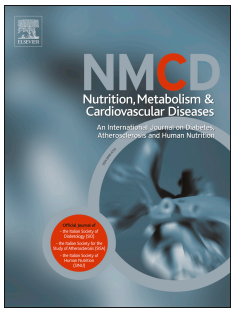
Accepted Manuscript



Intensive lifestyle intervention is particularly advantageous in poorly controlled type 2 diabetes

E. Sbroma Tomaro, R. Pippi, E. Reginato, C. Aiello, L. Buratta, C. Mazzeschi, C. Perrone, C. Ranucci, A. Tirimagni, A. Russo, C. Fatone, C. Fanelli, P. De Feo

PII: S0939-4753(17)30130-8

DOI: 10.1016/j.numecd.2017.06.009

Reference: NUMECD 1740

To appear in: *Nutrition, Metabolism and Cardiovascular Diseases*

Received Date: 28 September 2016

Revised Date: 4 May 2017

Accepted Date: 12 June 2017

Please cite this article as: Sbroma Tomaro E, Pippi R, Reginato E, Aiello C, Buratta L, Mazzeschi C, Perrone C, Ranucci C, Tirimagni A, Russo A, Fatone C, Fanelli C, De Feo P, Intensive lifestyle intervention is particularly advantageous in poorly controlled type 2 diabetes, *Nutrition, Metabolism and Cardiovascular Diseases* (2017), doi: 10.1016/j.numecd.2017.06.009.

Intensive lifestyle intervention is particularly advantageous in poorly controlled type 2 diabetes.

Authors: Sbroma Tomaro E.[a], Pippi R. [a], Reginato E.[a], Aiello C. [a], Buratta L. [a], Mazzeschi C. [a], Perrone C. [a], Ranucci C. [a], Tirimagni A. [a], Russo A. [a], Fatone C., Fanelli C. [a] and De Feo P. [a].

[a]HealthyLifestyleInstitute, C.U.R.I.A.Mo. (Centro Universitario Ricerca Interdipartimentale Attività Motoria), University of Perugia, Via G. Bambagioni, 19 06126 Perugia, Italy

Corresponding author:

Pierpaolo De Feo

C.U.R.I.A.Mo. (Centro Universitario Ricerca Interdipartimentale Attività Motoria)

Via G. Bambagioni

19 06126 Perugia

Italy

E-mail addresses: ***pierpaolodefeo@gmail.com***

Non-standard abbreviations

Type 2 diabetes (DM2); World Health Organization (WHO); American Diabetes Association (ADA); Heart Rate Reserve (HHR); One repetition maximum (1RM); Body Mass Index (BMI); Defined Daily Doses (DDD); Standard deviation (SD); Australian New Zealand Clinical Trials Registry (ACTRNR); Glycosylated haemoglobin (HbA1c).

Keywords: Type 2 diabetes, lifestyle intervention, Glycosylated haemoglobin, glycometabolic control, exercise.

Abstract

Background and aims: It is unknown whether lifestyle change is effective in people with type 2 diabetes with inadequate glucose control. The aim of this study was to asses, in a group of people with type 2 diabetes, the impact of baseline values of glycosylated haemoglobin (HbA1c) on the effects of an intensive lifestyle intervention on metabolic, clinical and strength parameters.

Methods and results: 222 people with type 2 diabetes with mean±standard deviation baseline HBA1c of 7.50%±1.27 (range 5.1-12.7%), were enrolled in a 3-month structured multidisciplinary lifestyle intervention. Anthropometric, biochemical, clinical and fitness measurements were collected at baseline, at the end of the lifestyle intervention program and at two-year follow-up visit. Significant improvements in glycometabolic control (HbA1c: $p \leq 0.0001$); anthropometric parameters (BMI $p \leq 0.0001$; waist circumference: $p \leq 0.0001$); and systemic blood pressure ($p \leq 0.0001$) were observed both at the end of the three month intensive lifestyle program and at the two-year follow up visit. In addition, defined daily doses of hypoglycaemic treatment significantly decreased ($p=0.001$).

Fitness measures exhibited significant increments in the whole sample at the end of the intensive intervention program ($p \leq 0.0001$). When patients were divided in tertiles considering the baseline value of HbA1c, the most marked improvements in HbA1c, blood glucose and triglycerides were observed in the group with inadequate glucose control (Hba1c ≥7.71%), both at the three-month and two-year follow-ups.

Conclusion: These results demonstrate that an intensive lifestyle intervention should be recommended for people with type 2 diabetes, particularly those with the most inadequate glycaemic control.

Registration Number: CURIAMO trial was registered in the Australian New Zealand Clinical Trials Registry, ACTRN12611000255987)

Introduction

The WHO reported the global prevalence of diabetes for 2014 as 9% among adults [1]. In 2012, diabetes was directly responsible for an estimated 1.5 million deaths [2], and is predicted to be the 7th leading cause of death in 2030 [3]. Type 2 diabetes (DM2), that accounts for about 90% of all diagnosed cases of diabetes worldwide, [4], is largely the result of excess body weight and physical inactivity. According to position statements published by the American Diabetes Association, American College of Sports Medicine and American Health Association, structured lifestyle intervention should be the first approach to diabetic disease [5,6]. The lifestyle intervention CURIAMO trial (Australian New Zealand Clinical Trials Registry, ACTRN12611000255987) performed at the Healthy Lifestyle Institute of Perugia University (C.U.R.I.A.MO., *Centro Universitario di Ricerca Interdipartimentale Attività Motoria*) is designed to promote participants' growth in three parallel fields: exercise, nutrition and psychological well-being [7]. The multidisciplinary approach involves multiple health care professionals (exercise physiologist, endocrinologist, sports medicine physician, psychologist, dietician, educator, nurse) who work together to support patients in achieving long-lasting lifestyle change.

Despite the clinical guidelines of scientific societies considering lifestyle change as a basic therapeutic option for DM2 prevention or treatment, there are no data on the efficacy of lifestyle intervention in relation to the degree of baseline glucose control. To the best of our knowledge there is one study that demonstrated, in a subgroup analysis limited to participants with a baseline HbA1c value >7%, greater improvement in

glycaemic control following an exercise program among persons with higher baseline haemoglobin A1c values over a six-month period [8].

Thus, the aim of this study was to assess the impact of patients' baseline value of glycosylated haemoglobin on the effects of an intensive lifestyle intervention on metabolic, clinical and strength parameters in a group of people with type 2 diabetes.

Methods

Subjects

Among 1 464 subjects enrolled in the CURIAMO trial from 2010 to 2014, 222 subjects (122 males and 100 females) with type 2 diabetes mellitus (according to the diagnostic criteria for diabetes from American Diabetes Association (ADA) guidelines [9]) participated and completed a three-month intensive lifestyle intervention program of the CURIAMO trial.

This model included follow-up visits performed annually for 5 years. We report data from baseline (T0), control visit after intensive intervention (T1 - three months), and two-year follow-up visit (T2). Analyses were limited to participants with baseline (T0) and control (T1) data on all measurements (n=222). 142 subjects participated at the two-year follow-up visit (T2).

The study was approved by the local Ethics Committee (CEAS Umbria Region, HREC number 1/10/1633). Full informed consent was given by all participants at the beginning of the treatment. Inclusion criteria were: age between 18 and 80 years, BMI > 27 Kg/ m^2 and type 2 diabetes. Exclusion criteria were orthopaedic or other medical conditions that would contraindicate exercise testing or the practice of physical activity.

Baseline characteristics of the study population with diabetes are shown in table 1.

Lifestyle intervention

The intensive phase of the three-month lifestyle intervention program involved different qualified personnel, as previously described in detail [7]. Briefly, during the intervention, patients underwent: 1) an initial medical examination; 2) an interview by a psychologist; 3) an assessment by a dietician and ~~a~~ nutritional intervention; 4) a physical examination by a sports medicine specialist; 5) an individualized program (groups of five to six patients) of 26 sessions (two per week) of structured indoor exercise, described elsewhere [7]; and 6) eight sessions of group therapeutic education conducted by a doctor of pedagogical sciences.

The initial interview with a psychologist was aimed at increasing the subject's motivation to change and to assess his/her compliance and psychological status [7].

The exercise program was performed in a gym twice a week for three months (total 26 sessions) and supervised by an exercise physiologist. Each session lasted 90 minutes. These were divided into 60 minutes of aerobic workout and 30 minutes of circuit training for muscular strength. The aerobic workout was performed using ergometers for cardiovascular work with a gradual increase of the workout intensity (5% every 3 weeks) up to 70% of Heart Rate Reserve (HHR), established by Karvonen's formula [10]. Muscular strength was assessed using isotonic machines starting with a load corresponding to 50% of one repetition maximum (1-RM); 1-RM is defined as the maximum weight that can be lifted by a subject for a single repetition in a specific exercise. The load was gradually increased every three weeks, if possible. In conjunction with the beginning of physical activity sessions, patients were invited to attend 8 focus

groups, conducted by a doctor in pedagogic sciences, in which participants were given the opportunity through self-narration and self-writing to express and free themselves of difficulties, fears and problems related to their disease which prevented their achieving lifestyle change [11]. During the intensive phase of the lifestyle intervention program, patients underwent a nutritional intervention that consisted of periodic individualized nutritional visits and four sessions of nutrition education, performed by dieticians. The aim of these visits was to support the change in nutritional habits based on national recommendations [12].

Measures

In the intensive lifestyle intervention, anthropometric variables such as height (cm), body weight (Kg), Body Mass Index (BMI, Kg/m^2), waist circumference (cm), and body composition were measured, as well as ~~the~~ systolic and diastolic blood pressure. Measurements of weight and body composition were performed by the TANITA body composition analyser BC-420MA (Tokyo, Japan). BMI was calculated by dividing weight in kilograms by height in metres squared. Waist circumference (WC) and clinostatic blood pressure were measured by trained clinicians. Blood pressure was measured by a UM-101 mercury-free sphygmomanometer (A&D Medical, Italy), using a properly sized blood pressure cuff.

The maximum dynamic force of the extensor muscles of the legs and of the flexor and the extensor muscles of the arms was measured at baseline and at three-months (T1), as follows. During the first week (two sessions) all the patients participated at pre-training sessions at CURIAMO and were instructed in the correct performance of all the

exercises. In the workouts n°3, n°4 and n°26 we used isotonic machines (Lat machine and Leg Press Technogym, Cesena, Italy) to evaluate the maximum dynamic force of extensor muscles of the leg and the flexor and extensor muscles of the arms. In order to estimate the 1RM we used the *Brzycki 1-RM prediction equation* [13,14]. A single test's session was composed of warm up on a treadmill and 10 repetitions of each exercise, using the amount of resistance used for the familiarization session. In order to carry out the test, the resistance was progressively increased until the subjects could perform only 12 or fewer repetitions of each exercise. The aim of the increase in resistance was to reach the suitable repetitions in 3–5 attempts.

The drug consumption of anti-diabetes and anti-hypertensive treatments were evaluated at baseline, after the lifestyle intervention and at the two-year follow-up visit using the count of the Defined Daily Doses, for antihypertensive (DDD-hyper) and hypoglycaemic drugs (DDD-glic) [15].

In the two-year follow-up visit (T2) anthropometric parameters (weight, BMI, waist circumference), glycometabolic data (glycaemia, glycosylated haemoglobin, lipid asset) and pharmacological treatment were collected.

Statistical analysis

Descriptive statistics of the measures at the baseline (T0), delta changes at T1 and T2 are presented as the mean ± standard deviation (SD). Differences between baseline, T1, T2 were assessed trough repeated measure ANOVA and significance was accepted at the $p < 0.05$ level. Quantitative variables are presented as mean changes ± SD of Δ1(T1-T0), Δ2 (T2-T0). In order to explore the effect of the baseline values of HbA1c, subjects were

grouped into tertiles. Repeated measure ANOVA was performed for the three groups. All statistical analysis was performed using the SPSS statistical package, release 20.0 (SPSS Inc., Chicago, IL).

Results

Data obtained from all patients at the beginning (time T0) and after 3 months of structured physical exercise (Δ1) show a statistically significant change (Table 2/a) in the following parameters: fat mass (expressed in *Kg* and in *percentage*), Lat Machine, Chest Press, Leg Press, Leg Extension and VO2 max.

Data analysed from all patients with an available two-year follow-up visit (baseline, T1 and T2) show a statistically significant change (Table2/b) in the following parameters: BMI, weight, waist circumference, blood glucose, HbA1c, triglycerides, total cholesterol, systolic blood pressure (SBP) and diastolic blood pressure (DBP). The parameters that failed to show a significant change were: HDL cholesterol and LDL cholesterol. Regarding the Defined Daily Doses, significant differences were observed for DDD-hyper and DDD-glic.

There were no differences between sexes in changes after intensive intervention for metabolic and anthropometric parameters. However, there were significant differences for strength measurements (LATΔ1: males 12.1±7.4 Kg, females 6.2±6.8 Kg, p= 0.000; CHESTΔ1: males13.3±7.4 Kg, females 7.2±5.7 Kg, p=0.000; PRESSΔ1: males 53.1±37.1 Kg, females 31.7±34.7 Kg, p=0.005; LEXTΔ1: males 18.1±11.0 Kg, females 11.1±9.1 Kg, p =0.002).

In the whole sample, the potential correlation was calculated between glycaemic control (expressed as the baseline value of HbA1c) and the changes of anthropometric, metabolic and strength parameters. Significant correlation was observed between the baseline value of HbA1c and the changes in fasting blood glucose (r: -0.337, p ≤0.0001), triglycerides (r: -0.275, p ≤0.0001) and HbA1c (r: -0.645, p ≤0.0001). Thus, in order to evaluate if

glycaemic control at baseline could have an impact on the improvement of metabolic parameters (HbA1c, fasting blood glucose and triglycerides), patients were divided into 3 groups according to HbA1c at baseline (T0):

GROUP 1 (good metabolic control): 78 patients with HbA1c≤6.8%, 39 males and 39 females, mean age: 59.25±8.76 years.

GROUP 2 (moderate metabolic control): 70 patients with HbA1c>6.81% but <7.7%, 43 males and 27 females, mean age: 59.60±9.21 years.

GROUP 3 (inadequate metabolic control): 74 patients with Hba1c ≥7.71%, 40 males and 34 females, mean age: 58.59±7.56 years.

During the intensive period of treatment, in Group 1 (namely patients with good glycometabolic control) HbA1c, blood glucose and triglycerides changed minimally (Δ1 of blood glucose = -6.3±18.8 mg/dl, Δ1of HbA1c= -0.1 ±0.4 % and Δ1 of triglycerides =-7.9±48.6 mg/dl). Patients in Group 2, with moderate glycometabolic control, showed a slight, although significant, change in the three parameters (Δ1 of blood glucose= -10.2±32.4 mg/dl; Δ1of HbA1c= -0.4 ±0.7% and Δ1 of triglycerides = -14.3±56.53 mg/dl) while patients with the worst metabolic control (Group 3) showed the most important beneficial effects of the intervention (Δ1 of blood glucose= -29.0±60.8 mg/dl; Δ1of HbA1c= -1.3±1.5 % and Δ1 of triglycerides = -51.4±128.0 mg/dl).

At the two-year follow-up, we observed the same trend in improvement in the three groups (tab.2/b). Most importantly, the patients included in the group with the worst metabolic control had made significant additional improvements in the values of blood glucose (**Δ2=**-43.7±55.1), HbA1c (**Δ2=**-1.6±1.5) and triglycerides (**Δ2=**-31.6±81.8).

To confirm these observations, a post-hoc analysis among groups (tertiles) was performed using Bonferroni's correction. This test validated the conclusion that people with type 2 diabetes and inadequate glucose control not only obtained the greatest initial improvement from the lifestyle intervention at three months as compared with people with good to moderate glucose control, they maintained this improvement long term (two years).

Discussion

Tackling diabetes and obesity is one of the major global health challenges of our time, one that requires all the available resources. The present study 1) supports the existing scientific evidence [16,17,18] by emphasizing the broader effectiveness of a structured lifestyle intervention on glycometabolic control, and 2) demonstrates for the first time that lifestyle changes give results not only in well controlled subjects with type 2 diabetes with good-to-moderate baseline HbA1c levels, but also in people with inadequate glycometabolic control, both in the short (three months) and long term (two years). Interestingly, in the latter study group we observed the most significant beneficial effect of the intervention on the absolute reduction in the mean level of fasting blood glucose, HbA1c and triglycerides. At two years, in the group with inadequate glycaemic control, fasting blood glucose and HbA1c improved quantitatively more when compared with the changes in the good and moderate glucose control groups (for both $p<0.0001$). As a consequence, several subjects in the inadequate glucose control group could change their status to good-to-moderate glucose control. Overall, for the patients, this level of reduction in the mean level of HbA1c (Δ1-1.3 ±1.5 %; Δ2: -1.6±1.5 %) could translate

into a significant reduction in microvascular complications, myocardial infarction, and diabetes-related mortality [19].

Interestingly, the improvement in HbA1c levels in people with inadequate glucose control was not the result of a more aggressive pharmacological therapy because the DDD of antidiabetic drugs significantly declined among the three groups after the intervention and at the two-year follow-up. Thus, intensive lifestyle intervention in people with type 2 diabetes and inadequate control is alone very effective in improving glucose control without the intensification of pharmacological treatment. In addition, the lifestyle intervention in the poorly controlled diabetic group could prove cost-effective for the healthcare sector.

It is of note, that the findings of our study would suggest that the prescription of an intensive lifestyle change should not be avoided in the presence of poorly controlled diabetes, if there are not concomitant situations which represent a contraindication to the practice of exercise. Actually, the fact that an intensive lifestyle program produces the best results on glycometabolic parameters in people with type 2 diabetes with inadequate glucose control indicates that those subjects might receive greater benefit from such intervention with the additional advantage of being exposed to less intensive pharmacological treatment.

A final consideration that supports intensive lifestyle intervention treatment, especially in poorly controlled subjects with type 2 diabetes, is the favourable effect on the psychological condition of the patients. In fact, generally, these patients worry that their high glycaemic levels will lead to injection therapy. The knowledge that intensive lifestyle intervention treatment will improve their glycaemic control and thus enable them

to avoid injection therapy will increase their motivation to maintain the lifestyle change [20].

It must be stressed that the present results have been obtained using a structured, individualized and supervised exercise regime, and lifestyle intervention. For this reason, the present study may not be replicable in a simple ambulatory counselling setting aimed at increasing regular exercise.

In conclusion, these results demonstrate that an intensive lifestyle intervention should be recommended for people with type 2 diabetes, particularly those with the most inadequate glycaemic control because it results in the greatest improvement of glycometabolic parameters while avoiding aggressive pharmacological treatment.

References

1. World Health Organization. (2014). Global status report on noncommunicable diseases 2014. Geneva, WHO.
2. World Health Organization. (2014). Global Health Estimates: Deaths by Cause, Age, Sex and Country, 2000-2012. Geneva, WHO.
3. Mathers CD, Loncar D.Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med. 2006; 3:e442.
4. World Health Organization. (1999). Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation. Geneva: WHO; (WHO/NCD/NCS 99.2).
5. Marwick TH, Hordern MD, Miller T, Chyun DA, Bertoni AG, Blumenthal RS, Philippides G, Rocchini A. Exercise training for type 2 diabetes mellitus: impact on cardiovascular risk: a scientific statement from the American Heart Association.Circulation. 2009; 119:3244-62.
6. Colberg SR, Sigal RJ, Fernhall B, Regensteiner JG, Blissmer BJ, Rubin RR, Chasan-Taber L, Albright AL, Braun B; American College of Sports Medicine.; American Diabetes Association.Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement. Diabetes Care. 2010;33:e147-67.
7. De Feo P, Fatone C, Burani P, Piana N, Pazzagli C, Battistini D, Capezzali D, Pippi R, Chipi B, Mazzeschi C. An innovative model for changing the lifestyles of persons with obesity and/or Type 2 diabetes mellitus. J Endocrinol Invest. 2011;34:e349-54.

8. N. B. Sanghani, D. N. Parchwani, K. M. Palandurkar, A. M. Shah,and J. V. Dhanani. Impact of lifestyle modification on glycemic control in patients with type 2 diabetes mellitus. Indian J Endocrinol Metab. 2013; 17:1030–1039.
9. Standards of Medical Care in Diabetes—2014. Diabetes Care 2014;37(Suppl. 1):S14–S80.
10. Karvonen M.J., Kentala E, Mustala O. The effect of training on heart rate: a longitudinal study. Ann Med Exp Biol Fenn, 1957; 35:307-15.
11. Piana N, Battistini D, Urbani L, Romani G, Fatone C, Pazzagli C, Laghezza L, Mazzeschi C, De Feo P. Multidisciplinary lifestyle intervention in the obese: its impact on patients' perception of the disease, food and physical exercise. Nutr Metab Cardiovasc Dis. 2013;23:337-43.
12. S.I.N.U. (2014). Livelli di Assunzione di Riferimento di Nutrienti ed energia per la popolazione italiana, IV Revisione.
13. UnaiseA.H., PrateekR., Mohd. Y.S., Mohd. E. H. Reliability of 1-Repetition Maximum Estimation for Upper and Lower Body Muscular Strength Measurement in Untrained Middle Aged Type 2 Diabetic Patients. Asian J Sports Med, 2012; 3: 267–273.
14. Nascimento MA do, Cyrino ES, Nakamura FY, Romanzini M, Pianca HJC, Queiróga MR. Validation of the Brzycki equation for the estimation of 1-RM in the bench press. Rev Bras Med. Esporte, 13:40e-42e.
15. Guidelines for ATC classification and DDD assignment, 5th edition. (2002) WHO Collaborating Centre for Drug Statistics Methodology, Oslo.
16. De Feo P. and SchwarzP.(2013). Is physical exercise a core therapeutical element for most patients with type 2 diabetes? Diabetes Care, 2013; 36 (Suppl 2):S149-54.

17. Nathan DM. Diabetes: Advances in Diagnosis and Treatment. JAMA, 2015; 314:1052-62.

18. Espeland MA, Glick HA, Bertoni A, Brancati FL, Bray GA, Clark JM, Curtis JM, Egan C, Evans M, Foreyt JP, Ghazarian S, Gregg EW, Hazuda HP, Hill JO Hire D, Horton ES, Hubbard VS, Jakicic JM, Jeffery RW, Johnson KC, Kahn SE, Killean T, Kitabchi AE, Knowler W, Kriska A, Lewis CE, Miller M, Montez MG, Murillo A, Nathan DM, Nyenwe E, Patricio J, Peters AL, Pi-Sunyer X, Pownall H, Redmon JB, Rushing J, Ryan DH, Safford M, Tsai AG, Wadden TA, Wing RR, Yanovski SZ, Zhang P; Look AHEAD Research Group. Impact of an intensive lifestyle intervention on use and cost of medical services among overweight and obese adults with type 2 diabetes: the action for health in diabetes. Diabetes Care. 2014;37:2548-56.

19. Maislos M. and Weisman D. Multidisciplinary approach to patients with poorly controlled type 2 diabetes mellitus: a prospective, randomized study. Acta Diabetol, 2004; 41:44–8

20. Mazzeschi C1, Pazzagli C, Buratta L, Reboldi GP, Battistini D, Piana N, Pippi R, Fatone C, De Feo P. Mutual interactions between depression/quality of life and adherence to a multidisciplinary lifestyle intervention in obesity. J Clin Endocrinol Metab. 2012; 97:E2261-5.

Table 1:

Characteristics	Total n=222	Men n=122	Women n=100	p
Age (year)	59.1±8.5	60.0±8.0	58.1±9.0	0.097
Diabetes duration (yrs)	8.1±7.6	8.7±7.9	7.4±7.2	0.220
Weight (kg)	91.1±18.1	96.8±18.2	84.0±15.3	0.000
BMI (kg/m^2)	32.0±5.5	31.8±5.5	32.2±5.5	0.598
WC (cm)	109.5±13.0	110.8±13.2	108.0±12.6	0.105
Fat mass (%)	35.1±8.6	30.0±6.9	41.4±5.9	0.000
Fat mass (kg)	32.6±11.8	30.1±12.1	35.7±10.6	0.000
Fat Free mass (kg)	58.5±12.2	66.7±9.9	48.6±5.9	0.000
Musc mass (kg)	55.7±11.6	63.6±8.8	46.1±5.7	0.000
Fasting blood glucose (mg/dl)	150.1±44.5	152.1±45.2	147.6±43.7	0.453
Hba1c (%)	7.5±1.3	7.5±1.4	7.5±1.2	0.986
Total cholesterol (mg/dl)	190.1±37.4	185.2±38.6	196.1±35.2	0.031
HDL cholesterol (mg/dl)	46.9±11.8	43.8±11.3	50.7±11.4	0.000
LDL cholesterol (mg/dl)	109.7±32.3	108.6±32.9	111.0±31.7	0.598
Triglycerides (mg/dl)	174.6±135.5	169.1±110.1	181.3±161.6	0.507
Uricemia (mg/dl)	5.5±1.3	5.8±1.2	5.1±1.2	0.000
SBP (mmhg)	140.3±16.0	141.5±16.5	138.9±15.2	0.223
DBP (mmhg)	82.8±8.9	83.7±9.2	81.7±8.4	0.098
LAT (kg)	38.3±9.9	43.9±8.7	30.8±5.4	0.000
CHEST (kg)	28.0±9.3	33.9±7.6	20.2±4.1	0.000
PRESS (kg)	150.7±32.3	166.9±28.5	129.1±23.2	0.000
LEXT (kg)	29.0±8.8	33.1±8.9	23.5±4.9	0.000
VO_2max (ml/Kg/min)	17.7±9.5	21.7±8.5	12.7±8.2	0.000

Table 1 Baseline characteristics of the subjects with type 2 diabetes.
Results are mean ±SD. Statistical significance was considered at $p<0.05$
Table 1: MUSC MASS = muscle mass; LAT = Lat Machine test value; CHEST = Chest press test value; PRESS = leg press test value; LEXT = leg extension test value; VO_2 max = maximum rate of Oxygen (O2) consumption.

Table 2 Anthropometric, biochemical, clinical and strength parameters in the total sample before (T0), after 3 months (T1) of structured physical exercise and at two years follow-up visit (T2).
Results are mean ±SD. Statistical significance was considered at p<0.05.

Characteristics	T0 n=222	Δ1 n=222	p
Uricemia (mg/dl)	5.5±1.3	0.1±0.8	0.2
Fat mass (%)	35.1±8.6	-1.7±3.1	≤0.0001
Fat mass (kg)	33.6±11.8	-2.4±4.2	≤0.0001
Fat Free mass (kg)	58.5±12.2	0.2±4.3	0.5
Musc mass (kg)	55.7±11.6	0.2±3.0	0.4
LAT (kg)	38.3±9.9	9.5±7.7	≤0.0001
CHEST (kg)	28.0±9.3	10.6±7.4	≤0.0001
PRESS (kg)	150.7±32.3	43.5±37.4	≤0.0001
LEXT (kg)	29.0±8.8	15.0±10.7	≤0.0001
VO_2max (ml/Kg/min)	17.69±9.5	7.53±5.6	≤0.0001

Table 2/a: *SBP =Systolic blood pressure; DBP =Diastolic blood pressure; WC =waist circumference; DDD hyper =Defined Daily Doses for antihypertensive drugs; DDD-glic= Defined Daily Doses for hypoglycaemic drugs.*

Characteristics	T0 n=222	Δ1 n=222	Δ2 n=149	p	Post hoc
Blood glucose (mg/dl)	150.1±44.5	-15.0±42.0	-15.0±43.0	≤0.0001	T1,T2 vs T0
Hba1c (%)	7.5±1.3	-0.6±1.1	- 0.5±1.3	≤0.0001	T1,T2 vs T0 T2 vs T1
Total cholesterol (mg/dl)	190.1±37.4	-2.5±29.0	-16.0±51.3	0.004	T2 vs T0 T2 vs T1
HDL cholesterol (mg/dl)	46.9±11. 8	-0.7±8.2	0.8±15.9	0.5	
LDL cholesterol (mg/dl)	109.7±32.3	1.7±25.6	-2.9±75.5	0.5	
Triglycerides (mg/dl)	174. 6±135.5	-24.4±87.2	-11.7±79.3	0.002	T1 vs T0
SBP (mmhg)	140.3±16.0	-8.6±15.6	-12. 5±16.8	≤0.0001	T1, T2 vs T0
DBP (mmhg)	82.8±8.9	-5.3±9.8	-8.7±12.1	≤0.0001	T1,T2 vs T0 T2 vs T1
Body mass (kg)	91.1±18.1	-2.5±8.0	-2.3±3.5	≤0.0001	T1,T2 vs T0
BMI (kg/m^2)	32.0±5.5	-0.9±2.50	-0.6±1.5	≤0.0001	T1,T2 vs T0
WC (cm)	109.5±13.0	-3.2±4.7	-3.4±6.5	≤0.0001	T1 vs T0
DDD-hyper	1.9±1.8	-0.1±0.8	-0.2±1.0	≤0.0001	T1 vs T0
DDD-glic	1.1±1.0	-0.1±0.3	-0.1±0.5	0.001	T1 vs T0 T2 vs T0

Table 2/b*: SBP = Systolic blood pressure; DBP = Diastolic blood pressure; WC = waist circumference; DDD hyper =Defined Daily Doses for antihypertensive drugs; DDD-glic= Defined Daily Doses for hypoglycaemic drugs.*
Between-group comparisons are reported in the last column of table 1/a. Significant differences are then followed by post hoc results (e.g., T0 vs. T1,T2 means that group T0 is different from groups T1–T2).

Table 3/a ***Table 3/a. Baseline parameters and changes in Groups 1, 2 and 3.***
Results are mean ±SD. Statistical significance was considered at p<0.05.

Characteristics	GROUP 1 Good metabolic control			GROUP 2 Moderate metabolic control			GROUP 3 Inadequate metabolic control		
	T0 n=78	Δ1 n=78	p	T0 n=70	Δ1 n=70	p	T0 n=74	Δ1 n=74	p
Uricemia (mg/dl)	5.6±1.1	-0.0±0.8	0.64	5.7±1.4	-0.0±0.9	0.79	5.2±1.3	0.2 ±0.8	0.06
Fat mass (%)	35.5±8.6	-1.8±3.3	0.00	33.8±9.0	-1.3±2.5	0.00	35.9±8.20	-2.0± 3.5	0.00
Fat mass (kg)	32.4±11.0	-2.0±3.5	0.00	31.6±12.7	-2.4±4.9	0.00	33.9 ±11.7	-2.9±4.3	0.00
Fat free mass (kg)	58.1±12.03	-0.1±4.5	0.79	58.6 ±11.9	0.4±4.8	0.50	58.9 ±12.9	0.3±3.4	0.40
Musc mass (kg)	55.2±11.5	0.2 ±3.0	0.54	56.2 ±10.8	-0.2 ±2.2	0.49	55.8 ±12.5	0.5±3.7	0.23
LAT (kg)	35.9±7.3	9.5±5.4	0.00	42.5 ±11.3	9.0±10.8	0.00	37.9 ±9.7	10.6±6.6	0.00
CHEST (kg)	25.6±6.6	9.3±5.4	0.00	32.3 ±11.4	10.6±10.7	0.00	27.2 ±9.05	12.2±5.3	0.00
PRESS (kg)	145.8±27.6	33.8 ±20.6	0.00	151.9±32.3	44.6±51.9	0.00	141.7±32.6	53.5 ±35.5	0.00
LEXT(kg)	26.3±7.8	12.1±6.4	0.00	29.9 ±11.1	15.6±14.3	0.00	28.7±8.7	17.9 ±10.9	0.00

MUSC MASS = muscle mass; LAT = Lat Machine test value; CHEST = Chest press test value; PRESS = leg press test value; LEXT = leg extension test value; ***Between-group comparisons are reported in the last column of table 1/a. Significant differences are then followed by post hoc results (e.g., T0 vs. T1,T2 means that group T0 is different from groups T1–T2).***

Table 3/b ***Table 3. Baseline parameters and changes in Groups 1, 2 and 3.*** *Results are mean ±SD. p < 0.05 vs. basal.*

	GROUP 1 Good metabolic control					GROUP 2 Moderate metabolic control					GROUP 3 Inadequate metabolic control				
	T0 n=78	Δ1 n=78	Δ2 n=50	p	Post hoc	T0 n=70	Δ1 n=70	Δ2 n=49	p	Post hoc	T0 n=74	Δ1 n=74	Δ2 n=43	p	Post hoc
Blood glucose (mg/dl)	123.6 ±22.2	-6.3 ± 18.8	-1.1 ±24.3	0.18		142.0 ±30.0	-10.2 ±32.4	-4.0 ±33.2	0.01	T1 vs T0	187.2 ±41	-29.0 ±60.8	-43.7 ±55.1	0.00	T1, T2 vs T0
Hba1c (%)	6.4 ±0.4	-0.1 ±0.4	0.3 ±0.6	0.00	T1, T2 vs	7.3 ±0.3	-0.4 ±0.7	-0.2 ±0.8	0.00	T1 vs T0	9.0 ±1.1	-1.3 ±1.5	-1.6 ±1.5	0.00	T1, T2 vs

					T0, T2 vs T1										T0
Total cholesterol (mg/dl)	191.7 ±39.2	-4.7 ±27.5	-4.7 ±36.3	0.62		183.6 ±36.8	-2.8 ±29.8	-24.3 ±57.9	0.09		182.8 ±36.9	0.0 ±29.9	-19.3 ±56.5	0.03	T2 vs T1
HDL cholesterol (mg/dl)	348 ±11.9	-2.3 ±7.2	0.04 ±9.4	0.19		48.9 ±13.6	-0.4 ±7.4	-0.9 ±8.7	0.79		43.9 ±11.4	0.6 ±9.6	3.8 ±25.5	0.40	
LDL cholesterol (mg/dl)	115.6 ±34.9	-1.3 ±26.0	6.9 ±120.1	0.7		108.2 ±28.4	0.4 ±25.4	-12.1 ± 25.7	0.00	T2 vs T0, T1	100.9 ±30.3	6.2 ±25.0	-3.9 ±32.8	0.02	T2 vs T1
Triglycerides (mg/dl)	154.7 ±90.9	-7.9 ±48.6	-7.5 ± 88	0.65		144.8 ±67.3	-14.3 ±56.5	0.8 ±63.8	0.07		192.2 ±125.7	-51.4 ±128.0	-31.6 ±81.8	0.00	T1 vs T0
SBP (mmhg)	142.2 ±16.4	-10.6 ±16.3	-13.5 ±16.7	0.00	T1, T2 vs T0	141.6 ±16.0	-8.2 ±15.5	-13.1 ±16.9	0.00	T1, T2 vs T0	142.5 ±14.6	-6.8 ±14.9	-10.6 ±17.0	0.00	T2, T1 vs T0
DBP (mmhg)	83.5 ±7.9	-6.9 ±9.9	-11.2 ±12.3	0.00	T1, T2 vs T0	82.2 ±7.7	-4.8 ±10.4	-6.6 ±10.8	0.00	T1, T2 vs T0	82.0 ±11.1	-4.2 ±9.0	-8.6 ±13.2	0.00	T2, T1 vs T0
Body mass (kg)	90.1 ±15.3	-3.2 ±12.6	-2.2 ±2.6	0.00	T1, T2 vs T0	91.3 ±17.6	-2.0 ±3.4	-2.1 ±4	0.00	T1, T2 vs T0	91.4 ±19.0	-2.3 ±3.7	-2.6 ±4.0	0.00	T2, T1 vs T0
BMI (kg/m^2)	30.9 ±5.1	-1.1 ±3.9	-0.7 ±1.6	0.00	T1, T2 vs T0	31.5 ±5.6	-0.7 ±1.2	-0.5 ±1.2	0.00	T1, T2 vs T0	31.9 ±5.1	-0.8 ±1.3	-0.6 ±1.7	0.01	T1 vs T0
WC (cm)	108.1 ±10.6	-3.3 ±4.8	-4.1 ±5.9	0.00	T1, T2 vs T0	109.2 ±14.6	-3.7 ±4.6	-3.8 ±6.3	0.00	T1, T2 vs T0	109 ±13.4	-2.6 ±4.7	-2.2 ±7.3	0.04	T1 vs T0
DDD-hyper	2.2 ±1.8	-0.4 ±0.3	-0.1 ±0.7	0.27		1.7 ±1.9	-0.3 ±1.3	-0.3 ±1.5	0.194		1.8 ±1.7	-0.1 ±0.4	-0.1 ±0.6	0.09	
DDD-glic	1.0 ±0.9	-0.1 ±0.2	-0.1 ±0.4	0.01	T1 vs T0	1.0 ±0.7	-0.1 ±0.2	-0.1 ±0.3	0.02	T1, T2 vs T0	1.3 ±1.1	-0.1 ±0.3	-0.1 ±0.6	0.16	

SBP = Systolic blood pressure; DBP = Diastolic blood pressure; WC = waist circumference; DDD hyper = Defined Daily Doses for antihypertensive drugs; DDD-glic = Defined Daily Doses for hypoglycaemic drugs.

Between-group comparisons are reported in the last column of table 2/a. Significant differences are then followed by post hoc results (e.g., T0 vs. T1,T2 means that group T0 is different from groups T1–T2).

Highlights:

- Clinical effects evaluation of structured multidisciplinary lifestyle intervention
- Improvement of anthropometric, biochemical and strength values in 252 subjects
- Broader effectiveness of CURIAMO trial on glycometabolic control in DM2 patients
- Significative results also in patients with poor glycometabolic control
- Importance of intensive lifestyle intervention for glucose control in all diabetics