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Brazilian Primary Care of T2D with Reactive-Homeostatic and Lifestyle Changing- Allostatic Approaches: A Cost-Effectiveness Data

Mariana Santoro Nakagaki[1, 2], Hugo Tadashi Kano[1, 3], Roberto Carlos Burini[1, *]

[1]Center for Nutritional and Physical Exercise Metabolism, Department of Public Health, Sao Paulo State University, School of Medicine, Botucatu, Brazil

[2]Physical Exercise Graduate Joint Program, Londrina and Maringa State Universities, Londrina, Brazil

[3]Pathology Graduate Program, School of Medicine, São Paulo State University, Botucatu, Brazil

Email address:

burini@fmb.unesp.br (R. C. Burini)

[*]Corresponding author

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Abstract: The Brazilian Health System is committed to offer free of charge medications for Diabetes, with the expenditure with prescription drug being the increasingly large component of overall health care costs of the Ministry of Health. The program for Hypertension and Diabetes (HiperDia) provides distribution of more than 15 medications for those two diseases. However, besides this onerous pharmaceutical care, Brazil is facing a greater burden of T2D. The lack of discontinuing the soaring T2D might be due to the lack of knowledge of underlying epigenetics of insulin resistance and, consequently the principles for its treatment. The homeostasis model adopted by physicians in restoring the "low level" of plasma glucose probably has been inappropriate because if one signal is suppressed by a drug, the brain compensates by driving all the others harder. By adding more drugs to a complex system increases the frequency of iatrogenesis and costs. Alternatively, the allostasis model can explain insulin resistance without postulating any true defect because blood glucose fluctuates according to match the ever-shifting prediction of what might be needed. Insulin resistance would be caused by prolonged exposure to high glucose level that reduces its receptor number and sensitivity. Additionally, insulin and other hormones that regulate fuel supply are modulated rigorously from the brain by standard signals for vigilance such as cortisol. Cortisol related signals are elevated during states of hypervigilance and of hyposatisfaction. For people of lower socioeconomic status potential sources of satisfaction are less available, but food is abundant and cheap. Elevated cortisol raises appetite for carbohydrate and fat and shifts the distribution of fat deposits toward the viscera and reduces insulin sensitivity. The allostasis model suggests that the brain overrides local negative feedback (metabolic satiety signals) and people eat. Obesity contributes to T2D as well as to metabolic syndrome and atherosclerosis creating a profoundly lethal cascade, and all follow the familiar epidemiological pattern of disrupted communities. The guiding principle for rational treatment of T2D, would be to reduce the need for vigilance and to restore small satisfactions. Among population-based strategies, diet and physical exercise are the pillars of T2D treatment. In our community-based dynamic cohort, the lifestyle change protocol with dietary counseling and supervised walking-jogging exercises, reduced T2D by four exercise protocols such as high intensity (75%), Academy (71.3%), Mixed (78.6%) and Hydro-gymnastic (34.3%). Besides effective, this allostatic model experience showed to be also a money-saving alternative to be implemented by the government.

Keywords: Type 2 Diabetes, Homeostatic Treatment, Allostatic Treatment, Cost-Effectiveness of Treatments

1. Introduction

Diabetes is a chronic disease that has spread widely, not only in high-income countries (HICs) but also in many low- and middle-income countries (LMICs) over recent decades. Data from the International Diabetes Federation (IDF) indicate that diabetes affected 382 million people worldwide in 2013, a number that is expected to grow to 592 million by 2035. The estimated global prevalence in 2013 amounts to 8.3 % among people aged 20–79 years, with the world's most populous countries, India and China, reaching prevalence rates between 9 and 10 %. Taken together, in 2013 about two-thirds of all individuals with diabetes lived in LMICs. The most prevalent form of diabetes by far is type 2 diabetes (T2D), affecting about 90 % of people with diabetes, while the remaining 10 % mainly have type 1 diabetes or gestational diabetes [1].

The rising prevalence of diabetes in LMICs appears to be fuelled by rapid urbanization, nutrition transition and increasingly sedentary lifestyles [2].

1.1. T2D Costs

Health care expenses for people with diabetes is more than double of that for people without diabetes; the USA direct and indirect expenditures attributable to diabetes in 2007 were conservatively estimated at $174 billion [3]. Direct costs were generally found to be higher than indirect costs. Direct costs ranged from $242 for a study in Mexico to $11,917 for a study in the USA, while indirect costs ranged from $45 for Pakistan to $16,914 for the Bahamas [4-6]. In Brazil, the costs of the two major drugs for T2D (metformin and glibenclamide) could be up to two working days of salary to purchase a monthly course treatment [7].

In 2011, the outpatient costs of T2D, in Brazil, estimated by the ESCUDI study [8] were US$ 2,108 per patient/year, which consisted mostly of direct costs (63.3%) [8]. According to another study, the individual cost would be US$ 12.66, totalizing a national expenditure of US$ 195 mi. a year [9].

The Brazilian Universal Health System (SUS) is committed to offer high-quality health care to the entire population, including the distribution free of charge of a list of essential medicines aimed at treating the most prevalent diseases in the population [10]. The program for Hypertension and Diabetes (HiperDia) began in 2001 and, the distribution of more than 15 medications for Hypertension and Diabetes, and governmental fueling pharmaceutical-care expansion, clearly shows the important role of drugs in the Brazilian Government's effort to tackle these two diseases [7].

There is a strong relationship between GDP per capita and expenditures for diabetes, with every additional international dollar in per capita GDP translating into an average increase in direct diabetes expenditures of about $0.04 [6].

The International Diabetes Federation (IDF) estimated that diabetes accounts for 5–10% of the total healthcare budget in many countries [11].

According to the Brazilian Ministry of Health [12] from 2002 to 2006, the expenditure with prescription drug increased 123.9% and was the increasingly large component of overall health care costs of that Ministry. However, as in other developing countries, Brazil is facing the greatest burden of this disease [13]. Thus, besides onerous, the pharmaceutical care of T2D, the self-reported prevalence of T2D increased 20% from 2006 to 2010, according to a national surveillance (VIGITEL) [7]. This lack of effectiveness in discontinuing the T2D burden might be related with the way the disease is understood, its epigenetic principles, leading causes and, consequently the principles for its treatment.

1.2. Homeostatic Approach

By following the homeostatic model, physicians try to restore each parameter to what they consider an "appropriate" level. Therefore, T2D is treated with drugs that target the primary effectors of hyperglycemia. Homeostasis describes mechanisms that hold constant a controlled variable by sensing its deviation from a "setpoint" and feeding back to correct the error. This definition has dominated physiology and medicine since Claude Bernard declared constancy to be the sole object of all vital mechanisms. His dictum has been interpreted literally to mean that the purpose of physiological regulation is to clamp each internal parameter at a "setpoint" by sensing errors and correcting them with negative feedback. Based on this model physicians reason that when a parameter deviates from its setpoint value, some internal mechanism must be broken. Consequently, they design therapies to restore the "inappropriate" value to "normal". However, in physiology, evidence accumulates that parameters are not constant and their variations, rather than signifying error, are apparently designed to reduce error. In medicine, major diseases now rise in prevalence, such as T2D, whose causes the homeostasis model cannot explain [14].

There are three problems with homeostatic model, by targeting low-level mechanisms. First, each signal evokes multiply cascaded effects, so even the most specific molecular antagonist will cause a cascade of effects. In T2D one effect of hyperglycemia is to elevate the signaling molecule, diacylglycerol that triggers protein kinase C, and thereby a host of signals. Although it might seem advantageous to antagonize an early step, such as the activation of protein kinase C, myriad other cascades with beneficial effects would also be affected and, it turns out that because of such cascading effects, low level inhibitors and antagonists tend to be strongly iatrogenic [15, 16]. Second, the variables targeted for treatment are being driven to their particular levels by concerted signals from the brain in response to predicted needs. Consequently, if one signal is suppressed by a drug, the brain compensates by driving all the others harder. These compensation signals have to be treated, in addition. But adding more drugs to a complex

system increases the frequency of iatrogenesis. Third, there is a cost to performance in clamping a variable to some target level by blocking the effectors designed to modulate it. Clamping renders that variable insensitive to predicted need, which opuses the whole point of physiological regulation. For all of these reasons, some medicated patients are not controlled. The major problem is considered to be "the very high rate of discontinuance or change in medications". These high discontinuance rates are considered to reflect, among other factors, "a combination of adverse drug effects, cost of drugs, and poor efficacy" [14].

1.3. Allostatic Approach

Rather than the homeostatic "lower-level setup" approach, a more rational goal of intervention in T2D would be to shift the predicted distribution of demand back toward its original level. In this sense, following the allostasis principles, the blood glucose fluctuates according to match the ever-shifting prediction of what might be needed. By this more rational therapy, when demand is reduced for long periods, the system re-adapts to the initial demand distribution. The mean response returns to its initial level while responsiveness is maintained [14].

When an intact person sits down to a meal, the sight, smell, and taste of food predict that blood glucose will soon rise, and this triggers insulin release via neural mechanisms well before freshly ingested glucose reaches the blood [17]. This anticipatory pulse of insulin signals muscle and fat cells to take up glucose, and signals the liver to cease releasing it. Thus, this prediction can prevent a large rise in blood glucose. A different prediction can do the opposite, that is, can elevate blood glucose above the most frequent level. Predicting an intense need for metabolic energy can raise blood glucose to diabetic levels and, prolonged exposure to high levels of its natural ligand (signaling molecule) reduces receptor number and sensitivity. Thus, when blood glucose is persistently elevated and triggers persistent secretion of insulin, insulin receptors eventually anticipate high insulin and downregulate. The system learns that blood glucose is supposed to be high and, it seems inevitable that the sustained presence of high blood glucose would gradually reduce insulin sensitivity; i.e. cause "insulin resistance", and thus T2D. Such changes are the appropriate adaptations to predicted demand [14]. Organisms are designed for efficiency and efficiency requires predicting what will be needed. Man, and animals are exposed to a large number of biological and environmental factors. The ability of the man and animal to fight against these stress-factors is important for maintenance of their health and productivity [18].

1.4. The Unsatisfactory Social-Related Diabetes

The allostasis model redirects therapy, away from manipulating low-level mechanisms (homeostatic model), toward improving higher levels in order to restore predictive fluctuation. This is because the allostasis model of physiological regulation, attributes diseases such as T2D to sustained neural signals. In fact, it is known that insulin and the myriad other hormones that regulate the fuel supply are modulated rigorously from the brain which bases its predictions on a continuous data stream regarding metabolic state that arrives via nerves from the liver and sensors in the cerebrovascular organs, such as the area postrema, and the hypothalamus [19]. These brain-generated signals may arise from unsatisfactory social interactions. The standard signals for vigilance, such as cortisol, which raise the appetite for sodium, also raise the appetite for carbohydrate and fat [20]. Consequently elevated cortisol shifts the distribution of fat deposits toward the viscera and, by reducing insulin receptors and their downstream mechanisms naturally reduce their sensitivities, just as every signaling system responds to prolonged, intense stimulation [14].

Cortisol and related signals are elevated, not only during hypervigilance, but also during states of hyposatisfaction – when outcomes prove less than expectations. Because satisfaction cannot be stored, it must be continuously renewed. So, if its potential sources become constricted, the brain must inevitably rely on those that remain: people needing a pulse of satisfaction will try to find it somehow. For those of higher socioeconomic status there are opportunities for satisfaction in work, achievement, and money. Mono-pursuit of such opportunities tends to spiral out of control ("workaholism", "type A" behavior, etc). This may occur especially when expectations are so high as to be intrinsically unsatisfiable. On the other side, for people of lower socioeconomic status potential sources of satisfaction are less available, but food is abundant and cheap. So the allostasis model suggests that the brain overrides local negative feedback (metabolic satiety signals) and people eat. For the reasons just cited, satisfaction is fleeting – so people eat even more [19].

1.5. Lifestyle Changes

The core idea of allostasis is a coordinated variation to optimize performance at the least cost [14]. Yet the goal is not constancy, as stated by Claude Bernard. According to Neel's hypothesis, the rise in obesity and type 2 diabetes has been attributed to "thrifty genes" [21]. Hence, certain human groups were selected to "eat up" in times of plenty to protect against times of famine [22]. This implies that body fat is not regulated to a setpoint, but varies according to some prediction, in this case, future hunger. Noting that the most explosive increases are in populations that have suddenly changed from food scarcity to plenty. This theory would be entirely consistent with the allostasis model [14].

Roughly more than half of Brazilian and US adults are obese, a condition that contributes to T2D. Both, obesity and type 2 diabetes jointly contribute to a constellation of pathologies termed "metabolic syndrome", which includes hypertension, glucose intolerance (diabetes), hyperinsulinemia, dyslipidemia, visceral obesity, atherosclerosis, and hypercoagulability [22, 23]. Together these factors create a profoundly lethal cascade, and all follow the familiar epidemiological pattern: elevated with

divorce, low socio-economic status, and disrupted preindustrial communities [22, 24].

Homeostasis cannot explain the growing prevalence of type 2 diabetes. Its core feature, insulin "resistance", involves changes at many levels, including decreased concentrations of insulin receptors, kinase activities, concentration and phosphorylation of IRS-1 and IRS–2, PI (3)K activity, glucose transporter translocation, and the activities of intracellular enzymes Although these changes are termed "defects", they do not arise from alleles, so "defect" denotes, not their origins, but rather their unwanted effects [25]. The allostasis model can explain both obesity and insulin resistance without postulating any true defect. The rising prevalence of diabetes in LMICs appears to be fuelled by rapid urbanization, nutrition transition and increasingly sedentary lifestyles [2, 26].

The allostasis model hints that the biggest improvements in health might be achieved by enhancing public life. The guiding principle would be: do everything that promises to reduce the need for vigilance and to restore small satisfactions. Enhance contact with nature by building more parks and by providing communal opportunities to garden – i.e. not just to look at but to grow flowers and vegetables. Enhance opportunities to walk and cycle by restricting automobile traffic. Prevent this restriction from becoming an annoyance by improving public transportation. Encourage broader participation in sports especially among youth – by constructing public facilities for gymnastics, skating, skate-boarding, climbing, and swimming [14].

Lifestyle characteristics, such as leisure time physical activity has been inversely related to T2D and metabolic syndrome [7, 19, 21]. A similar inverse association with the risk for T2D has been documented regarding cardiorespiratory fitness (CRF), which is developed and maintained by regular exercise practice independently of age [21-25].

In a community-based dynamic cohort, the lifestyle change protocol with dietary counseling and supervised exercises have reduced T2D in a 24 and 10 weeks of mixed (walking+strength) exercises [27, 28].

Now, we are showing that this high costless effectiveness can be obtained also with other physical- exercise protocols.

2. Material and Methods

2.1. Subjects

Participants were enrolled at the "Move for Health Program" (*Programa Mexa-se Pró-Saúde*), an ongoing epidemiology project conducted, as extension-assistance of the university, since 1991. The program introduces healthy lifestyle into subject's diary activities by promoting nutritional re-education and supervised physical exercise as primary care for chronic non-communicable diseases. As a community -based project it includes adult (>35 yrs old) from both genders that come to the clinic either spontaneously or by a friend or doctor indication looking for preventive health examination and further non-medicated interventions. Upon registration and accomplishing ethical requirements the subjects are assessed multi professionally for clinical, anthropometric, dietary, physical activity, blood analysis, fitness (aerobic, strength and flexibility), and postural. From these baseline assessments the participants are able to choose follow-up interventions involving supervised exercises combined with weekly counseled (or supervised) dietary interventions (LiSM program). The follow-up assessments occur every 10 weeks. The assessments as well as physical exercises and dietary interventions are conducted by graduate students holding institutional fellowships. The program is opened for beginners three times a year and is free of charge for the first 10 weeks [28, 29].

2.2. Measurements

Physical activity level (PAL), socio-demographic characteristics (gender, age, marital status, family income and education) and health status were obtained by applying the International Physical Activity Questionnaire (IPAQ version 8 - long form) [30]. Marital status was classified as married (married and stable union) and unmarried (single, widowed, divorced, and separated). The schooling level was classified as fundamental complete and incomplete, secondary education and higher. Family income ranked from up to five minimum wages (<5SM) or greater/equal to five times the minimum wage (≥5SM). Health perception was rated as good (excellent, very good or good) or bad (fair and poor).

Body weight and height measurements were taken [31] with subsequent calculation of body mass index ($BMI=kg/m^2$) classified as normal weight when up to 24.9 kg/m^2, overweight 25 up to 29.9 kg/m^2 and obese with values greater than 30 kg/m^2 [32]. The waist circumference (WC) was measured with millimeter tape inextensible and inelastic on the midpoint between the last intercostal space and iliac crest. The value of 88 cm, for females, and 104 cm, for males, was adopted as cutoff for abdominal obesity [31]. Body muscle and fat composition was performed in the supine position by bioelectrical impedance (BIA) (Biodinâmics®, model 450, USA) with the calculation of muscle mass by the equation [33] and, calculated as muscle mass index (MMI) [34]. Sarcopenia classification adopted was: Normal-IMM>5.45kg/m^2, Sarcopenia - IMM ≤5.45 kg/m^2 [33]. The percentage of fat used as normal was 20-35% for female and up to 25% for male [35].

The aerobic fitness illustrated by VO^2max. was determined by the Balke's protocol in electronic treadmill [36] whereas strength fitness was obtained through the values of hang grip [37].

The antecubital-vein blood sampling was drawn after an overnight fast (8-12 hours), using standard venipuncture vacuum. Plasma glucose was quantified by Dry Chemical method (System Vitros Johnson & Johnson) and insulin was measured by chemiluminescent method. All blood samples were measured in the Clinical Research Unit (UPECLIN) of the Botucatu Medical School - UNESP.

DM2 was defined by blood glucose value ≥ 126 mg/dL. State of glucose intolerance was defined as blood glucose ≥ 100 mg/dL [38]. Insulin resistance was determined by the homeostasis (homeostasis model assessment - insulin resistance) (HOMA-IR), a product of fasting insulin (μUI/mL) and fasting plasma glucose (mmol/L) divided by 22.5. It was adopted 3.5 as the upper limit of normal range [39].

2.3. Lifestyle Modification Protocol

Nutritional counseling was conducted weekly through lectures in groups with relevant nutritional context in which subjects were comprised. Physical Exercises Protocols consisted by supervised exercise sessions in accordance with the ACSM's guidelines for exercise prescription and treatment of chronic non-communicable diseases [40].

1) Academy exercises (PAc) with equipments adapted to elderly weight-lift distributed in a circuit sequence. Daily sessions were conducted three days a week, alternately. Each 60min. supervised- session was composed by 10min. dynamic- warm up/stretching, 40min. of resistance training (3 sets of 8-12 repetitions at 60%-70% 1RM each exercise) finishing up with 10min. cool down- stretching. The strength training sessions were preceded by 2wk-exercise familiarization and 1 RM test realization [41].

2) Daily-Mixed Exercises (PMi): The physical exercise protocol was composed by daily sessions of 90 min, including 10min dynamic- warm up/ stretching, 30 min walking (60-80% VO_{2max}), 40min strength in academy (3x 8-12 rep, 60-70% 1RM) and 10min stretching and cool down. Strength exercises were alternated in different days, for upper and lower limbs. The PMi protocol should be attended at least three days during the week [41].

3) High-intensity interval training (HIT) protocol (PHit): The whole 60-min exercise-protocol was composed by initial (5 minutes) and final (10 minutes) stretching; the latter was intended as an aid to cool down for baseline-heart rate recover. The 43min. high-intensity interval training on treadmill included 10 minutes of warm-up at 70% of maximum heart rate (HR max), followed by 4 series of 4 minutes each on 90% HR max with 3-min intervals between series for active recovery at 70 % of FC max. The HIT was conducted twice a week, in alternated days [39].

4) Hydrogymnastic exercises (PHy): Exercises were conducted twice a week in alternated days in a 29°C swimming pool. The 60 minutes of exercise was predominantly aerobic, composed by 10min. warm up, 10min. stretching, 30min. principal and ending up with 10min. slowing down towards heart rate stabilization [41].

2.4. Statistical Analysis

Results were expressed as mean and standard deviation for continuous variables and frequency and percentage for categorical variables. The proportion comparisons were done by chi-square test (χ^2), the ANOVA repeated measure for symmetric quantitative variables and the range model repeated measures for the asymmetric quantitative. SAS for Windows, version 9.1 was used with a significance level of 5% or corresponding p-value.

3. Results

The inclusion criteria for this experiment was fulfilled by 236 subjects enrolled into the Move for Health program during the 2011-2012 period. Sample was 55.5±10.8 yrs. old, 65% below 60 yrs. old, predominantly female (88%), married (80%), low-income class (92%) with elementary schooling (80%), 9% lower than recommended physical activity, 22% lower strength, 37% lower aerobic capacity and, 67.8% self-referring in good-health status (Table 1). Even with that self-perception, 80.5% was overweight (50% obese), 1.5% sarcopenic, 38.5% altered HOMA-IR, 37.7% altered IFG and 11.3% T2D.

Table 1. *General base-line characteristics of the sample in the physical-exercise protocols.*

Variables/Protocols	PHy	PHit	PAc	PMi	TOTAL
Age (years)	60.2±10.4	53.3±8.8	57.5±12.7	53.4±10.2	55.5±10.8
<60	32 (50.8%)	36 (83.7%)	29 (58%)	98 (67.1%)	195 (64.6%)
>60	31 (49.2%)	7 (16.3%)	21 (42%)	48 (32.9%)	107 (354%)
Gender					
Female	62 (98.4%)	43 (100%)	39 (78%)	122 (83.5%)	266 (88.1%)
Male	1 (1.6%)	0 (0%)	11 (22%)	24 (16.5%)	36 (11.9%)
Marital status					
Married	54 (85.7%)	34 (79.1%)	43 (86%)	110 (75.3%)	241 (79.8%)
Non-married	9 (14.3%)	9 (20.9%)	7 (14%)	36 (24.7%)	61 (20.2%)
Family income					
Up to 5 minimum wage	60 (95.2%)	38 (88.4%)	41 (82%)	140 (95.9%)	279 (92.4%)
>5 minimum wage	3 (4.8%)	5 (11.6%)	9 (18%)	6 (4.1%)	23 (7.6%)
Schooling					
Elementary	55 (87.3%)	36 (83.7%)	40 (80%)	110 (75.3%)	241 (79.8%)
High school/college	8 (12.7%)	7 (16.3%)	10 (20%)	36 (24.7%)	61 (20.2%)
Health Eating Index					

Variables/Protocols	PHy	PHit	PAc	PMi	TOTAL
Inadequate	38 (100%)	26 (96.3%)	30 (90.9%)	118 (94.4%)	212 (95.1%)
Adequate	0 (0%)	1 (3.7%)	3 (9.1%)	7 (5.6%)	11 (4.9%)
Body weight					
Overweight	54 (85.7%)	36 (83.7%)	36 (72%)	117 (80.1%)	243 (80.5%)
Eutrophy	9 (14.3%)	7 (16.3%)	14 (28%)	29 (19.9%)	59 (19.5%)
Physical activity level					
Recommended	58 (92.1%)	41 (95.4%)	44 (88%)	132 (90.4%)	275 (91.1%)
Lower than recommended	5 (7.9%)	2 (4.6%)	6 (12%)	14 (9.6%)	27 (8.9%)
Hand grip strength					
Low	15 (23.8%)	5 (11.6%)	10 (20%)	37 (25.3%)	67 (22.2%)
Good	48 (76.2%)	38 (88.4%)	40 (80%)	109 (74.7%)	235 (77.8%)
Cardiorespiratory fitness					
Low	4 (25%)	7 (21.9%)	6 (50%)	20 (51.3%)	37 (37.4%)
Good	12 (75%)	25 (78.1%)	6 (50%)	19 (48.7%)	62 (62.6%)

Mean±SD, PHy=hydrogymnastic; PHit=treadmill high intensity; PAc=academy; PMi=mixed academy/endurance exercises
The prevalence of T2D, at baseline, varied from 4.8%(PHit) to 16%(PAc) (Figure 1A) while IFG varied from 33.3%(PHy) to 41.4%(PMi) (Figure 1B).

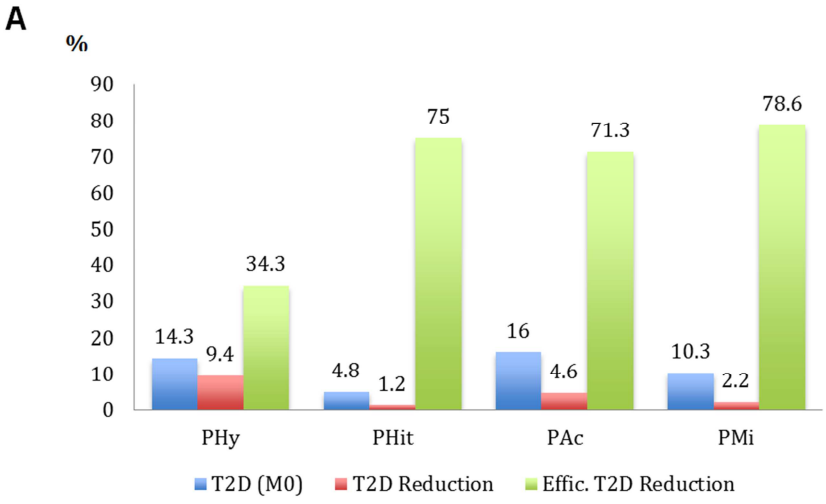
The aerobic and strength fitness responded differently to the different exercise-protocols (Table 2).

Table 2. *Effects of 10w-physical exercises protocols on physical fitness and T2D frequency in adult-based adults.*

	PHy		PHit		PAc		PMi	
	M0	**M1**	**M0**	**M1**	**M0**	**M1**	**M0**	**M1**
Handgrip strength (kg)	26.1±6.5 aB	26.4±6.7 aB	29.5±6.0 aA	29.9±5.9 aC	31.7±12.9 aA	34.6±13.3 bA	29.6±10.6 aA	31.2±10.0 bAC
VO^2max (ml/kg/min)	27.9±5.2 aA	32.7±4.9 bA	32.3±5.4 aB	37.2±5.9 bB	31.8±8.9 aAB	35.1±9.2 bAB	29.9±5.9 aAB	33.5±6.2 bA
T2D (≥126)	9 (14.3%) aA	2 (4.9%) bA	2 (4.8%) aA	1 (3.6%) aA	8 (16%) aA	5 (11.4%) aA	15 (10.3%) aA	10 (8.1%) aA
IFG (≥100)	21 (33.3%) aB	10 (24.4%) bB	15 (35.7) aB	2 (7.1%) bA	17 (34%) aB	7 (15.9%) bA	60 (41.4%) aB	30 (24.4%) bB
Normal	33 (52.4%) aB	29 (70.7%) aC	25 (59.5%) aB	25 (89.3%) aB	25 (50%) aB	32 (72.7%) aB	70 (48.3%) aB	83 (67.5%) aC
	N=63	N=41	N=42	N=28	N=50	N=44	N=145	N=123

Phy= hydrogymnastic; PHit= treadmill high intensity; Pac= academy; PMi= mixed academy/ endurance exercises; M0= baseline; M1= after 10 weeks; lowercase letters: different letters show significant difference between M0 vs. M1; uppercase letters: different letters show significant difference between altered vs. normal; $p<0.05$.

The 10-wk exercise-protocols reduced T2D significantly in all 4 protocols. PHy, differed from the other by the lowest effectiveness of 34.3% (Figure 1A). All other protocols had the effectiveness in the range of seventies (Figure 1A). On the other hand, 10-wk intervention normalized IFG highly in PHit with 29.8% rate and 80.1% effectiveness and, minorly in PHy with 18.3% rate and effectiveness of 26.7% (Figure 1B).



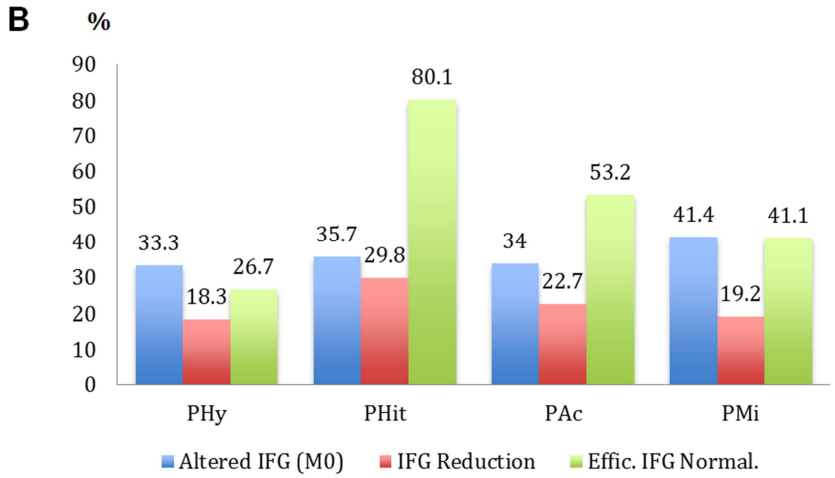


Figure 1. *Effects of 10-wk Physical Exercises Protocols on T2D (A) and IFG (B).*

Thus, after 10-wk intervention, the most effective protocol was PHit either in reducing T2D or promoting IFG normalization. PAc and PMi followed closely PHit for T2D reduction but presented lower effectiveness in IFG normalization. PHy showed the lowest effectiveness either for T2D reduction or IFG normalization (Figure 1A and 1B).

4. Discussion

In this experiment, an urban community-based sample of predominantly mature women, married, elementary schooled, low-income class showed 50% obesity, 37.7% IFG, 38.5% altered HOMA-IR and 11.3% T2D. From these figures we found that not only IFG but also T2D rates from this cohort have increased since our first publication [42]. At that time the prevalence of T2D was 7.8% (18.7% high fasting plasma glucose levels). Four years later, the prevalence of T2D was 9.5% [43] and presently 11.3%. This trend follows very much the burden of T2D experimenting by Brazilian adults. It is amazing that 6.8% of our T2D (plasma glucose >_126mg/dL) patients were medicated non-controlled T2D [44] clearly evidencing the ineffectiveness of the allopathic conduct adopted by the national HIPERDIA program.

The main determinants of insulin resistance are preventable factors and, the determinant variables of insulin resistance are interconnected by acting as a cause or consequence of one another. The abdominal adiposity, a key factor for the diagnosis of insulin resistance, is associated with low fiber intake and higher fat consumption along with lower physical activity. The superposition of these variables contributes to increased oxidative stress and inflammation that contribute to aggression to liver and muscle tissues resulting in insulin resistance [42]. Hence, lifestyle is directly related to the incidence of type 2 diabetes and studies have shown that it is possible to achieve primary prevention of T2D by changing lifestyle (diet and exercise) in subjects with impaired glucose tolerance [45, 46]. The present 10-wk exercise-protocols reduced T2D and IFG significantly in all 4 different physical exercise protocols.

There is epidemiological evidence indicating that regular physical activity is associated with reduced rates of T2D and all-cause mortality [47]. Regular exercise is probably the lifestyle intervention with the most profound up regulating effect on hundreds of genes involved in tissue maintenance and homeostasis [48].

Among the T2D responses the protocols, PHy, differed from the other by its lowest effectiveness (34.3%) while all others showed effectiveness in the percentage-range of seventies. Specifically, PMi has had the highest effectiveness by reducing baseline T2D in 78.6%. A possible contribution for that might be the PMi lower fitness at baseline (51.3% low aerobic capacity and 25.3% low strength) among groups. Additionally, PMi protocol offered the highest volume (length and frequency) of physical exercises/session/week. Therefore, on therapeutic basis, PMi responded better than others because, by beginning from a worse condition (fitness) it received a higher intervention dose (exercise volume). In other words, a better insulin sensitivity response occurred in unfit individuals submitted to a higher exercise volume.

From the existing literature it is known that muscle contraction enhance glucose uptake through translocation of glucose transporter type 4 (GLUT-4) protein. Muscle contraction stimulates AMP-activated protein kinase (AMPK) and Ca++/calmodulin-dependent kinase (CaMK), both of which regulate phosphorylation of AS160 (Akt substrate), the most distal insulin signaling known to be important for insulin-stimulated glucose transport. AMPK has two other mechanisms which may reduce insulin resistance. One by stimulating PGC-1α, increasing fatty oxidation and reducing the cellular fat levels and, the other by stimulating IL-6 synthesis and therefore blocking TNF-α mRNA [49]. The exercise reduces activation of both TLR4 and the NLRP3 inflammasome and therefore reduce the levels of IL-1beta as well as the NF-κB. All these epigenetic modifications ensure the proper functions at the cellular level, because the inflammatory responses are balanced by the expression of anti-inflammatory genes, in physical exercises [50]. Additionally, during strength exercise, Glut-4 expression is mediated by the binding of myocyte enhancer factor 2A

(MEF-2A) to its cis-element on the Glut-4 promoter. MEF2 transcriptional activity is modulated by Ca++/calmodulin-dependent kinase (CaMK) [51]. Hence, our PMi protocol accomplished both principles aerobic (AMPK-PGC-1alpha stimulation) and strength (MEF-Glut-4 expression) besides giving higher volume of exercises.

PHit showed the highest effectiveness of IFG normalization (80.1%) and, coincidently PHit was the only protocol using high-intensity exercises. HIT is expected to lead muscular glycogen depletion faster than moderate exercises and one of the most efficacious modes to prevent the development of insulin resistance is exercise of large muscle masses to lower skeletal muscle stores of glycogen and triglycerides. Additionally, reintroduction of physical activity, even when the muscle is already insulin resistant secondary to lack of utilization of excessively stored fuel, can restore metabolic flexibility potentially reversing insulin resistance [52].

Hence, the present data have shown that all physical-exercises protocols were effective in reducing hyperglycemic abnormalities with PHy being less effective than the others and, PHit being more effective in reducing T2D while PMi was more effective in normalizing impaired-fasting glucose. On economic basis, if this intervention program (with 60.5% effectiveness) would be applied to the 11.25 million of Brazilian (15.4% of total) suffering from T2D and IFG [10, 43, 44], it would allow a Brazilian Public Health saving of US$ 16.49 mi from expending less oral hypoglycemiant drugs [42].

Thus, as already widely accepted, physical exercises have profound implications for public health and should be used as a natural remedy for recovering part of the imbalance caused by modern life-styles, costless and without the side effects of many pharmacological treatments [53].

5. Conclusion

The expansion of pharmaceutical care and the free distribution of T2D medications play an important role in the Brazilian Government's effort to tackle this disease. However, besides onerous, this homeostasis model of care has been demonstrated ineffective in controlling this disease. By following the epigenetic thriftiness of insulin resistance and the allostatic principles for its control, it was presented data from a Community-based Lifestyle Change experience showing high effectiveness of different exercise protocols in insulin-resistance situations. The proposed approach would be an alternative effective and money-saving, for the T2D care by the Brazilian Public Health.

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Conflict of Interest

The authors declare that they have no competing interests

References

[1] International Diabetes Federation (IDF). Diabetes atlas. 6th ed. International Diabetes Federation; 2013.

[2] Hu FB. Globalization of diabetes: the role of diet, lifestyle, and genes. Diabetes Care. 2011;34:1249–1257.

[3] American Diabetes Association (ADA). "Economic costs of diabetes in the US in 2007," *Diabetes Care*. 2008; 31:596–615.

[4] Arredondo A, Zúñiga A, Parada I. Health care costs and financial consequences of epidemiological changes in chronic diseases in Latin America: evidence from Mexico. Public Health. 2005; 119:711–720.

[5] Condliffe S, Link CR, Parasuraman S, Pollack MF. The effects of hypertension and obesity on total health-care expenditures of diabetes patients in the United States. Appl Econ Lett. 2013; 20:649–652.

[6] Seuring T, Archangelidi O, Suhrcke M. The Economic Costs of Type 2 Diabetes: A Global Systematic Review. Pharmacoeconomics. 2015; 33(8): 811–831.

[7] Bertoldi AD, Kanavos P, França GVA, Carraro A, Tejada CA, Hallal PC, et al. Epidemiology, management, complications and costs associated with type 2 diabetes in Brazil: a comprehensive literature review. Globalization and Health. 2013 Dec 3;9(1):62.

[8] Bahia LR, Araujo DV, Schaan BD et al. The costs of type 2 diabetes mellitus outpatient care in the Brazilian public health system. *Value in Health*, 2011;14 (5 Suppl 1):S137–S140.

[9] Malerbi DA, Franco LJ. Multicenter study of the prevalence of diabetes mellitus and impaired glucose tolerance in the urban Brazilian population aged 30-69 yr. The Brazilian Cooperative Group on the Study of Diabetes Prevalence. Diabetes care. 1992 Nov;15(11):1509–16.

[10] Bertoldi AD, Helfer AP, Camargo AL, Tavares NUL, Kanavos P. Is the Brazilian pharmaceutical policy ensuring population access to essential medicines? Global Health. 2012;8:6.

[11] International Diabetes Federation (IDF), *Diabetes Atlas*, International Diabetes Federation Diabetes Atlas, Brussels, Belgium, 3rd edition, 2006.

[12] Vieira FS. Gasto do Ministério da Saúde com medicamentos: tendência dos programas de 2002 a 2007. Rev Saúde Pública. 2009;34(2):206–9.

[13] Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Research and Clinical Practice. 2010;87(1):4–14.

[14] Sterling P. Principles of Allostasis: Optimal Design, Predictive Regulation, Pathophysiology, and Rational Therapeutics. In: Jay Schulkin, editor. Allostasis, homeostasis, and the costs of physiological adaptation. 2004; p. 17.

[15] Buchman TG. The community of the self. Nature. 2002 Nov 14;420(6912):246–51.

[16] Sterling P, Eyer J. Biological basis of stress-related mortality. Social science & medicine Part E, Medical psychology. 1981;15(1):3–42.

[17] Schwartz MW, Woods SC, Porte D, Seeley RJ, Baskin DG. Central nervous system control of food intake. Nature. 2000 Apr 6;404(6778):661–71.

[18] Rahal A, Kumar A, Singh V, Yadav B, Tiwari R, Chakraborty S, et al. Oxidative stress, prooxidants, and antioxidants: the interplay. BioMed research international. 2014 Jan 23;2014:761264.

[19] Saper CB, Chou TC, Elmquist JK. The need to feed: homeostatic and hedonic control of eating. Neuron. 2002 Oct 10;36(2):199–211.

[20] Schulkin J, McEwen BS, Gold PW. Allostasis, amygdala, and anticipatory angst. Neuroscience and biobehavioral reviews. 1994;18(3):385–96.

[21] McLellan KCP, Manda RM, Sloan LA, Burini RC. Epigenetics of Glucose Metabolism and the Basis for T2DM Interventions. In: Type 2 Diabetes. InTech; 2013.

[22] Diamond J. The double puzzle of diabetes. Nature. 2003 Jun 5;423(6940):599–602. American College of Sports Medicine. ACSM's Guidelines for Exercise Testing and Prescription. 9th ed. 2013.

[23] Burini RC, Kano HT, Burini FHP and McLellan KCP. Metabolic Syndrome - From the Mismatched Evolutionary Genome with the Current Obesogenic Environment to the Lifestyle Modification as a Primary Care of Free-Living Adults in a Brazilian Community. In: Morton Jody, editor. Metabolic Syndrome: Clinical Aspects, Management Options and Health Effects. 2016. p. 54.

[24] Zimmet P, Alberti KGMM, Shaw J. Global and societal implications of the diabetes epidemic. Nature. 2001 Dec 13;414(6865):782–7.

[25] Saltiel AR, Kahn CR. Insulin signalling and the regulation of glucose and lipid metabolism. Nature. 2001 Dec 13;414(6865):799–806.

[26] Popkin BM. Nutrition Transition and the Global Diabetes Epidemic. Curr Diab Rep. 2015; 15(9): 64.

[27] Mota JF, Moreto F, Burini FHP, Medina WL, Rimm EB and Burini RC. Effect of Physical Conditioning with Lifestyle Intervention on A Community-Based Hyperglycemic-Overweight Adults. Journal of US-China Medical Science. 2011;8(No. 10 (Serial No. 83)):581–7.

[28] Burini RC, Torezan GA, McLellan KCP. Behavioral risk factors and effects of lifestyle modification on adults with Diabetes: A Brazilian community-based study. Emerging Issues in Medical Diagnosis and Treatment. Concept Press Ltd. 2013; 1.

[29] Moreto F, Kano HT, Torezan GA, Oliveira EP, Manda RM, et al. Changes in malondialdehyde and C-reactive protein concentrations after lifestyle modification are related to different metabolic syndrome-associated pathophysiological processes, Diabetes and Metabolic Syndrome. 2015; 9: 218-222.

[30] Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc. 2003; 35: 1381-1395.

[31] Heyward VH. Avaliação da composição corporal aplicada (1st Edn.) São Paulo. 2000.

[32] World Health Organization. OBESITY Preventing and managing the global epidemic: report of a WHO Consultation on Obesity. Geneva: World Health Organization. 1998.

[33] Janssen I, Baumgartner RN, Ross R, Rosenberg IH, Roubenoff R. Skeletal muscle cutpoints associated with elevated physical disability risk in older men and women. Am J Epidemiol. 2004; 159: 413-421.

[34] Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, et al. Epidemiology of sarcopenia among the elderly in New Mexico. Am J Epidemiol. 1998; 147: 755-763.

[35] Bray G. An approach to the classification and evaluation of obesity. In: Bjorntorp P, Brodoff BN. Obesity. 1992; 294-308.

[36] Balke B, Ware RW. An experimental study of Air Force personel. US Armed Forces Med J 1959; 10: 675-88.

[37] Baumgartner TAJ, A. S. Measurement for evaluation in physical education and exercise science. 8th Edition ed1995.

[38] American Diabetes Association (ADA). Diagnosis and classification of diabetes mellitus. Diabetes Care 2010;32(S1): S62-S67.

[39] Nakagaki MS, Michelin E, Teixeira O, Burini RC. Cardiorespiratory Fitness and Insulin Sensitivity Response to high-Intensity Interval Training in Overweight Post-menopausal Women. Diabetes Obes Int J 2017, 2(2): 000152.

[40] ACSM's Guidelines for Exercise Testing and Pescription. 9th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins Health, 2014.

[41] Burini RC, Nakagaki MS, Michelin E, Burini FHP. Treating Blood Hypertension in a Brazilian Community: Moving from Reactive Homeostatic Model to Proactive Allostatic Healthcare. Ann Clin Hypertens. 2018; 2: 001-016.

[42] Mota JF; Moreto F; Medina WL; Pereira ECL; Burini RC. Nutritional and metabolic risk factors for insulin resistance in adults. International Journal of Nutrition and Metabolism. 2011; 3(7): 90-96.

[43] Burini RC, Torezan GA, Sloan LA, Corrente JE, McLellan KCP. Dietary Intake Association with IFG and Responses of a Lifestyle Changing Protocol in a Community-B based Adult Cohort. Endocrinol Metab Synd 2014; 3:125.

[44] Burini FHP, Salatini R, Nakagaki MS, Corrente JC, Rimm EB, Burini RC. Medicated Non-controlled Wholesomely Non-communicable chronic disease Patients - A Costless Effective Outcome Under "exercise is Medicine" Program: 1445 Board #238 May 28, 9. Medicine and Science in Sports and Exercise. 2015 May 1;47(5S):389.

[45] Tuomilehto J; Lindström J; Eriksson JG; Valle TT; Hämäläinen H; Ilanne-Parikka, P. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. New England Journal of Medicine, 2001; 344:1343-1350.

[46] Knowler, W. C.; Barret-Connor, E.; Fowler, S. F.; Hamman, R. F.; Lachin, J. M.; Walker, E. A. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. New Englanf Journal of Medicine. 2002; 346:393-403.

[47] Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, et al. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. Lancet. 2012; 380: 219-229.

[48] Fiuza-Luces C, Garatachea N, Berger NA, Lucia A. Exercise is the real polypill. Physiology (Bethesda). 2013; 28: 330-358.

[49] Ventura-Clapier R; Mettauer B; Bigard X. Beneficial effects of endurance training on cardiac and skeletal muscle energy metabolism in heart failure. Cardiovascular Research.2007;73: 10–18.

[50] Ostrowski K, Rohde T, Asp S, Schjerling P, Pedersen BK. Pro- and anti-inflammatory cytokine balance in strenuous exercise in humans. J Physiol. 1999; 515: 287-291.

[51] Huang SH; Czech MP. The GLUT4 glucose transporter. Cell Metabolism. 2007;5:237–252.

[52] Chakravarthy MV; Booth FW. Eating, exercise, and "thrifty" genotypes: connecting the dots toward an evolutionary understanding of modern chronic diseases. Journal of Applied Physiology. 2004;96: 3-10.

[53] Burini RC, Kano HT, Nakagaki MS, Nunes CNM, Burini FHP. The lifestyle modification effectiveness in reducing Hypertension in a Brazilian Community: From the epigenetic basis of Ancestral Survival to the Contemporary Lifestyle and Public Health Initiatives HUMAN HYPERTENSION. Heighpubs J Clin Hypertens. 2017;1:010–31.