardiographic parameters, metabolic indices, cardiovascular, remodeling and inflammation biomarkers, functional capacity, epicardial, pericardial and abdominal adipose tissue volumes, coronary calcium score and HRQoL (Table 2).

Safety and Adverse Reactions

Although metformin is a widely used drug, its use at the dose of 1,000 mg twice daily is associated with gastrointestinal (GI) side effects at the onset of treatment. These side effects are reduced if the medication is taken with food and the dose titrated from once daily to twice daily over several weeks.

Potential non-gastrointestinal (non-GI) side effects include, but are not limited to: severe headache, moderate edema, disabling leg cramps, arthralgia, myalgia, dizziness, mild rashes, and dysmenorrhea.

If non-GI side effects considered likely to be due to metformin occur and require cessation of treatment during Step 1, metformin will be stopped for 4 weeks. If the non-GI symptoms disappear, a second attempt to introduce metformin will be performed after 4 weeks. If symptoms re-occur, metformin will be discontinued one more time. A last try will be performed after 4 weeks. If metformin continues to be not tolerated, the patient will be excluded from the trial.

Table 1 Study population: inclusion and exclusion criteria

Inclusion criteria

- 40-65 years old
- Metabolic syndrome, AHA/NHLBI criteria [3] (at least 3 of the following):
  - Waist circumference ≥102 cm in males or ≥88 cm in females;
  - Fasting plasma triglycerides ≥150 mg/dL or on drug treatment for elevated triglycerides;
  - Fasting HDL cholesterol <40 mg/dL in males or <50 mg/dL in females or on drug treatment for reduced HDL;
  - Systolic blood pressure≥130 mmHg or diastolic blood pressure≥85 mmHg or on antihypertensive drug treatment in a patient with history of hypertension;
  - Fasting plasma glucose≥100 mg/dL.
- Rest left ventricle diastolic dysfunction, based on the mean of septal and lateral E′ (E'_{mean})
  - E'_{mean}<10.2 cm/s if 40–59 years old;
  - E'_{mean}<7.2 cm/s if aged 60 to 65 years old.
- Stable dose of antihypertensive or antidislypidemic medication at least 1 month prior to recruitment.
- Able to perform a cardiopulmonary exercise test.

Exclusion criteria

- Diabetes mellitus according to the ADA criteria [27] (at least one of the following):
  - fasting plasma glucose ≥126 mg/dL;
  - 2-h plasma glucose ≥200 mg/dL during an oral glucose tolerance test, as described by the WHO;
  - random plasma glucose ≥200 mg/dL in a patient with classical symptoms of hyperglycemia or hyperglycemic crisis;
  - hemoglobin A1C≥6.5 % using a method that is NGSP certified and standardized to the DCCT assay or ≥48 mmol/mol reported in IFCC units.
- Ischemic heart disease (history of angina, acute coronary syndrome, acute myocardial infarction or coronary artery bypass graft surgery);
- Left ventricle ejection fraction less than 50 % (assessed by transthoracic echocardiography);
- Moderate or severe valvular heart disease;
- Pericardial disease;
- Uncontrolled atrial or ventricular tachyarrhythmias;
- History of myocarditis;
- Renal disease or dysfunction (creatinine clearance <60 mL/min, calculated by the Cockcroft-Gault formula)
- Significant liver disease (aspartate aminotransferase or alanine aminotransferase ≥2.5 times upper limit of normal)
- Females who are pregnant, planning to become pregnant or who admit sexual activity without appropriate contraception;
- Lactation.

Table 2 Primary and secondary endpoints

Primary endpoint

- Mean of septal and lateral early diastolic mitral annular velocities (E'_{mean})—baseline, 6, 12, 24 months

Secondary endpoints

- Diastolic echocardiographic parameters:
  - E/E′ratio; Isovolumetric relaxation time (IVRT); E/A ratio, E wave deceleration time, diastolic dysfunction grades according to the ASE/ESE consensus, strain rate during IVRT (SR-IVRT) and E/SR-IVRT ratio
- Metabolic biomarkers:
  - Insulin and glucose plasma levels, insulin resistance (HOMA—Homeostasis Model Assessment) and adiponectin levels;
- Cardiovascular biomarkers:
  - N-terminal pro-BNP and high sensitivity C-reactive protein;
- Remodeling and inflammation biomarkers:
  - TNF-α (tumor necrosis factor α) , TIMP1 (type 1 tissue inhibitor of matrix metalloproteinase) e GDF-15 (growth-differentiation factor 15);
- Functional capacity during cardiopulmonary exercise test:
  - Peak oxygen uptake, anaerobic threshold and ventilatory efficiency
- Epicardial, pericardial and abdominal adipose tissue volumes, and coronary calcium score, assessed by cardiac multidetector CT (MDCT)
- Health-related quality of life, according to Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36).

If non-GI side effects occur that are considered likely due to metformin during Step 2, Step 3 or Target Dose, the participant will drop back to the previous titulation step for 4 weeks. A second attempt to restart the corresponding dose will be made after 4 weeks. If symptoms re-occur during this second attempt, the participant is restarted at the previous titulation step for 4 weeks again. A third attempt to uptitrate metformin is made after 4 weeks. If this third attempt fails, the participant will be maintained with the dosing of the previous titulation step for the remainder of the follow-up.

GI side effects will be managed in the same way as non-GI symptoms but each interruption period (if in Step 1) or dose reduction (if in other titulation steps) will last only 1 week.

Statistical Plan

Statistical Analysis

To specifically address Objective 1, the analysis of the primary endpoint will be performed on an intention to treat basis by repeated-measures analysis of covariance (ANCOVA) including the following variables: baseline mean E′, age and mean arterial pressure, treatment group, gender, treatment with drugs that affect the renin-angiotensin-aldosterone axis at baseline, presence or absence of signs/symptoms of heart failure and baseline degree of diastolic dysfunction. Serial measurements will include baseline, month 6, month 12 and month 24 assessment. An interim analysis of the primary endpoint is planned at the end of the first 12 months of follow-up.

To address trial Objective 2 we will explore the ANCOVA model previously described assessing interaction between treatment group and baseline levels of metabolic indices and inflammatory and remodeling biomarkers.

All statistical tests will be two-sided, with an alpha level of 0.05.

Power and Sample Size

Considering the prespecified analysis of the primary endpoint at 12 months of follow-up, a sample size of 21 patients for each group was estimated to allow the detection of a difference in means of 1.5 cm/s with a power of 80 % and an alpha of 0.05, assuming a standard deviation of 2.3 cm/s in each group [25] and a conservative baseline/follow-up measurement correlation of 0.3. Considering a potential drop-out rate of 20 %, the final estimated sample size needed in each allocation arm was 27 patients.

Ethical and Legal Issues

All eligible participants should be able and willing to provide written informed consent in order to be included in this study.

This randomized trial was approved by the Local Ethics Committee, Portuguese Data Protection Agency, INFARMED (National Pharmacy and Medicines Institute) and CEIC (National Ethics Committee for Clinical Research). It is registered in www.clinicaltrials.gov with the Identifier NCT02017561. The study will be conducted in accordance with the Declaration of Helsinki.

Conclusion

MET-DIME is a pragmatic trial designed to evaluate if adding metformin to the standard treatment of patients with MS improves diastolic dysfunction, assessing its impact in metabolic homeostasis, proinflammatory state, functional capacity and HRQoL.

Conflicts of interest The authors declare that they have no conflict of interest.

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