A Multidisciplinary Weight Loss Program at AUB-MC
An open label pilot randomized controlled trial

1- Abstract:

Background:

Obesity has reached alarming rates worldwide. Despite all the data on the excess weight related morbidity and mortality, obesity under-diagnosis and under-treatment still represent a major challenge in Western countries, and more so in the Middle East region. Scientific societies recommend a multidisciplinary approach, including counseling on diet and physical activity, behavioral intervention, in addition to pharmacologic and/or surgical interventions, as needed. While several weight loss programs are currently available in the US, such programs in developing countries, including Lebanon, are still scarce.

Aim:

Assess the feasibility and efficacy of a multi-disciplinary weight loss program, with an innovative dietary intervention, to address the obesity care gap.

Methods:

This is a 6-month open label pilot randomized controlled that will be conducted in patients with obesity, presenting for medical weight loss. All patients will receive metformin, at a dose of 850 mg twice per day, and will be randomized to Arm 1 – intervention arm: multidisciplinary weight loss program (diet and behavioral therapy, based on a curriculum inspired from the successful landmark Western weight loss trials, in addition to supervised exercise sessions), or Arm 2 - standard care. The dietary intervention aims at achieving a caloric restriction of 500 Kcal/d, through individual face-to-face sessions, and daily contact with a dietician on WhatsApp for the first month.

We will enroll 20 obese Lebanese adults per arm. The primary outcome is the mean percent weight loss per treatment arm. The primary analysis will be an intention to treat of unadjusted analysis. We will use Wilcoxon sum-rank to compare results between treatment arms.

Discussion:

We expect that a multi-disciplinary weight loss approach with innovative strategies, customized to individual participants' needs, increases adherence to lifestyle changes and improves weight loss and quality of life.

2- Background and rationale

Obesity prevalence and related co-morbidities

Obesity has reached alarming rates worldwide [1,2]. The Global Burden of Disease (GBD) study systematically collected data on body mass index (BMI) from representative studies conducted in 195 countries, and reported an obesity rate of 5% in children and 12% in adults [3]. Countries from the Middle East and North Africa (MENA) register obesity rates as high as ≥ 30% in adults [4]. Lebanon is no exception [5,6]. The 2017 WHO population based STEP survey of Lebanese adults revealed that up to 65% are overweight and 27% are obese [WHO 2017 Fact Sheets, unpublished data from the Lebanese Ministry of Public Health]. Obesity is associated with an increased risk of various non-communicable diseases (NCDs), 6-12 fold increase in diabetes mellitus risk, and 2-3 fold increased risk of cancer and cardio-vascular diseases [7]. In the GBD study, a high BMI accounted for 7.1% of all-cause mortality [3]. Currently, NCDs are the leading cause of death worldwide and in the Middle East, including Lebanon [8].

Guidelines recommendations on the approach to weight management

Several scientific societies from the US, Canada and UK have issued guidelines on the diagnosis and treatment of obesity (see Appendix 1)[9-18]. All these guidelines agree on the necessity of a multidisciplinary approach, including counseling on diet and physical activity, behavioral intervention, in addition to pharmacologic and/or surgical interventions, as needed (see Appendix 1). Dietary counseling is crucial for patient education on food composition and food caloric content [19]. Physical activity allows weight loss, and improves insulin sensitivity, cardiovascular and muscle fitness, and quality of life [20]. Behavioral interventions include individual and group meetings, for stimulus control, systematic approaches for problem solving, stress reduction, cognitive restructuring, motivational interviewing, and social support. All these interventions would help obese patients make healthy and mindful dietary choices, and allow not only weight loss, but also helps in weight maintenance [21]. Indeed, the importance of a multidisciplinary approach in the implementation of lifestyle changes for weight loss was demonstrated in landmark trials such as the Diabetes Prevention Program and the Look AHEAD studies [22,23], as discussed below.

Multi-disciplinary weight loss programs

Currently, several multidisciplinary weight management programs are available in the US. All these programs are led by physicians with a multidisciplinary team consisting of dieticians, nurses, psychologists, and physical activity specialists. Such programs imply frequent patients encounters, initially for weight loss, and later on, for weight maintenance.

Weight loss outcomes of various programs were published. The "Lifestyle Challenge Program" at Albany Medical College consisted of a team of a physician specializing in nutrition, pharmacist and behavioral psychologist [24]. A cohort of ninety obese patients enrolled in the program was followed up for the 20-week program period [24]. In addition to a significant mean weight loss of 5 kg (5% weight loss from baseline), the program allowed an improvement in quality of life, depressive symptoms, and binge eating disorders [24]. The "Clinical Weight Management Intervention Program" in Iceland included a 3-month intensive phase, consisting of one hour dietary and behavioral advice, and one hour of supervised physical activity, followed by a tapering phase, of less frequent clinical contacts [25]. A sample of 144 participants was followed up for 6 months and 56% of participants experienced 5-10% body weight loss [25]. A pilot study (N=48) evaluated a medically supervised program for weight loss in obese patients suffering from back pain, at the Ottawa Hospital, Canada [26]. The program consisted of sessions/workshops for behavioral, dietary and/or physical activity interventions [26]. At one year, there was a significant drop in

pain scores and in weight (mean weight loss ~ 15 kg) [26]. A Clinic-Based Multi-Disciplinary Weight Management Program at the Brigham and Women's Hospital (BWH) – Boston, including physicians, registered dieticians and bariatric surgeons, enrolling 232 participants over a period of 20 months, showed that the clinic no-show rates improved from 18% initially to 5.1% with telephone reminders (Obesity Society Abstract 2017). Weight loss in the medical treatment arm was 4.2-4.8%, depending on the use or not of medications (Obesity Society Abstract 2017). A more structured program at the BWH "Program for Weight Management" consisting of weekly sessions on behavioral, dietary interventions and exercise, showed a mean weight loss of 15 (6) kg at 6 months (Unpublished data, Personal communication with Dr F. Halperin)

Obesity under-diagnosis and under-treatment

Despite all the available data on mortality and morbidity and the current treatment options, obesity is still under-diagnosed and under-treated. In fact, several observational studies assessed obesity diagnosis and treatment rates in the primary care and other outpatient settings [27-29]. In US healthcare systems, the availability of BMI, a simple parameter, calculated from anthropometric measures, varied between 18 and 88%, depending on the health care plan [30]. Overweight and obesity prevalence rates (combined) ranged between 49 and 78% [27,31-33], while obesity rates were around 25 - 26% [29,34]. Despite these high prevalence rates, diagnosis rates were only 16-30% [28,29,32,34-36]. Furthermore, a much lower proportion (< 20% of those diagnosed) received counseling on weight reduction, diet and exercise [28,32], and there was a trend for a decline in weight reduction counseling among US physicians, despite the rising obesity rates[37]. In addition, even when weight reduction advice was given, only one third of patients received instructions to lose weight [38].

This illustrates a wide gap in the identification and management of obesity, worldwide and more so in our region. This gap has been traditionally related to physicians and covering agencies specific barriers, but more importantly patient's awareness, readiness and decision to embark on a weight loss program. Indeed, adherence to weight loss strategies remain the key for success [39]. Accordingly, establishing programs with innovative methods, easy to follow by the patients, is crucial.

The current project aims at evaluating the feasibility and efficacy of a multi-disciplinary weight loss program, using an innovative and simple dietary intervention. Such intervention is expected to enhance patients' compliance and adherence to lifestyle changes. In addition, the program includes supervised exercise sessions and behavioral therapy. Therefore, our project proposes an evidence based approach to close obesity treatment gaps.

3- Specific Aims

Hypothesis

A multi-disciplinary weight loss program, that includes an innovative and simple dietary intervention, behavioral therapy and physical education / supervised exercise sessions, on top of drug therapy, allows higher weight loss, compared to standard care.

Objectives
Comparing the 2 treatment arms, the multi-disciplinary weight loss program, and the standard care:

- Primary objective : Percent weight loss at 6 months after enrollment
  Percent weight loss is calculated using the following formula:
  [(baseline weight-follow up weight at 6 months)/ baseline weight] X 100
- Secondary and exploratory objectives:
  Change in body composition
  Change in the Quality of Life score (SF36)
  Change in the depression and anxiety
  Change in self-esteem and well being
  Change in physical fitness
  Change in levels of appetite hormones and metabolic markers
  Participants' compliance

4- Research design and Methods

a- Study design

This is a 6-month open label pilot randomized controlled trial that will be conducted in Lebanese subjects with obesity presenting for medical weight loss. All participants will receive Metformin at a dose of 850 mg twice per day. Patients will be randomized to 2 arms, as follows: arm 1 – a multidisciplinary weight loss program, including diet, behavioral therapy and physical education/supervised exercise sessions; diet and behavioral therapy are based on the curriculum of landmark studies, the Look AHEAD[22] and the Diabetes Prevention Program[23]; arm 2 – standard of care.

b- Study setting

This study will be conducted at AUB-MC, in the Endocrine clinics, private and Out-Patient Department (OPD), and at the Metabolic and Bariatric Surgery Unit (MBSU). The latter clinic is a host for obese patients who present for medical weight management. Participants will be approached by their primary physician (Drs. Marlene Chakhtoura, Sami Azar, and Ramzi Alami) who introduces the trial. Those who are interested are invited to meet the research assistant who will provide them with all the details related to the trial. Also, trial flyers (Appendix 2) will be available in the OPD and posters will be hung in Endocrine private clinics and OPD, and MBSU. Those who are interested will directly contact the RA using the extension available on the flyer.

c- Eligibility criteria

Inclusion Criteria:
-Lebanese adult with obesity (≥18 years), obesity being defined as BMI ≥ 30 kg/m^2
-Patients committed to frequent visit trials as per study protocol
-Patients not traveling outside Lebanon for at least the 6-month period of the trial
-Patients tolerating Metformin after a run-in period of 2 weeks

Exclusion criteria:
-Patients who have taken other weight reducing drug therapy in the previous 6 months

-Patients who have undergone bariatric therapy or endoscopic procedure, or planning to do so in the near future (at < 6 months)
-Patients with diabetes
-Patients working at our institution, as we will not be able to assess the adherence to study visits nor the feasibility of such a program in the general population, presenting to AUB-MC only for clinical care
-A family member of a patient already enrolled in the study, as the participants will not be independent
-Pregnant obese patients
-Patients with pacemakers
-Patients known to have hypertension, cardiac, pulmonary, renal or liver disease, active cancer or psychiatric illnesses
-History of any surgery of less than 6 weeks duration
-Patients known to have disabling osteoarthritic or orthopedic problems
-Patients secondary uncontrolled endocrine disorders (thyroid disorders, polycystic ovary, Cushing disease), or drug induced obesity (such as anti-psychotic, steroids, hormonal therapy).

Patients will be screened with laboratory tests (blood glucose measured by glucometer, taken randomly at pre-screening and fasting blood tests: glucose, AST, and creatinine levels) and through a questionnaire.

d- A description of plans for recruitment of subjects, the nature of the information provided to prospective subjects, the method of obtaining consent and, if applicable, a copy of the informed consent form to be used

Patients will be identified in the Endocrine Clinic, the Metabolic and Bariatric Surgery Unit, and Endocrinology and Internal Medicine Outpatient Department. The primary physician, namely Dr. Marlene Chakhtoura, Dr. Sami Azar, and Dr. Ramzi Alami, will introduce the trial to the potential participants. Those who are interested will meet the research assistant to get the full details of the protocol. Also, trial flyers (Appendix 2) will be available in the OPD. Those who are interested will directly contact the RA using the extension available on the flyer. The research assistant will explain the trial aims and intervention using a lay language, and will make sure that the participant understands the research purposes, that his/her participation is completely voluntary, that he/she can withdraw at any time from the study and that withdrawal will not affect his/her care at AUB-MC. Participant will take his/her time in reading the consent form, the RA will answer all the questions, and will give the participant a copy of the consent form.

e- The specific data to be collected

The data that will be collected include participants' past history, weight history, medications, anthropometrics and vital signs. In addition, data will be collected through questionnaires on quality of life, anxiety, depression, self-esteem, and well-being (See Appendix 3). Physical fitness will be assessed using the 6 minute walk test. These variables will be collected at baseline and at various time points throughout the study.
Table 1 includes a summary of the trial events, questionnaires and outcome measures.

f- The means by which the data will be collected, analyzed and interpreted

The research assistant will be responsible of participants' screening and recruitment, and of the data collection, under the supervision of the principal investigator and co-investigators. Standard operating procedures will be developed to all measurements performed through physical examination and these

include weight and height, waist circumference, neck circumference, blood pressure, heart rate, body composition and 6-min walk test.
The study visits will take place in the Metabolic and Bariatric Surgery Unit, AUB-MC 3rd floor.

The RA will contact those who are interested over the phone to check for eligibility criteria. Participants who are found to be eligible will be invited for a pre-screening visit.

Study visits:
Pre-screening visit – All arms:
Participants who are eligible and agree to participate in the trial will meet the research assistant (RA). The RA will go over the trial details, review eligibility criteria and those who are and interested will be provided with a laboratory test request (for screening studies), anthropometrics, a random blood glucose level will be checked, and a screening visit will be scheduled. If screening blood studies were done by the participants in the past 3 months for clinical purposes, these studies will not be repeated. Screening blood studies include fasting blood glucose, ALT, and Creatinine. Those who meet the eligibility criteria will be called and invited to present to the screening visit.

Screening visit– All arms
During this visit, the RA will fill a baseline questionnaire (age, gender, demographics, lifestyle history, past medical and surgical history, medications, obesity history), and assess the participant's anthropometrics, body composition, vital signs and physical fitness using the 6-min walk test. Questionnaires on quality of life (SF36), depression, anxiety, self-esteem, psychological wellbeing will be filled- See Appendix 3. Body composition will be assessed using the Tanita BC 418 MA Segmental Body Composition Analyzer which will measure total body measurements for: Weight, BMI, BMR, Fat %, Fat Mass, Fat Free Mass, Total Body Water [40-43].

All participants will be prescribed metformin sufficient for a 2-week duration to be slowly up –titrated to 850 mg twice per day. The Metformin tablets will be stored in a locked closet in the study site (Metabolic and Bariatric Surgery Unit). They will be contacted and invited for Visit 1 at 2 weeks after starting Metformin. Those who will not be able to tolerate Metformin will be excluded.

Visit 1 - Week 1(W1) – All arms
Participants tolerating Metformin will present for the first trial visit. During this visit, the participant meets the RA (for a questionnaire, diet and exercise recall, and assessment of anthropometrics and vital signs). The questionnaire includes assessment of medications, adverse events and compliance to Metformin.
The remaining part of the visit depends on which treatment arm the participant was randomized to:

-if the participant was randomized to the intervention arm, he/she will meet the dietician, the behavioral therapist and will have the first session of supervised exercise; see details below.
-if the participant was randomized to the standard care arm, the research assistant will provide him/her with advice on healthy lifestyle (See Appendix 4), and he/she will be dismissed.

Dietician session – Duration 40 minutes (for Arm 1 only):
A thorough dietetic evaluation will be conducted at baseline. Assessment includes ideal body weight, adjusted body weight or adjusted ideal body weight, energy needs (BMR), protein needs, and food recall.

- An accurate 24-hour recall will be conducted which will reveal the amount of calories the patient usually consumes.

- Environmental factors will be assessed which will reveal number of meals eaten per day, number of snacks, who prepares the food, availability of healthy food/home-made food, number of meals eaten outside home, presence of a food pattern (vegetarian, vegan, etc.), do patients eat just to have something to do ("I wanted something to do while watching TV or reading).
- A Meal Planning Booklet will be provided to the participant. The dietitian will explain and fill the booklet with a meal plan that meets the participant's prescribed total caloric needs.

- Plan:
  - Prescribe a minimum of 1,200 kcal/d for women and 1,500 kcal/d for men (kilocalorie levels are usually adjusted for the individual's body weight while maintaining an energy deficit of at least 750 kilocalories per day) with appropriate fluid and protein needs.
  - Educate patients on food composition and food caloric content and tailor programs to the dietary preferences of the individual.
  - Advise patients to limit the consumption of high calorie foods and drinks (ie, sodas, juices, alcohol, etc).
  - Explain appropriate portion sizes of the different food groups (Carbohydrates, meat, fat, fruits, dairy)
  - Reinforce the exercise plan given or that will be given by the physical therapist
  - Patient will be introduced to the dietary intervention component on WhatsApp. - Every participant will be provided with a set of measuring cups and spoons. He/she will be asked to send to the research assistant, through WhatsApp, the pictures of his/her breakfast, lunch and snacks, until 4 pm, on a daily basis. The research assistant will provide the participant with a direct feedback, within 1-2 hours, including suggestions regarding dinner and additional snacks. This intervention will last for the first 4 weeks of the study.

Behavioral therapy session – Duration 45-50 minutes (for Arm 1 only): *Introduction to Therapy and Healthy Eating*

- The behavioral therapist will discuss the goals of therapy and patient's expectations will be recorded to see if they are realistic. She will emphasize the importance of a regular meal pattern and eating slowly. She will review personal activity history and likes and dislikes about physical activity. She will help participants begin self-monitoring of physical activity as well as food intake and learn to find the time to be physically active each day by including short bouts (10–15 min) and healthy lifestyle activities, e.g., climbing stairs and walking extra blocks from the bus stop [23].

Physical education session – Duration 60 minutes (for Arm 1 only):

During this session:

- The therapist will screen for any disability hampering exercise due to pain: location, circumstances, difference between morning and evening, and irradiation of pain will be documented. Pain is quantified on numeric rating scale by asking the patient to rate pain intensity from 0 to 10: 0 being no pain at all and 10 being maximum pain possible value is documented by the therapist on patient's chart
- The joint range of motion measured by goniometer in case of stiffness to screen limited joint mobility that might lead to hampering of exercise program
  - *Exercise description in the supervised exercise session:*

- At the beginning of every session resting blood pressure, oxygen saturation, heart rate and perceived exertion will be recorded. The objective of the exercise protocol is to have the patient exercise with an exertion rate sufficient enough to optimize weight loss, with exercise heart rate around 80% from maximum estimated heart rate [44,45].
- Each session will include exercises on treadmill and leg ergometer, strengthening, in addition to stretching exercises, as follows:
    - 20 minutes treadmill done at the speed relative to patient exercise capacity calculated from the six minute walk test results using the following equation:
    - VO2 (ml.kg-1.min-1) = distance walked (m)*0.1 +3.5 ml.kg-1. min-1 (min)
      Treadmill is interrupted if patient reports rating of perceived exertion (RPE) scale score of 4 or above, SpO2 < 90% or heart rate exceeds 85% estimated maximum heart rate.
    - 20 minutes leg ergometer done at speed calculated from the results of the 6 minute walk test based on leg ergometer metabolic equation:
      VO2 (ml.kg-1.min-1) = [Work Load*1.8 + 7]/ Body weight
      Same reasons of interruption as treadmill apply to leg ergometer exercise
    - Strengthening exercise will be performed by tailored exercise plan discussed with each patient individually. Strengthening exercises will span over 15 minutes for upper and lower extremities against elastic band and ankle weights depending on muscle strength measured in manual muscle testing.
    - Stretching exercises for upper and lower extremities for 5 minutes to cool down after exercise with a plan tailored for each patient needs.
    - At the end of each modality, blood pressure, SpO2, heart rate and dyspnea will be recorded. Similarly, blood pressure, SpO2, heart rate and dyspnea will be recorded at the end of each session before the patient leaves physical therapy.

The patient will be provided with home exercise program to perform daily with the recommendations to exercise with parameters set during each session, increasing intensity gradually every 2 to 3 days as tolerated. (See Appendix 5)
Two exercise sessions will take place during the first week of the program. One of them will coincide with the diet and behavioral sessions, and the other one will be scheduled on another day.
All participants will be also provided with Metformin Tablets, enough for 5 weeks.

Visit 1A - W2– For Arm 1 only
During the second week, participants will attend 2 exercise sessions, each extending over 60 min. For *exercise description*, please refer to initial physical education session.

Visit 1B - W3- For Arm 1 only:
The visit in the third week of the first month will include a session with dietician, behavioral therapy and 2 supervised exercise sessions. One of the latter sessions will be scheduled on the same day of the dietitian and behavioral sessions, and the other one will be scheduled on another day.

Dietician session – Duration 40 minutes:

- The dietician will assess the adherence to the dietary intervention will be assessed using the food recall as well as review of the record for the Daily Tracking of Food Images completed by the research assistant (gathered from WhatsApp images). She will assess also body composition and patient's lifestyle habits. She will introduce the concept of self-monitoring of food intake using a food log (3-4 days) to track eating habits (2 weekdays and 1 weekend) during one week in a month. She will reinforce dietary and exercise instructions.

Behavioral therapy session – Duration 45-50 minutes: *Take charge of What's Around You and The 4 Keys to Healthy Eating Out*

- The behavioral therapist will introduce the principle of stimulus control, and identify cues in the participant's home environment that lead to unhealthy food and activity choices and discuss ways to change them. She will introduce four basic skills for managing eating away from home: anticipating and planning ahead, positive assertion, stimulus control, and making healthy food choices.

Physical education session – Duration 60 minutes:
For *exercise description*, please refer to initial physical education session.

Visit 2: W6– All arms

This visit includes a questionnaire, led by the RA, on medications, adverse events and compliance to Metformin, measurement of anthropometrics and vital signs.
Participants enrolled in the intervention arm will meet the dietician, the behavioral therapist and will have a supervised exercise session, as described earlier.

Dietician session – Duration 40 minutes:

- The dietician will assess the adherence to the dietary intervention, using the food recall and/or the food log sheet filled out by the patient. She will assess also body composition and patient's lifestyle habits. She will train the participant to practice self-monitoring skills, including weighing and measuring foods and estimating portion size of foods. She will teach ways to eat less fat: eat high fat foods less often, eat smaller portions, and substitute lower fat foods and cooking methods. She will reinforce dietary and exercise instructions.

Behavioral therapy session – Duration 45-50 minutes: *Problem Solving*

- Part 1: The behavioral therapist will present the five-step model of problem solving: describe the problem as links in a behavior chain, brainstorm possible solutions, pick one solution to try, make a positive action plan, evaluate the success of the solution, apply the problem-solving model to eating and exercise problems.
- Part 2: The behavioral therapist will help the patient do a practice identification of common patterns of self-defeating, negative thoughts and learn to counter these thoughts with positive statements.

Physical education session – Duration 60 minutes:
For *exercise description*, please refer to initial physical education session.

All participants will be provided with Metformin Tablets for 4 weeks.

Visit 3:W10: All arms

This visit includes a questionnaire, led by the RA, on medications, adverse events and compliance to Metformin, diet and exercise recall, and measurement of anthropometrics and vital signs and withdrawal of a blood sample.

Participants enrolled in the intervention arm will meet the dietician, the behavioral therapist and will have a supervised exercise session.

Dietician session – Duration 40 minutes:

- The dietician will assess the adherence to the dietary intervention, using the food recall and/or the food log sheet filled out by the patient. She will assess also body composition and patient's lifestyle habits. She will review self-monitoring skills of food intake discussed in the previous visit and address patient's questions and concerns. For example, confirm that patient is estimating portion sizes correctly and that patient is able to substitute high fat foods with lower fat foods. She will educate patient on reading food labels to help them choose healthier foods. She will reinforce dietary and exercise instructions.

Behavioral therapy session – Duration 30-45 minutes*:* *Make Social Cues Work for You and Managing Stress*

- Part 1: The behavioral therapist will present strategies for managing problem social cues, e.g., being pressured to overeat, and will help participants learn to use social cues to promote healthy behaviors, e.g., making regular dates with a walking partner or group. She will review specific strategies for coping with social events such as parties, vacations, and holidays.
- Part 2: Managing Stress: The behavioral therapist will highlight the importance of coping with stress (e.g., positive assertion, engaging social support, problem solving, planning, talking back to negative thoughts, and being physically active)

Physical education session – Duration 60 minutes:
For *exercise description*, please refer to initial physical education session.

All participants will be also provided with Metformin Tablets for 8 weeks.

Visit 3A: W14: For Arm 1 only
Participants enrolled in the intervention arm will meet the dietician, the behavioral therapist and will have a physical education session

Dietician session – Duration 40 minutes:

- The dietician will assess the adherence to the dietary intervention using the food recall and/or the food log sheet filled out by the patient. She will assess also body composition and patient's lifestyle habits. She will review the self-monitoring skills of food intake and address patient's questions and concerns. She will assess the patient's ability to read food labels and make healthier choices. She will emphasize the importance of a healthy meal pattern and eating slowly. She will use the MyPlate (USDA) as a model for healthy eating and compare personal eating patterns to these recommendations [46]. She will reinforce dietary and exercise instructions.

Physical education session – Duration 60 minutes:
For *exercise description*, please refer to initial physical education session.

Visit 4:W18: All arms

This visit includes a questionnaire, led by the RA, on medications, adverse events and compliance to Metformin, measurement of anthropometrics and vital signs. Participants enrolled in the intervention arm will meet the dietician.

Dietician session – Duration 40 minutes:

- The dietician will assess the adherence to the dietary intervention will be assessed using the food recall and/or the food log sheet filled out by the patient. She will assess also body composition and patient's lifestyle habits. She will compare the patient's eating patterns to MyPlate recommendations. She will educate patients on how to handle lifestyle balance when on vacation or eating out. She will confirm with the patient that he/she has all the required nutritional information to maintain a healthy eating pattern. She will reinforce dietary and exercise instructions.

Behavioral therapy session – Duration 30-45 minutes: *The Road of Lifestyle Change and Ways to Stay Motivated*

- The behavioral therapist will emphasize that slips are normal and learning to recover quickly is the key to success. She will teach participants to recognize personal triggers for slips, their reactions to those slips, and what it takes to get back on track. She will introduce other strategies for staying motivated including posting signs of progress, setting new goals, and seeking social support

Patients will be also provided with Metformin Tablets for 6 weeks.

Visit 5 - Study completion visit -W24: All arms

It includes a questionnaire led by the RA, on medications, adverse events and compliance to Metformin, diet and exercise recall, and measurement of anthropometrics, vital signs, and body composition, assessment of physical fitness, in addition to withdrawal of a blood sample. Participant will be asked to fill the questionnaires on quality of life (SF36), depression, anxiety, self-esteem, psychological wellbeing at this end of trial visit.

Participants enrolled in the intervention arm, will attend the last supervised exercise session.

Physical education session – Duration 60 minutes:

For *exercise description*, please refer to initial physical education session.
This session includes reassessment of the 6-min walk test for all participants

Throughout the first 15 weeks of the study, and as part of the intervention, participants enrolled in Arm 1 will also receive tips on healthy lifestyle twice per week (Monday and Friday) via WhatsApp to motivate them to adhere to the lifestyle instructions that they learned during the program. In addition, after the first month, participants in Arm 1 will be contacted every 2 weeks, by the RA, to check on adverse events and to emphasize adherence to the program recommendations.

g- Data entry and quality control

During each visit, the RA will fill the information on the Case Report Forms (CRF). After the visit, data will be entered online on RedCap. The principal investigator will review regularly the CRF, and makes sure that all trial procedures follow standard operations. The trial team members will meet on a weekly basis to review routine operations, and trouble shoot problems occurring during trial implementation, data collection, data entry or management. All data will be entered manually in duplicate, with the exception of body composition results (done at baseline and study completion) that will be entered electronically via migration from TANITA software. The CRF hard copy and the online sheet will look very similar, in order to minimize mistakes during data entry. We will verify data entry through software built range checks with automatic error prompts, comparison of duplicate data entry, and by performing ascending/descending order view of variables, in addition to simple descriptive analysis.

h- Data analysis and management:

Data analysis will be performed by the principal investigator and the biostatistician, Dr Martine Bejjani.

i- Data housing

Participants' charts will be kept under lock in the principal investigator's office. The online database will remain under lock with a password protection

j- Outcome measures

All measurements will follow the Standard Operating Procedures as detailed in the CRF.

- Anthropometric measurements and vital signs:

Weight and height will be measured at every visit by the research assistant or the dietician, in duplicate, using a calibrated scale. The same scale will be used throughout the trial. Waist and neck circumference will be measured using a graduated tape, by the research assistant following standard operating procedures.
Blood pressure and heart rate will be measured in duplicate by the research assistant using a calibrated sphygmomanometer. It will be done after that the participant sits and rests for 5 minutes before blood pressure checking. The participant extends his/her arm and supports it on a flat surface. The arm should be at the same level as the heart.

- Body composition

Body composition analysis is conducted as part of the nutrition assessment performed by the dietitian during the patient visit to the clinic at no extra charge. The equipment used is Tanita BC 418 MA Segmental Body Composition Analyzer. It utilizes the bioelectrical impedance analysis (BIA) technology which delivers a very low, safe electrical signal. This provides readings for each leg, arm and abdominal area as follows [47]:

  - Segmental Measurements for: right arm, left arm, left leg, right leg and trunk, Fat %, Fat Mass, Fat Free Mass, and Predicted Muscle Mass
  - Total Body Measurements for: Weight, BMI, BMR, Fat %, Fat Mass, Fat Free Mass, Total Body Water.

- Laboratory tests

At visit 3 and completion visit (visit 5), blood samples will be withdrawn for various hormones and proteins related to appetite and satiety including Gastric inhibitory polypeptide (GIP), Leptin, Glucagon like peptide 1 (GLP1), Irisin, Insulin, Ghrelin, Orexin, IL6, Crosslaps, Osteocalcin. These samples will

be processed and preserved in the Calcium Metabolism and Osteoporosis Program lab in AUBMC Main building, 5th floor., and the tests will be run later on, when additional funds are available.

- Other outcomes

  - Quality of life assessed using the SF-36 questionnaire
    SF-36 is a self-report questionnaire composed of a set of coherent, and easily administered quality-of-life measures [48]. This questionnaire is available in Arabic (Appendix 2).
  - Depression and anxiety, using Beck Depression Scale (BDI-II)[49] and Beck Anxiety Scale (BAI)[50], respectively.
    - The Beck Depression Inventory (BDI-II) is a 21-item, self-report rating inventory that measures characteristic attitudes and symptoms of depression [49]. The BDI is available in Arabic (Appendix 2).
    - The Beck Anxiety Inventory (BAI) is a self-report questionnaire composed of 21-items. It serves as a severity indicator for anxiety in primary care patients with different anxiety disorders (social phobia, panic disorder with or without agoraphobia, agoraphobia or generalized anxiety disorder), depressive disorders [50]. The BAI is available in Arabic (Appendix 2)
  - Self-esteem assessed by using the Rosenberg Self-esteem scale.
    The Rosenberg self-esteem scale is a 10-item scale that measures global self-worth by measuring both positive and negative feelings about the self. Answers are done using a 4-point Likert scale format ranging from strongly agree to strongly disagree [51]. The Rosenberg Self-Esteem Scaler is available in Arabic. (Appendix 2)
  - Psychological well-being, using the Obesity Related Well-being (ORWELL 97) questionnaire[52] (Appendix 2).
  - 6-min walk test
  - Adherence to the dietary intervention ([Number of days the dieticians are contacted/ Total number of days] X 100), and to program visits ([number of visits attended/ Total number of visits] X 100)
  - Compliance to metformin
  - Adverse events

k- Trial intervention

Participants will be randomized to one of the 2 arms, after initiating and tolerating Metformin for 2 weeks, as follows:

-Arm 1- Multi-disciplinary weight loss program: in the intervention arm, participants will receive individual sessions on dietary therapy, behavioral therapy and physical education. The curriculum will follow the Diabetes Prevention Program [23] and Look Ahead Trial [22]. The program will include intensive sessions during the first 3 months and less intensive ones thereafter.

-Arm 2 - Control arm – Standard care: In this arm, patients with obesity starting Metformin for weight loss will be advised on lifestyle changes and to see a dietician, a behavioral therapist and to do exercise, on their own. They will present for study follow up visits on a monthly basis.

The intervention will extend over 6 months with the aim of "weight loss". It will be followed by a "weight maintenance" phase that is beyond the scope of this proposal.

l- Randomization and Allocation Concealment

The randomization sequence will be computer generated by Dr. Bejjani, Biostatistician on this project. It will be sent to a Clinical Trial Coordinator, Mrs. Maya Rahme, independent of the research team. The allocation concealment will be secured using sealed, opaque envelopes. These envelopes will be used to communicate the allocation of each participant to the RA.

m- Sample size

Sample size calculation is based on the primary outcome, the mean percent weight loss at 6 months after randomization.

The Look Ahead trial and the Diabetes Prevention Program showed a 7-8% weight loss at 6-12 months, comparing intensive lifestyle intervention to standard therapy [23,53]. Using a conservative approach, and estimating a 5% weight loss difference at 6 months, comparing Arm 1 (multi-disciplinary approach) to Arm 2 (standard therapy), using a standard deviation for weight loss of 8% [53], for an 80% power and α 0.05, the sample size needed is 41 per arm, and total number of participants would be 82. Considering a dropout rate of 40%, the total sample size needs to be inflated to 137 participants.

The current protocol is a pilot study of 15 participants per arm (around 20% of the sample size) to assess the feasibility of the intervention before embarking of the whole project. We expect a drop-out rate of 20%, and 10% intolerance rate to Metformin. In order to secure that 15 participant will complete the study, we will inflate the number of enrolled participants by 30%. Therefore, we will enroll 20 participants per arm.

n- Description of the statistical analysis plan

Statistical methods

Baseline demographic characteristics will be summarized using frequencies and percentages for categorical variables, and mean ±SD (or median and range) for continuous variables.

- Primary analysis (unadjusted)

Primary outcome: we will compare the mean % weight loss between treatment arms, at 6 months after enrollment, using the Wilcoxin sum-rank

Secondary and exploratory outcomes: Comparisons between treatment arms will be performed using Chi-square tests for the categorical variables and Wilcoxin sum-rank test for continuous variables.

The primary analysis is an intention to treat analysis of unadjusted results. We will report P-values to four decimal places.
For the primary outcome, we will consider p-values statistically significant if ≤ 0.05. We will use SPSS version 24 to conduct the statistical analysis.

o- Potential risks, their likelihood and seriousness. Describe alternative treatments and procedures that might be advantageous to the subject.

There are possible risks, secondary to the use of Metformin which include: gastrointestinal disturbances such as diarrhea, nausea and vomiting, flatulence, indigestion, abdominal discomfort, headache, metallic taste – this risk is reduced with slow up-titration of the dose by 1/2 tablet every 3 days. Also there is a risk of developing anorexia, lethargy, hyperventilation, and/or hypotension. In case the patient develops these symptoms, he/she will be advised to stop Metformin to avoid the small risk of lactic acidosis. In addition, the long term use of Metformin (≥ 4 years) may lead to vitamin B12 deficiency with long term intake (around 4 years) of Metformin related to reduced intestinal absorption of B12 which might result in peripheral neuropathy and rarely megaloblastic anemia - this risk is not applicable since the participants will receive Metformin for only a 6 month duration

Moreover, in case of imaging contrast exposure, patients will be advised to stop Metformin for 24 hours before imaging appointment and 48 hours after it.

Exercise is also associated with minimal risks such as musculoskeletal injury which might present as acute strains and tears, inflammation of various types, chronic strain, stress fractures, traumatic fractures, nerve palsies, tendonitis, and bursitis; dehydration; hyperthermia; hypothermia; and very small risk of myocardial infarction. These risks are minimized since all exercise sessions are done under the supervision of experienced physiotherapist with slow up titration. Furthermore, patients with uncontrolled hypertension and cardiac disease will be excluded from the study.

Blood withdrawal is associated with a minimal risk routinely encountered during any peripheral sampling: skin infection, phlebitis, or hematoma.

p- Interpretation of the results:

We expect that participants enrolled in Arm 1 would experience the largest weight loss, at 6 months, compared to standard care. In addition, we expect that participants in this arm will learn how to make healthy food selections, and improve their dietary behaviors on the long term run.
This pilot study will provide preliminary data on the feasibility and efficacy of a multi-disciplinary weight loss program at our institution, similar to the programs available in the US. Lessons learnt from this project will allow the eventual implementation of an evidence based multi-disciplinary weight loss program in practice, with intensive sessions early on to allow weight loss, and less frequent sessions thereafter for weight maintenance. This program includes a special dietary intervention, with one-to-one and instantaneous feedback on a daily basis that, to our knowledge, has never been assessed earlier. It is a unique program, not only targeting weight loss, but also aiming at implementing modification in lifestyle habits. The program will include several disciplines who will be meeting regularly to discuss issues related to program implementation, challenges and patient related difficulties

Limitations
The trial duration is relatively small, aiming at achieving weight loss. An extension phase for weight maintenance may be considered later on. Body composition is assessed on TANITA machine, and not on the gold standard DXA machine. However, results from the former differed only by few percent, in various measurements, from the DXA based results [41].

Time frame of the study:

The study is expected to start in spring 2019 and to extend over 1 year. Three months for screening and recruitment, 6 months for trial implementation and 3 months for data analysis.

Study team

Principal Investigator:
Marlene Chakhtoura, MD, MSc
Instructor of Clinical Medicine, American University of Beirut - Lebanon
Role: Responsible for study conception, study design, proposal development, protocol update(s) and revision(s), oversight of trial implementation, data collection, data entry, data review, data analysis and interpretation, and review of manuscript drafts, revision and approval of final versions submitted for publication.
10% of her time will be allotted for this project.

Trial Coordinator
Dalal Habli, LD, BSc
American University of Beirut – Lebanon
Role: Responsible for recruitment, data collection, data entry, protocol update, data analysis and interpretation.

Co-investigators and collaborators:
Co-investigators:
-Ramzi Alami, MD
Assistant Professor, American University of Beirut
Role: Involved in study design and protocol write-up, data analysis and interpretation, review of manuscript drafts and approval of final versions.
2.5% of her time will be allotted for this project

-Sami Azar, MD
Professor, American University of Beirut
Role: Involved in study design, data analysis and interpretation, review of manuscript drafts and approval of final versions.

-Martine Bejjani, PhD
Instructor, American University of Beirut
Role: Involved in study design, statistical methods, analysis and interpretation

-Florenica Halperin, MD
Brigham and Women's Hospital

Role: Involved in study design and protocol write-up, sharing expertise in medical weight management and multidisciplinary weight loss program, data analysis and interpretation, review of manuscript drafts and approval of final versions.

Collaborators

- Rassil Ghazzaoui, MA
American University of Beirut
Role: Involved in the design and implementation of behavioral therapy
5% of her time will be allotted for this project

-Widad Ayass, CD
American University of Beirut
Role: Involved in the design and implementation of dietary therapy
2.5% of her time will be allotted for this project

-Lara Istaitie, CD
American University of Beirut
Role: Involved in the design and implementation of dietary therapy
5% of her time will be allotted for this project

-Mariam Allaik, CD
American University of Beirut
Role: Involved in the design and implementation of dietary therapy
5% of her time will be allotted for this project

-Claude Maroun, DPT, MPH
Role: Involved in the design and implementation of physical therapy
2.5% of her time will be allotted for this project

-Michel Rayes, MPT
American University of Beirut
Role: Involved in the design and implementation of physical therapy
5% of her time will be allotted for this project

Table 1: Description of the intervention

	Arm 1: Multidisciplinary Weight Loss Program										Arm 2: Standard of Care			
	Questionnaire and physical exam done by RA	**Lab tests[4]**	**Duration (min)**	**Body composition**	**Dietician session**	**Duration (min)**	**Behavioral individual session**	**Duration (min)**	**Supervised exercise session**	**Duration (min)**	**Questionnaire and physical exam done by RA**	**Lab tests[4]**	**Duration (min)**	**Body composition**
Pre-screening/ Screening visit	X[1]	X[5]	20	X							X[1]	X[5]	20	X
2 weeks after Metformin Visit 1 W1	X[2]				X	30	X	45	X (2 sessions)	60 (each session)	X[2]			
Visit 1A W2									X (2 sessions)	60 (each session)				
Visit 1B W3					X	30	X	45	X (2 sessions)	60 (each session)				
Visit 2 W6	X[2]		20		X	30	X	45	X	60	X[2]		20	
Visit 3 W10	X[2]	X	20		X	30	X	45	X	60	X[2]	X	20	
Visit 3A W14					X	30			X	60				
Visit 4 W18	X[2]		20		X	30	X	45			X[2]		20	
Visit 5 Study completion W24	X[3]	X	20	X					X		X[3]	X	20	X

Abbreviations:
W1: Week 1; W2: Week 2; W3: Week 3; W6: Week 6; W10: Week 10; W14: Week 14; W18: Week 18; W24: Week 24; min: minutes
Footnotes:
[1] Questionnaire at screening visit includes baseline characteristics (demographics, past history, medications), quality of life (SF36), Beck Depression Scale II, Beck Anxiety Scale, Rosenberg Self-esteem Scale, Obesity Related Well-being Scale, and assessment of physical fitness. Physical exam includes height, weight, waist circumference, neck circumference and vital signs.

[2] Assessment includes compliance, adverse events, and physical exam: height, weight, waist circumference, neck circumference, diet and exercise recall, and vital signs.
[3] Assessment includes quality of life (SF36), Beck Depression Scale, Beck Anxiety Scale, Rosenberg Self-esteem Scale, Obesity Related Well-being Scale and assessment of physical fitness. Physical exam includes height, weight, waist circumference, and vital signs, in addition to physical fitness.
[4] with the exception of the screening visit, at all trial visits whereby blood tests are taken, samples will be preserved until further funds are available. Mineral hormonal and various parameters will be assessed.
[5] screening lab tests include blood sugar check using a glucometer, done randomly; and fasting blood tests for creatinine, ALT, and fasting glucose.

References

1. Abarca-Gómez L, Abdeen ZA, Hamid ZA, et al. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128· 9 million children, adolescents, and adults. *The Lancet* 2017.
2. WHO Obesity and overweight Fact Sheet. http://www.who.int/mediacentre/factsheets/fs311/en/. (accessed in August 2018)
3. Afshin A, Forouzanfar MH, Reitsma MB, et al. Health effects of overweight and obesity in 195 countries over 25 years. *The New England Journal of Medicine* 2017; **377**(1): 13-27.
4. Institutes of Health Metrics and Evaluation Health Data. http://www.healthdata.org/sites/default/files/files/infographics/Infographic_IHME_GBD2013_Obesity.jpg. (accessed in August 2018)
5. Nasreddine L, Naja F, Chamieh MC, Adra N, Sibai A-M, Hwalla N. Trends in overweight and obesity in Lebanon: evidence from two national cross-sectional surveys (1997 and 2009). *BMC Public Health* 2012; **12**(1): 798.
6. Matta J, Nasreddine L, Jomaa L, et al. Metabolically healthy overweight and obesity is associated with higher adherence to a traditional dietary pattern: a cross-sectional study among adults in Lebanon. *Nutrients* 2016; **8**(7): 432.
7. Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. *BMC Public Health* 2009; **9**(1): 88.
8. WHO Non-communicable diseases Fact Sheet http://www.who.int/mediacentre/factsheets/fs355/en. (accessed in August 2018)
9. Screening for and Management of Obesity in Adults: U.S. Preventive Services Task Force Recommendation Statement 2012. http://annals.org/aim/article/1355696/screening-management-obesity-adults-u-s-preventive-services-task-force. (accessed in August 2018)
10. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. http://www.onlinejacc.org/content/accj/63/25_Part_B/2985.full.pdf. (accessed in August 2018)
11. Obesity prevention and management University of Michigan Health System 2013. http://www.med.umich.edu/1info/FHP/practiceguides/obesity/obesity.pdf. (accessed in August 2018)
12. Clinical practice guidelines for the management of overweight and obesity in adults, adolescents and children in Australia. National Health and Medical Research Council 2013. https://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/n57_obesity_guidelines_131204_0.pdf? (accessed in August 2018)
13. VA/DoD clinical practice guideline for screening and management of overweight and obesity. Department of Veterans Affairs, Department of Defense 2014. https://www.healthquality.va.gov/guidelines/CD/obesity/.(accessed in August 2018)
14. Obesity: identification, assessment and management of overweight and obesity in children, young people and adults National Institute for Health and Care Excellence (NICE); 2014. https://www.nice.org.uk/guidance/cg189. (accessed in August 2018)
15. Recommendations for prevention of weight gain and use of behavioral and pharmacologic interventions to manage overweight and obesity in adults in primary care Canadian Task Force on Preventive Health Care 2015. http://www.cmaj.ca/content/187/3/184.long. (accessed in August 2018)
16. AACE/ACE Comprehensive clinical practice guidelines for medical care of patients with obesity 2016. http://journals.aace.com/doi/10.4158/EP161356.ESGL?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed&code=aace-site. (accessed in August 2018)

17. AGA Practice Guide on Obesity and Weight Management, Education, and Resources 2017. https://www.clinicalkey.com.ezproxy.aub.edu.lb/service/content/pdf/watermarked/1-s2.0-S1542356516309880.pdf?locale=en_US. (accessed in August 2018)
18. Pharmacological Management of Obesity: An Endocrine Society Clinical Practice Guideline 2015. https://academic.oup.com/jcem/article-lookup/doi/10.1210/jc.2014-3415. (accessed in August 2018)
19. Spahn JM, Reeves RS, Keim KS, et al. State of the evidence regarding behavior change theories and strategies in nutrition counseling to facilitate health and food behavior change. *Journal of the American Dietetic Association* 2010; **110**(6): 879-91.
20. Donnelly JE, Blair SN, Jakicic JM, Manore MM, Rankin JW, Smith BK. American College of Sports Medicine Position Stand. Appropriate physical activity intervention strategies for weight loss and prevention of weight regain for adults. *Medicine and Science in Sports and Exercise* 2009; **41**(2): 459-71.
21. Ades PA, Savage PD. Potential benefits of weight loss in coronary heart disease. *Progress in cardiovascular diseases* 2014; **56**(4): 448-56.
22. Group LAR. The Look AHEAD study: a description of the lifestyle intervention and the evidence supporting it. *Obesity (Silver Spring, Md)* 2006; **14**(5): 737.
23. Group DPPR. The diabetes prevention program (DPP). *Diabetes care* 2002; **25**(12): 2165-71.
24. Malone M, Alger-Mayer SA, Anderson DA. The lifestyle challenge program: a multidisciplinary approach to weight management. *Annals of Pharmacotherapy* 2005; **39**(12): 2015-20.
25. Riebe D, Greene GW, Ruggiero L, et al. Evaluation of a healthy-lifestyle approach to weight management. *Preventive Medicine* 2003; **36**(1): 45-54.
26. Roffey DM, Ashdown LC, Dornan HD, et al. Pilot evaluation of a multidisciplinary, medically supervised, nonsurgical weight loss program on the severity of low back pain in obese adults. *The Spine Journal* 2011; **11**(3): 197-204.
27. Baer HJ, Karson AS, Soukup JR, Williams DH, Bates DW. Documentation and diagnosis of overweight and obesity in electronic health records of adult primary care patients. *JAMA Internal Medicine* 2013; **173**(17): 1648-52.
28. Bleich SN, Pickett-Blakely O, Cooper LA. Physician practice patterns of obesity diagnosis and weight-related counseling. *Patient education and counseling* 2011; **82**(1): 123-9.
29. Lemay CA, Cashman S, Savageau J, Fletcher K, Kinney R, Long-Middleton E. Underdiagnosis of obesity at a community health center. *The Journal of the American Board of Family Practice* 2003; **16**(1): 14-21.
30. Arterburn DE, Alexander GL, Calvi J, et al. Body mass index measurement and obesity prevalence in ten US health plans. *Clinical Medicine & Research* 2010; **8**(3-4): 126-30.
31. Breland JY, Phibbs CS, Hoggatt KJ, et al. The obesity epidemic in the Veterans Health Administration: Prevalence among key populations of women and men Veterans. *Journal of general Internal Medicine* 2017; **32**(1): 11-7.
32. Kordik A, Adams M, Plunkett B. Obesity is underdiagnosed and undertreated among reproductive-aged women. *Obstetrics & Gynecology* 2014; **123**: 94S.
33. Pettersson J, Johansson K, Rössner S, Neovius M. Prevalence of obesity and abdominal obesity in Swedish primary care and occupational health clinics. *Obesity Facts* 2008; **1**(5): 251-7.
34. Fitzpatrick SL, Stevens VJ. Adult obesity management in primary care, 2008–2013. *Preventive Medicine* 2017; **99**: 128-33.
35. Ma C, Avenell A, Bolland M, et al. Effects of weight loss interventions for adults who are obese on mortality, cardiovascular disease, and cancer: systematic review and meta-analysis. *BMJ* 2017; **359**: j4849.
36. Marques-Vidal P, Paccaud F, Ravasco P. Underdiagnosed and undertreated: obesity in the portuguese population. *Archives of Internal Medicine* 2011; **171**(16): 1511-2.
37. Kraschnewski JL, Sciamanna CN, Stuckey HL, et al. A silent response to the obesity epidemic: decline in US physician weight counseling. *Medical Care* 2013; **51**(2): 186-92.

38. Villareal DT, Fontana L, Das SK, et al. Effect of two-year caloric restriction on bone metabolism and bone mineral density in non-obese younger adults: a randomized clinical trial. *Journal of Bone and Mineral Research* 2016; **31**(1): 40-51.
39. Gibson AA, Sainsbury A. Strategies to Improve Adherence to Dietary Weight Loss Interventions in Research and Real-World Settings. *Behavioral Sciences* 2017; **7**(3): 44.
40. Li Y-C, Li C-I, Lin W-Y, et al. Percentage of body fat assessment using bioelectrical impedance analysis and dual-energy X-ray absorptiometry in a weight loss program for obese or overweight Chinese adults. *PLoS One* 2013; **8**(4): e58272.
41. Völgyi E, Tylavsky FA, Lyytikäinen A, Suominen H, Alén M, Cheng S. Assessing body composition with DXA and bioimpedance: effects of obesity, physical activity, and age. *Obesity* 2008; **16**(3): 700-5.
42. Neovius M, Hemmingsson E, Freyschuss B, Uddén J. Bioelectrical impedance underestimates total and truncal fatness in abdominally obese women. *Obesity* 2006; **14**(10): 1731-8.
43. Pietrobelli A, Rubiano F, St-Onge M, Heymsfield S. New bioimpedance analysis system: improved phenotyping with whole-body analysis. *European Journal of Clinical Nutrition* 2004; **58**(11): 1479.
44. AACVPR Guidelines for Pulmonary Rehabilitation Programs (4th Edition). http://summitmd.com/pdf/pdf/1_2_Bauldoff.pdf. (accessed in August 2018)
45. Guidelines for Cardiac Rehabilitation and Secondary Prevention Programs 5th Edition.
46. Raynor HA, Champagne CM. Position of the Academy of Nutrition and Dietetics: interventions for the treatment of overweight and obesity in adults. *Journal of the Academy of Nutrition and Dietetics* 2016; **116**(1): 129-47.
47. Jebb SA, Cole TJ, Doman D, Murgatroyd PR, Prentice AM. Evaluation of the novel Tanita body-fat analyser to measure body composition by comparison with a four-compartment model. *British Journal of Nutrition* 2000; **83**(2): 115-22.
48. Ware Jr JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. *Medical Care* 1992: 473-83.
49. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Archives of general psychiatry* 1961; **4**(6): 561-71.
50. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. *Journal of Consulting and Clinical Psychology* 1988; **56**(6): 893.
51. Rosenberg M. Rosenberg self-esteem scale (RSE). *Acceptance and Commitment Therapy Measures Package* 1965; **61**: 52.
52. Mannucci E, Ricca V, Barciulli E, et al. Quality of life and overweight: the obesity related well-being (Orwell 97) questionnaire. *Addictive Behaviors* 1999; **24**(3): 345-57.
53. Group LAR. Long term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes: four year results of the Look AHEAD trial. *Archives of Internal Medicine* 2010; **170**(17): 1566.