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Original Article

Fasting, Physical Activity, and Art Therapy Improve Metabolic Syndrome and Inflammasomes: An Italian Residential Experience

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Background: Diet, physical activity, and general lifestyle modifications are implicated in metabolic pathway prevention and may improve some chronic diseases such as metabolic syndrome. The aim of this study is to measure the effectiveness of a short-time nutrition restriction regime combined with a daily practice of physical and creative activities on metabolic syndrome parameters, inflammasome status, and the compliance of the patients to the proposed scheme.
Methods: This pilot study analyzed 95 volunteers who took part in a residential one-week lasting experimental lifestyle period. The program proposed was structured in a four-day detox nutrition based only on vegetable products derived from organic, biologic, synergic, and integrated farming, without animal proteins, fats, and simple sugars. These four days were followed by a three-day fasting or fasting-mimicking diet, consisting of one or two hypocaloric meals based on complex sugars, vegetables, oleaginous seeds, and only in some cases vegetable proteins. Finally, a three-day "weaning" period was administered. During the whole period, 95 participants were offered a daily postural physical activity and a creative activity program. The basal data of the participants were collected (T_0). A medical evaluation was conducted to collect the personal and anthropometric data. During this basal evaluation (T_0), height, waist circumference, waist-to-height ratio (WtHR), glycemic value, and blood pressure were collected and reevaluated at the end of the 10-day experience (T_1).
Results: The data were evaluated according to the three metabolic syndrome parameters (i.e., WtHR, glycemic value, and blood pressure). A significant improvement in the variables analyzed at the end of the program was observed.
Conclusion: This study revealed that a short integrated lifestyle program can influence some well-defined metabolic parameters and might decrease damage from metabolic syndrome.

Keywords: Caloric restriction, Creativity, Diet, Plant-based, Exercise, Inflammasomes, Metabolic syndrome, Preventive medicine

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INTRODUCTION

Lifestyle plays a relevant role on overall mortality and morbidity and on metabolic syndrome (SMet) development and prognosis. Diet, physical activity and distress- reducing lifestyle modifications (in terms of mindfulness, meditation, art therapy and creativity) are implicated in primary and tertiary health and cancer prevention and might improve SMet and chronic low grade inflammation status (inflammasome) [1,2].

SMet has been demonstrated to correlate with some diseases such as cardiovascular, neurodegenerative and oncological diseases. Calorie balance might not be the only way to control SMet, because calories might be "empty" and lacking important macro and micronutrients [3]. There are calories such as those deriving from sugar, ultra-processed food and alcohol that do not have any nutritional value. In our experience it is more important to contrast SMet with the introduction of the "nutritional density" concept, without junk food [4]. Also physical activity plays a role in disease risk reduction if characterized by moderate intensity (> 7.5 metabolic equivalent of task): this implication is extremely relevant for diabetes, hypertension and cancer such as breast, colon, lung, cervical and endometrial ones [5,6]. Postural activity and creativity could act on metabolic pathways, leading to a health improving process [7-10]. SMet needs an epigenetic intervention capable of changing the microbiota gut and correcting chronic low grade inflammation status and oxidative stress [11,12].

Moreover, a change in metabolic and cell signal pathway towards a virtuous anti-SMet pathway seems to be obtainable just after a short period of nutritional and life-style intervention [13,14].

The change of lifestyle through diet, physical and creative activities has been demonstrated to be useful in decreasing many chronic pathologies. Usually, studies are based on a long period of change instead of a short one.

Since fasting-mimicking diet (FMD) activates metabolic pathways (decrease insulin levels, fight insulin resistance, trigger a cell restoration) in a few days, we think that a short-time scheme of change is sufficient to promote a health status.

The aim of this study was to measure the effectiveness of a short-time nutrition restriction regime joined to a daily practice of physical and creative activities on SMet parameters, inflammasome status and the compliance of the patients to the proposed scheme.

MATERIALS AND METHODS

1. Population

The pilot study was conducted at Laboratorio Energia Mentale's Patients' Center (Mental Energy Laboratory, LEM) and involved 95 volunteers (18-70 years), both sexes were accepted. Their socio-demographic characteristics, together with lifestyle and health status were collected at baseline. A residential 10 days lasting period was offered to the entire group: 4 days detox-3 days fasting mimicking-3 days weaning. All the participants signed an informed consent according to the approval no. CS/1053 of the Intercompany Ethics Committee of the A.O.U Città della Salute e della Scienza di Torino. The wellness and health consciousness activities were stratified into three macro-areas, during the whole period: nutrition, physical and creative activity. During the first 4 days, a detox nutrition plant based, derived from organic, biologic, synergic and integrated farming, without animal proteins, fats and simple sugars was offered. Specifically, during the whole period, two meals a day were given to the participants, with a combination of whole grains (50%), legumes (25%), cooked vegetables (20%) and fermented ingredients (5%) (Table 1). The dish composition was derived from the results of previous research and certified by Consiglio per la ricerca in agricoltura e l'analisi dell'economia agraria based on the latest revision of National Recommended Energy and Nutrient Intake Levels guidelines (2014).

A cooking course was attended by the participants. These 4 days were followed by a 3-days mimicking-fasting regime, consisting in two hypocaloric meals a day, based on carbohydrates (complex sugar), vegetables, and addition of some vegetable proteins for people with a very low body mass index (BMI) (< 20 kg/m^2) (Table 1). A daily postural physical activity and creativity program was followed by participants according to the scheme in Table 2.

The physical and creative activities were organized in groups according to the participants' skills, abilities and preferences. It is important to take in consideration that the LEM location is situated in a mountain landscape (near to 1.000 meters high) where participants had also the possibility to keep in contact with nature.

2. Data collection

Participants' basal data were collected at first examination (T_0). All the participants had a postural evaluation based on a flexibility and strength test. A personalized

Table 1. Dish composition

	Detox's dish	Mimicking-fasting's dish
Whole grain cereals (g)	60	40
Legumes (g)	30	15 (body mass index < 20)
Cooked vegetables (g)	200	60
Fermented products (g)	20	0

Table 2. Activity scheme

Timetable	Activity	Duration
07:00 A.M.	Qi gong	1 hour
08:00 A.M.	Break with kukicha tea	40 minutes
08:40 A.M.	Arts (murals, mosaic, free-hand drawing)	1 hour and 50 minutes
10:30 A.M.	Cooking lesson[a)]	2 hours
12:30 A.M.	Lunch	1 hour and 30 minutes
02:00 P.M.	Break with kukicha tea	1 hour and 30 minutes
03:30 P.M.	Tai Chi, Pilates, yoga	2 hours
05:30 P.M.	Cooking lesson[a)]	2 hours
07:30 P.M.	Dinner	1 hour and 30 minutes
09:00 P.M.	Conference about lifestyle, diet, health	1 hour
10:00 P.M.	Sleep	

[a)]During the 3 mimicking-fasting days the scheme was modified substituting cooking classes with arts and physical activities.

Table 3. Participants' socio-demographic characteristics

	Female (n = 85)	Male (n = 10)	Total (n = 95)
Age (yr)	57.80±9.95	54.20±15.53	57.41±10.63
Weight (kg)	68.81±14.19	71.60±9.43	69.11±13.76
Height (m)	1.64±0.06	1.74±0.07	1.65±0.07
Body mass index (kg/m^2)	25.61±5.11	23.75±3.48	25.42±4.98
Education			
Diploma	42 (49.41)	2 (20.00)	44 (46.32)
Degree	43 (50.59)	8 (80.00)	51 (53.68)
Job			
Employed	50 (58.82)	6 (60.00)	56 (58.95)
Dis/unemployed	2 (2.35)	0 (0.0)	0 (0.0)
Retired	32 (37.65)	4 (40.00)	36 (37.89)
House worker	1 (1.18)	0 (0.0)	1 (1.05)
Smoking status			
Yes	6 (7.06)	2 (20.00)	8 (8.42)
No	79 (92.94)	8 (80.00)	87 (91.58)

Values are presented as mean±standard deviation or number (%).

adapted physical activity card was given to all the subjects involved. A medical evaluation was carried out to collect the personal and anthropometric data. Data such as age, tobacco smoking habit, educational level and current (or last occupied) job for the social, demographic, economic sphere, and data on medical history (previous cancer, cardiovascular, diabetic and thyroid disease, current use of medication and eventual dietary supplements) are respectively reported in Table 3. During basal evaluation (T_0), anthropometric values (height, waist circumference, waist-to-height ratio, [WHtR]), glycemic and blood pressure values were collected and re-evaluated after 10 days (T_1). The metabolic risk was defined according to the WtHR-predefined score (Table 4).

Table 4. Metabolic risk evaluation

Waist-to-height ratio	Metabolic risk
≤ 0.45	0
0.46-0.50	1
0.51-0.55	2
≥ 0.56	3

3. Statistical analysis

For all participants' socio-demographical characteristics (age, weight, height, BMI, education, job) and their clinic parameters (presence of ongoing or previous pathologies: cancer, cardiovascular disease, thyroid disease, diabetes), were reported in terms of absolute numbers and percentages for categorical variables and with average values and standard deviations for continuous variables.

To detect possible changes in subjects after the wellness program participation (i.e. improvements in T_1 in respect of moment T_0), McNemar's test for paired data was calculated (with the exact correction when cell frequencies were less than 5), considering subjects who improved (i.e. moved from high risk category to a lower one), subjects who stayed in the same category (i.e., same category in T_1 as in T_0), and also

subjects who worsened (i.e. moved from low risk category to a higher one). For computational reasons metabolic risk and glycemic value categories were dichotomized in: metabolic risk ≤ 0.50 and > 0.50 and glycemic value ≤ 94 mg/dL and ≥ 95 mg/dL.

RESULTS

1. Baseline characteristics

Table 3 shows participants' socio-demographic characteristics. The majority of participants were women: 85 women out of 95 participants. Mean age was in the upper fifties in both genders. Education was high among all participants. BMI was about 26 kg/m^2 for women and about 24 kg/m^2 for men. Only 8 participants were smokers.

As far as previous/ongoing pathologies are concerned, 24 women reported a tumoral disease (mainly breast cancer: 18 women) and one male had a previous prostate cancer. Moreover, 11 women and 4 men declared a cardiovascular disease; 12 women declared a thyroid disease; one woman only had diabetes.

2. Wellness program and metabolic risk

The metabolic risk of the participants changed at the end of the programs (Table 5). At baseline (T_0) the risk score was 0 for 20 volunteers (21%), 1 for 22 (23%), 2 for 17 (18%) and 3 for 36 (38%). At the end of the project (T_1), the number of subjects in the highest risk category (3) decreased to 22 (23%). When considering participants allocated to two categories only (low risk ≤ 0.50 vs. high risk > 0.50), our data show that in T_0 56% (n = 53) of subjects had a metabolic risk of 0.5 or higher. But after the program (T_1), among them 12 people (23%) entered into the correct category with a metabolic risk below or equal to 0.5; this change was statistically significant (exact McNemar p-value = 0.001).

Table 5. Differences in clinical data in phase T_0 and T_1

	T_0	T_1
Metabolic risk		
0 (≤ 0.45)	20 (21)	32 (34)
1 (0.46-0.50)	22 (23)	22 (23)
2 (0.51-0.55)	17 (18)	19 (20)
3 (≥ 0.56)	36 (38)	22 (23)
Glycemic value (mg/dL)		
65-94	45 (47)	72 (76)
95-114	46 (48)	21 (22)
115-125	4 (4)	2 (3)
Diastolic blood pressure (mmHg)		
≤ 89	76 (80)	86 (91)
≥ 90	19 (20)	9 (9)
Systolic blood pressure (mmHg)		
≤ 139	78 (82)	88 (93)
≥ 140	17 (18)	7 (7)

Values are presented as number (%).

3. Wellness program and glycemic value

We have evaluated the impact of the wellness program on glycemic value change (Table 5). We stratified glycemic value in three classes of ranges: class 1 (between 65 mg/dL and 94 mg/dL), class 2 (95 mg/dL and 114 mg/dL) and class 3 (115 mg/dL and 125 mg/dL). At the T_0 moment, the glycemic value class was 1 for 45 volunteers (47%), 2 for 46 (48%), 3 for 4 (4%). At the end of the project, the glycemic value decreased in the whole group of participants: at the T_1 moment, the glycemic value class was 0 for 72 volunteers (76%), 1 for 21 (22%) and 2 for 2 (3%). When considering participants allocated to two categories only (low risk ≤ 94 mg/dL vs. high risk ≥ 95 mg/dL), our data show that in T_0 53% (n = 50) of subjects were in the high risk category. But after the program (T_1), among them 32 people (64%) entered into the correct category with a glycemic value below or equal to 94 mg/dL; this change was statistically significant (exact McNemar p-value < 0.001).

4. Wellness program and blood pressure

Finally, we have evaluated the impact of the wellness program on the blood pressure change (Table 5), and a reduction was detected for both diastolic and systolic blood pressure. In T_0, 19 subjects (20%) had diastolic blood pressure at high risk (≥ 90 mmHg), but after the wellness program 14 of them (74%) reached a normal value below or equal to 89 mmHg; this change was statistically significant (exact McNemar p-value < 0.031). In T_0, 17 subjects (18%) had systolic blood pressure at high risk (≥ 140 mmHg), but after the wellness program 12 of them (71%) reached a normal value below or equal to 139 mmHg; this change was statistically significant (exact McNemar p-value < 0.013).

DISCUSSION

Many factors seem to influence and decrease inflammasome status: diet, caloric restriction and FMD, gut microbiota, physical activities and life- style, creativity. Diet is the object of several pre-clinic and clinic research during the past years and its impact on well-being is currently clear: for example, a plant based diet with poor animal components is recommended by the World Cancer Research Fund [15,16]. Periodic starvation, or fasting-like dietary regimen,

can have pronounced effects on insulin-like growth factor 1, insulin, glucose, insulin-like growth factor-binding protein 1, and ketone body levels, thereby generating a protective environment for normal cells while creating a metabolic environment that does not favor precancerous and/or cancer cells [17-20].

When humans switch from eating three full meals per day to an intermittent eating regimen, such as one moderate size meal every other day or only 500-600 calories 2 day/week, they experience strong changes in energy metabolism: increased insulin sensitivity, reduced level of insulin and leptin, mobilization of fatty acids and elevation of ketone bodies levels. All the biochemical, genetic and epigenetic changes reported in the literature after a change in life-style might correspond to a change in clinical aspects and serum parameters that are easier to monitor [21]. Longo and Anderson [22] reported that different organisms (yeast, bacteria, worms, flies, mice) are capable of adapting and surviving under different forms and durations of food deprivation. In response to starvation cells enter either a non-dividing or a low-dividing state and invest energy resources in cellular protection against various insults. Intermittent (16 hours/day) starvation was yet investigated in women with moderate/high risk for breast cancer [23]. Previous studies analyzed biochemical and hematological values, demonstrating many positive effects on animal models and also on humans [24-26].

The aim of this study was to measure the effectiveness of a caloric restriction regime joined to a daily practice of physical and creative activities on some easily evaluable SMet parameters (glycemic value, waist circumference, blood pressure), the correlation with the metabolic risk index (WHtR) and the compliance of the patients to the proposed scheme. We used the SMet index (WHtR) to evaluate visceral fat as an indicator of SMet risk [27].

We chose three pillars in conducting our study: nutrition, physical activity and creativity.

1. Nutrition

The nutritional regime included fermented products, known to be beneficial for their influence on the composition and/or activity of the gastrointestinal microbiota [11,12,28]. Also the dish respects the indications of the guidelines in order to induce a reduction of the SMet and the postprandial glycemic peak that leads to chronic inflammation [15-29]. The frequency of daily meals is under study and debatable according to a huge amount of dietary schemes: our study is based on two meals a day food, with a great attention on food rich in micronutrients, therefore deriving only from intact soil or synergistically integrated crops [30,31]. The statistically significant change in the glycemic value reinforced the idea that a low insulinemic peak nutrition together with increased interval between meals could impact on carbohydrates metabolism.

2. Physical activity

Physical activity has been demonstrated to be much effective if carried out in load and with postural attention. Recent studies have shown a relationship between SMet and sarcopenia [32] and physical activity acts on sarcopenia status. They both are related with insulin-resistance, adipose tissue, chronic inflammation, etc. [5,6]. In addition, tai chi and yoga have demonstrated a strong impact on chronic systemic inflammation [33]. Furthermore, many outdoor activities have been proposed to the volunteers of our study, since evidence states that there is a strong positive impact on health when spending at least 120 minutes in nature weekly [34].

3. Creativity

The role of art therapy for the reduction of cortisol level was brought into consideration with the demonstrated efficacy in some studies [35,36]. Cortisol level is involved in the mechanism of induction and maintenance of SMet. Therefore, we decided to also integrate creativity to physical activity and nutrition in order to obtain a better result. This is the first prospective, pilot study that evaluates the effects of the integration of a short lifestyle change, based on fasting or mimicking-fasting regime (subdivide into a starting preparatory phase, a maintaining phase and a de-escalation fast mimiking [FM] phase) with leisure time and physical activity, on SMet parameters (WHtR, glycemic value and blood pressure).

Our results suggest that FM together with a scheme of leisure time and physical activity, significantly impact on risk factors for SMet such as insulin-resistance and moreover WHtR and induce a reduction of systolic and diastolic pressure in more than 70% of participants.

Compliance and adherence were excellent, and no patients left the program. No side effects were reported supporting the efficacy and tolerability of our nutrition proposal, in a short interval, associated with leisure and creative time proposals. We do not know if more cycles of combined-FMD would be of higher impact, likely yes, such as reported in the DIRECT trial, about the efficacy of FMD on chemotherapy cancer treatment: the more cycles of FMD were adhered, the higher tumor cell loss (> 90%) in the surgical specimen was seen [23]. Furthermore, 10 days of lifestyle change have proven to be able to impact SMet. One of the limits of this study is the lack of further hematological blood tests. Another limitation is that, even though 10 days are likely able to turn off the

wrong DNA switches and turn on the correct ones also in the gut microbiome, we cannot demonstrate it because we did not perform the microbiome test.

CONCLUSION

In conclusion, generally speaking, lifestyle is referred to nutrition, physical activity, leisure time, art-therapy and spending time outdoors in unpolluted areas, that means a lot of different food regimens and protocols proposed during the last decades: however recent data strongly support a multiple pathway of factors, sharing the same unique biochemical principles. Our multifactorial lifestyle proposal goes in the same direction that means modification of metabolism. The limitation to this report is represented by the small number of patients involved. Our nutrition proposal, calories-independent based, is innovative and well accepted by patients, and also physical activities compliance is high and well tolerated. The strategies we pursued have not been directed to lower weight or calories but to change the metabolism and its measurable anthropomorphic expression. These findings provide direct support for the levels of activity recommended for SMet prevention not only in terms of quantity but primarily in terms of quality, and provide actionable evidence for ongoing and future chronic disease and also cancer related metabolism shift prevention efforts.

NOTES

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- **Authors' contributions:** M.P.M. participated in conception and design of study. A.M. participated in acquisition of data. F.G. participated in analysis. M.P.M. and M.G.B. participated in interpretation of data. A.M., A.S., and M.B. participated in drafting the manuscript. A.S. and M.P.M. participated in revising the manuscript critically for important intellectual content.
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