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REVIEW ARTICLE

Ma-Pi 2 macrobiotic diet and type 2 diabetes mellitus: pooled analysis of short-term intervention studies

C. Porrata-Maury[1]*
M. Hernández-Triana[2]
V. Ruiz-Álvarez[2]
M. E. Díaz-Sánchez[2]
F. Fallucca[3]
W. Bin[4]
B. Baba-Abubakari[5]
M. Pianesi[6]

[1]*Finlay Institute, Havana, Cuba*
[2]*Institute of Nutrition, Havana, Cuba*
[3]*University La Sapienza, Rome, Italy*
[4]*Traditional Tibetan Medicine Hospital, Beijing, China*
[5]*Tamale Teaching Hospital, Tamale, Ghana*
[6]*International Association Un Punto Macrobiotico, Tolentino, Italy*

*Correspondence to: Carmen Porrata-Maury, Finlay Institute, Havana, Cuba.
E-mail: cporrata@infomed.sld.cu; cporratamauri@gmail.com; manumacondo@hotmail.com

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Summary

The macrobiotic, Ma-Pi 2 diet (12% protein, 18% fat and 70% carbohydrate), has shown benefit in adults with type 2 diabetes mellitus (T2DM). This pooled analysis aims to confirm results from four, 21-day intervention studies with the Ma-Pi 2 diet, carried out in Cuba, China, Ghana and Italy. Baseline and end of study biochemical, body composition and blood pressure data, were compared using multivariate statistical methods and assessment of the Cohen effect size (d). Results showed that all measured indicators demonstrated significant changes ($p < 0.001$); most of them with a *very high* ($d \geq 1.30$), or *high* ($d = 0.80$–1.29) effect size. The global effect size of the diet was Italy (1.96), China (1.79), Cuba (1.38) and Ghana (0.98). The magnitude of the individual effect on each variable by country, and the global effect by country, was independent of the sample size ($p > 0.05$). Similarly, glycemia and glycemic profiles in all four studies were independent of the sample size ($p = 0.237$). The Ma-Pi diet 2 significantly reduced glycemia, serum lipids, uremia and cardiovascular risk in adults with T2DM. These results suggest that the Ma-Pi 2 diet could be a valid alternative treatment for patients with T2DM and point to the need for further clinical studies. Mechanisms related to its benefits as a functional diet are discussed. © 2013 The Authors. *Diabetes/Metabolism Research and Reviews* published by John Wiley & Sons, Ltd.

Keywords Ma-Pi 2 macrobiotic diet; type 2 diabetes; adults; vegetarian diets; whole-grain cereals

Introduction

Diet and type 2 diabetes mellitus

Poor metabolic control is a frequent finding in diabetes; in Italy, for example, two-thirds of institutionally-treated patients with type 1 diabetes and half of those with type 2 diabetes mellitus (T2DM) do not show good metabolic control (according to plasma glucose, HbA1c, low-density lipoprotein (LDL) cholesterol and blood pressure), and 39% of them have microalbuminuria [1]. The conventional management of T2DM and severe insulin resistance is recognized as being difficult and frustrating [2] and continuous quality improvement initiatives are needed to reduce the social, clinical and economic burden of this disease.

An appropriate diet is central for T2DM management [3,4], yet there are many different dietary recommendations; these are frequently contradictory and lack medical evidence of effect. Results from scientific studies currently suggest that an effective diet for diabetes must be rich in fibre, whole-grain cereals, vegetables and legumes and poor in simple carbohydrates, refined cereals, fats and foods of animal origin [5–9].

Carbohydrate

Carbohydrate intake is the first determinant of the post-prandial glycemic response; however, this response displays great individual variability. This variability is thought to be related to several factors, including the type of carbohydrate or starch (amylose versus amylopectin), the food preparation methods (cooking procedures, heating); the fasting time, the pre-prandial glucose level, the distribution of macronutrients in the diet and the individual doses of insulin and resistance levels [10]. Moreover, some studies suggest that the current standard definition of macronutrients fails to capture important information [11].

Whatever the reason for individual variation in glycemic response, evidence from medium-term studies suggests that replacing high-glycemic index (GI) and high-glycemic load carbohydrates with low-GI forms (such as whole-grain cereals) can improve glycemic control and reduce hypoglycemic episodes among diabetic subjects treated with insulin [12]. This replacement technique has also been associated with a decrease in cardiovascular diseases [13–15]. Taken together, overall results suggest that a good diet for T2DM should not only take into account the GI and glycemic load, but also the supply of dietary fibre, micronutrients and phytochemical compounds with recognized biological activity (bioactive compounds), which could have important consequences on health status and on carbohydrate metabolism.

Whole-grain fibre has been associated with an improvement in peripheral insulin sensitivity and also with increases in the pancreas β-cell secretory capacity. More significant physiological responses to whole-grain fibre intake include a decrease in serum cholesterol, modification of the glycemic response and improvement in bowel functioning. Almost all water-soluble whole-grain fibre fractions reduce serum cholesterol. Good sources of this dietary fibre are whole-grain cereals, legumes and green vegetables. A high intake of water-soluble fibre is able to reduce serum cholesterol and LDL cholesterol levels by 25%. In particular, inulin (high in chicory and onions) has shown a remarkable hypolipemic effect in subjects affected by obesity and hyperlipemia. Evidence suggests that as little as 9 g of inulin per day for four weeks is enough to have a favourable effect on serum lipids [16–21].

Diets rich in whole-grain cereals and legumes are also rich in micronutrients such as magnesium (Mg), manganese (Mn), zinc (Zn) and chromium (Cr), which are directly related to improving glucose metabolism, insulin sensitivity, β-cell insulin synthesis and secretion and preventing oxidative damage [22–25]. In addition, several phenolic compounds from whole-grain cereals have a strong antioxidant capacity *in vivo*. Many of these bioactive compounds are bound to grain cell walls and reach the colon unchanged, and are then released during the fermentation process [26,27]. Whole-grain cereals are excellent sources of fat-soluble antioxidants, such as phytosterols (as gamma-oryzanol), tocopherols and tocotrienols (72–612 ppm), which inhibit HMG-CoA reductase, the key enzyme in cholesterol synthesis [28,29].

Whole-grain cereals are thought to exert their effect by decreasing the post-prandial blood glucose response, slowing gastric emptying and/or delaying starch digestion and starch-derived glucose absorption. Studies show that an evening meal rich in non-digestible carbohydrates can reduce post-prandial glucose after a high-GI breakfast; this response is thought to be caused by short-chain fatty acids (SCFAs: acetate, propionate and butyrate) produced by the fermentation of non-digestible carbohydrates by the colonic microbiota [30–32]. Several hypotheses have been postulated as to how SCFAs mediate the glucose-lowering effect. SCFAs may delay gastric emptying [33], have insulin-like properties [34], increase insulin sensitivity by decreasing free fatty acid concentrations [35], have anti-inflammatory effects [36] or promote insulin-independent glucose sparing [35].

Recent studies, using the dual isotope technique, have shown that a glucose-associated rise in pro-inflammatory cytokines can be moderated by the previous evening meal. This research was also able to show that a reduced glucose response to a 50-g oral glucose tolerance test after an evening meal of barley was because of higher glucose uptake in peripheral tissue, reflected by the glucose clearance rate [37]. This indicates that food-associated factors can acutely influence peripheral insulin sensitivity and suggests that butyrate, derived from colonic fermentation of non-digestible carbohydrates, could be involved in the overnight meal effect, and could prevent the late post-prandial rise in pro-inflammatory cytokines IL-6 and TNF-α, after a glucose load in the morning [38]. Moreover, this effect may be due to the anti-inflammatory properties of SCFAs [39].

The Health Professionals Follow-up Study and the Nurses' Health Study I and II, conducted by the Harvard School of Public Health, estimated that replacing the daily intake of white rice with 50 g of brown rice (raw, equivalent to one-third serving per day) was associated with a 16% lower risk of T2DM, whereas the same replacement

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with whole-grains as a group, was associated with a 36% lower diabetes risk [40].

A high-fat diet containing Japanese millet protein concentrate (prolamin) fed to type 2 diabetic mice for 3 weeks has been shown to significantly increase plasma levels of adiponectin and high-density lipoprotein cholesterol [high-density lipoprotein (HDL) cholesterol] and to decrease the levels of glucose and triglycerides, compared with control animals with a high-fat diet containing casein. Considering the physiological significance of adiponectin and HDL cholesterol for T2DM, these findings suggest that dietary millet may also have the potential to ameliorate this disease [41–44].

In summary, current evidence supports the recommendation that most dietary carbohydrate should come from whole-grains to prevent T2DM, and to obtain lower blood glucose concentration peaks [40,45,46].

Fat and proteins

A low-fat diet is also a valid recommendation for the treatment and prevention of T2DM; low-fat diets encourage weight loss, whereas high-fat diets are strongly associated with obesity, glucose intolerance and increased insulin resistance [47].

A high intake of animal protein is also inappropriate for T2DM, because it induces the accumulation of anions, which cannot be metabolized and which result in long-term (and often overlooked) metabolic acidosis. Animal protein contains sulphur-containing amino acids (methionine, homocysteine and cysteine), whose oxidation generates sulphate, a non-metabolizable anion, which constitutes a major determinant of the daily acid load. This metabolic acidosis increases progressively with age as a result of the physiological decline in kidney function. Usually, the kidneys implement compensating mechanisms, aimed at restoring acid-based balance, such as the removal of anions, the conservation of citrate, the enhancement of kidney ammoniogenesis, and the urinary excretion of ammonium ions. These adaptive processes result in low serum bicarbonate, high serum anion gap, a low urine pH, hypocitraturia and nitrogen and phosphate wasting. Research has shown that people consuming a diet based on animal protein have higher renal net acid excretion and a more acidic urinary pH than people eating a plant-based diet [48]. Urinary sulphate excretion is inversely correlated with urine pH. Univariate analysis of a cross-sectional study on healthy subjects found that urinary sulphate was significantly higher in insulin-resistant subjects, compared with those with normal insulin sensitivity. These findings suggest a link between animal protein, endogenous acid production and insulin resistance [49,50]. Even a very mild degree of metabolic acidosis, which induces skeletal muscle resistance to insulin action and dietary acid load, may be an important variable in predicting hypertension and cardiovascular risk in the general population and in diabetes and chronic kidney failure [51–53].

The significant functional changes that take place in the kidney in response to metabolic acidosis include increases in renal plasma flow and in the glomerular filtration rate. Unlike animal products, vegetable proteins do not induce renal vasodilation or glomerular hyperfiltration [54]. High animal protein intake and excessive body weight have been shown to result in similar hemodynamic adaptations in both type 1 and T2DM where elevated renal plasma flow, glomerular filtration rate and kidney size have been noted early in the course of the disease, compared with non-diabetic individuals. Both the consumption of vegetable proteins and the careful metabolic control of diabetes help to ameliorate these modifications in kidney function through an improvement of the acidosis state [55]. In healthy individuals, even a slight degree of metabolic acidosis results in a decreased sensitivity to insulin and subsequent impairment of glucose tolerance. The incidence of diabetes mellitus and glucose intolerance is much higher in persons with a lower urinary pH than in normal volunteers [56].

The modern Western-type diet is very high in 'fast foods,' energy, fat, animal proteins, processed, canned and fried foods, sugars and refined carbohydrates, salt, dairy products and cholesterol and very low in fruits, vegetables, whole-grain cereals, essential micronutrients, antioxidants, dietary fibre, probiotics and prebiotics. These relatively recent changes in dietary lifestyles have contributed to the dramatic modification of the human global health picture and have generated a permanent high level of acidification and inflammation in those consuming these Western diets [57].

Ma-Pi 2 diet

The macrobiotic Ma-Pi 2 diet has attempted to encompass all the general principles of good dietary management for T2DM. It was conceived by Mario Pianesi, conceiver, founder and president of the Un Punto Macrobiotico Association, in Italy, for the treatment of T2DM [58]. This diet has been shown to reduce plasma glucose, HbA1c, serum cholesterol, serum triglycerides, blood pressure and insulin consumption, and increase urine pH, in short-term studies (21 days), longer-term studies (3 months), and in studies of 6 months duration, in adults with T2DM [59–67].

These study analyses pooled results obtained using the Ma-Pi 2 diet in short-term intervention studies (21 days) from several countries, with the aim of assessing the effects of this diet on the metabolic control of T2DM patients.

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Methodology

Four prospective, 21-day intervention studies with the Ma-Pi 2 diet in adults with T2DM were included in this pooled analysis. These studies were carried out in Cuba in 2007 [64]; China in 2008 [65]; Ghana in 2011 [66]; and Italy, in 2012 [67]. In all studies, patients were selected from specialized endocrinology services according to the same inclusion and exclusion criteria.

In all four studies, the same Ma-Pi 2 diet was administered to each patient. It consisted of 40–50% whole-grain (rice, millet and barley); 30–40% vegetables (carrots, savoy cabbage, chicory, red radish, onions, parsley, cabbage and, because of the local lack of some vegetables, other varieties not included in the original Ma-Pi 2 diet were used such as kale, broccoli, lettuce and chive); and 8–10% legumes (adzuki beans, chickpeas, lentils and black beans); plus gomashio (roasted ground sesame seeds with unrefined sea salt); fermented products (miso, tamari and umeboshi); seaweeds (kombu, wakame and nori); and Bancha tea (caffeine-free green tea). Daily average energy intake was 2000 kcal (12% protein, 18% fat and 70% carbohydrate). The Ma-Pi 2 diet contained 18% saturated, 46% monounsaturated and 36% polyunsaturated fat, without trans-fatty acids and an *n*-6 : *n*-3 polyunsaturated fatty acid ratio of 5 : 1. It provided nutrients and phytocompounds with antioxidant, hypoglycemic and hypolipemic effects, such as vitamin C, β carotene, magnesium (700 mg/day), manganese (16 mg/day), zinc (15 mg/day), chromium, phytosterols (326 mg/day), dietary fibre (50–60 g/day), inulin (9 g/day), poliphenols, tocotrienols, folates (more than 500 μg/day), quercetin and prebiotic and probiotic products [58].

In every study, foods were always prepared by Un Punto Macrobiotico macrobiotic cooks, and offered to patients at breakfast, lunch, dinner and as snacks. Individual foods varied, according to availability in each country.

In Italy and Ghana, patients were kept in a hotel or in a hospital, respectively, for the duration of the study. In Cuba and China, patients attended institutions only during the day, where they received meals, snacks and medical assistance.

Data extraction

Common indicators of metabolic control were selected in the four studies for comparison of baseline data (t0) with study end (t21) (after 21 days of dietary intervention), these were the following: glycemic profile in capillary blood, venous glycemia, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides; total cholesterol : HDL cholesterol ratio, LDL : HDL cholesterol ratio, urea, urine pH, blood pressure, body weight, BMI, and percent of body fat.

Statistical procedure

Quantitative variables at t0 and t21 were compared. The Wilcoxon test was used for matched-pair comparison with a significance level of $p \leq 0.05$. The Monte Carlo simulation was used to corroborate the reliability of statistical decisions. The Principal Component Analysis (PCA) was used to explore the behaviour of variables (this method reduces the number of variables, detects patterns in their relationships and classifies new variables). The number of subjects who achieved metabolic targets in each group was evaluated using the McNemar test.

The Cohen's effect size (d) was used to describe the relationship between the dependent variables (blood glucose, serum lipids, blood pressure, etc.) and the independent variable (Ma-Pi 2 diet). The effect size indicates the standard deviation of the differences, removing any influence from the different study sample sizes. This technique allowed the authors to compare several different studies (with different sample sizes, instruments, procedures and statistical methods used), quantify the differences and describe their relevance. Standardized mean differences, using Cohen's d, the corresponding confidence intervals (CI 95%), and the coefficient of determination R^2, were obtained and used to express the magnitude of the effect of the diet on every evaluated variable by using the following expressions [68]:

$$\text{Cohen's } d = \frac{Mean_{\text{posttest}} - Mean_{\text{pretest}}}{StandardDeviation_{\text{posttest}}}$$

$$\text{CI 95\% :}$$
$$\text{Lower Limit} = d - (1,96)(\text{Standard Error of } d);$$
$$\text{Upper Limit} = d - (1,96)(\text{Standard Error of } d)$$

$$\text{Standard Error of } d = \sqrt{\frac{N_1 + N_2}{(N_1)(N_2)} + \frac{d^2}{2(N_1 + N_2)}}$$

$$R^2 = \left(\frac{d}{\sqrt{d^2 + 4}}\right)^2$$

The global effect of the diet on the dependent variables was also calculated as a quantitative result of this analysis. The magnitude of the size effect was evaluated using the following cut-off points for classification [68]: small: $d = 0.20$–0.49; moderate: $d = 0.50$–0.79; high: $d = 0.80$–1.29; and very high: $d \geq 1.30$ [69].

Results

A total of 124 subjects participated in the four studies; Cuba ($n = 61$), China ($n = 16$), Ghana ($n = 23$) and Italy ($n = 24$). The majority were women (56%) and the mean age was 58.6 ± 10.2 years. Almost all Cuban, Chinese and Ghanaian patients were being treated with hypoglycemic drugs, including insulin. Only two Italians were receiving insulin; 78% of all patients showed fasting glycemia values higher than 6.1 mmol/L at baseline. Physical activity was similar in the Cuban and Chinese patients, a little bit higher in Italians, and lower in Ghanaians, the latter of which were hospitalized.

With the exception of HDL cholesterol, all measured indicators of metabolic control showed a significant reduction from baseline to study end ($p < 0.05$). The main improvements (deltas) in order of magnitude of reduction were capillary glycemia 2 h after breakfast, capillary glycemia 2 h after lunch, triglycerides, fasting capillary glycemia, urea, venous glucose, LDL cholesterol : HDL cholesterol, LDL cholesterol, total cholesterol : HDL cholesterol, total cholesterol, urinary pH, systolic blood pressure, and diastolic blood pressure (Table 1).

Figure 1 shows the behaviour of venous glycemia levels between t0 and t21 in all 124 subjects and also by country. Individuals from Ghana and Cuba had the highest uncontrolled carbohydrate metabolism at t0, individuals from Italy had the lowest uncontrolled carbohydrate metabolism at t0. Data dispersion was high at t0 in all studies. In all comparisons, a remarkable reduction of glycemia values was observed. The data dispersion decreased at intervention end (t21).

Mean capillary glycemia (fasting, and 2 h after breakfast and lunch) decreased in all studies, almost reaching desired values (target), from the third day of dietary intervention to a plateau at study end (t21).

Table 2 shows the percentage of patients, at t0 and t21, accomplishing goals for metabolic control. At t0, few individuals had goal measurements, by study end there were significant increases in the percentage of patients' achieving these goals. Four principal components (PC) of control were highlighted using PCA: PC1 was characterized by lipid variables; PC2 by glycemic ones; PC3 by blood pressure; and PC4 by urea and urine pH. These four components explained almost 70% of the total variance. No difference in the score of the PC2 ($p = 0.237$) by the one-way analysis of variance was found, which indicates a similar glycemia response pattern to the Ma-Pi 2 diet in all countries studied.

Tables 3a–3c show the size of the effect of the Ma-Pi 2 diet on each measured indicator as a global effect. Results suggest that capillary blood glucose (fasting, 2.86; 2 h after breakfast, 2.82; and 2 h after lunch, 2.24); venous glycemia, 1.83; triglycerides, 1.59; urine pH, 1.47; and total cholesterol, 1.35, were affected most by the Ma-Pi 2 diet (very high effect size $d \geq 1{,}30$). Conversely, BMI and body fat were only affected to a small extent (small effect size $d = 0.20$) and HDL cholesterol and weight were not affected at all (no effect size $d < 0.20$).

These same tables also highlight the high values of the coefficient of determination (R^2), which indicates how much of the variance is determined by the diet, mainly by capillary glycemia values. In China, for example, 92.5% ($R^2 = 0.925$) of the variance for glycemia 2 h after

Table 1. Descriptive statistical analysis of all variables common to the four countries ($n = 124$).

	t0		t21			
Variable	Mean	SD	Mean	SD	*p*-value*	Change (%)
Glycemia (mmol/L)	9.0	3.6	6.1	1.6	0.000	−32.2
Fasting capillary glycemia (mmol/L)	9.6	3.4	5.8	1.3	0.000	−39.6
Capillary glycemia 2 h after breakfast (mmol/L)	11.8	5.0	6.3	1.9	0.000	−46.6
Capillary glycemia 2 h after lunch (mmol/L)	11.0	5.1	6.3	2.1	0.000	−42.7
Total cholesterol (mmol/L)	5.36	1.47	4.11	0.93	0.000	−23.3
HDL cholesterol (mmol/L)	1.13	0.36	1.12	0.29	0.468	−0.9
LDL cholesterol (mmol/L)	3.34	1.20	2.44	0.88	0.000	−26.9
LDL/HDL ratio (mmol/L)	3.35	1.90	2.35	1.13	0.000	−29.9
Total cholesterol/HDL cholesterol (mmol/L)	5.29	2.46	3.90	1.33	0.000	−26.3
Triglycerides (mmol/L)	2.18	1.38	1.27	0.57	0.000	−41.7
Urea (mmol/L)	6.8	3.4	4.3	2.0	0.000	−36.8
Urinary pH	5.4	0.5	6.1	0.5	0.000	13.0
Systolic blood pressure (mmHg)	129	15	119	13	0.000	−7.8
Diastolic blood pressure (mmHg)	78	10	73	8	0.000	−6.4
Weight (kg)	75.1	16.8	72.5	15.6	0.000	−3.5
BMI (kg/m^2)	28.2	5.3	27.2	5.0	0.000	−3.5
Body fat (%)	33.5	9.2	31.7	8.9	0.000	−5.4

LDL, low-density lipoprotein; HDL, high-density lipoprotein; BMI, body mass index.
*Wilcoxon test

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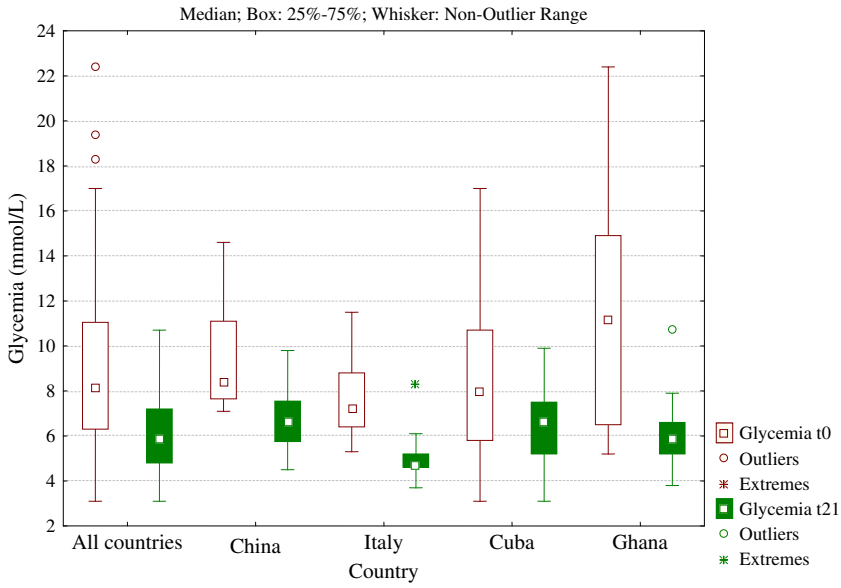

Figure 1. Box plot of venous glycemia by country

Table 2. Number of patients at baseline and 21 days achieving the recommended metabolic goals of diabetes treatment for maximal risk reduction.

Variable	Target value	t0 *n* (%)	t21 *n* (%)	*p*-value*
Glycemia (mmol/L)	≤6.1	27 (21.8)	66 (53.2)	0.000
Capillary fasting glycemia (mmol/L)	≤6.1	16 (12.9)	76 (61.3)	0.000
Capillary glycemia 2 h after breakfast (mmol/L)	≤7.8	31 (25.0)	101 (81.5)	0.000
Capillary glycemia 2 h after lunch (mmol/L)	≤7.8	38 (30.6)	102 (82.3)	0.000
Total cholesterol (mmol/L)	≤5.2	63 (50.8)	111 (89.5)	0.000
HDL cholesterol (mmol/L)	≥1.03	69 (55.6)	68 (54.8)	1.000
LDL cholesterol (mmol/L)	≤2.6	39 (31.5)	73 (58.9)	0.000
LDL/HDL ratio (mmol/L)	Men < 3.5 Women < 3.2	76 (61.3)	101(81.5)	0.000
Total cholesterol/HDL cholesterol ratio (mmol/L)	Men < 5.0 Women < 4.5	66 (53.2)	96 (77.4)	0.000
Triglycerides (mmol/L)	≤1.7	59 (47.6)	105 (84.7)	0.000
Urinary pH	≥5.5	55 (44.4)	115 (92.7)	0.000
Systolic blood pressure (mm Hg)	≤130	79 (63.7)	112 (90.3)	0.000
Diastolic blood pressure (mm Hg)	≤80	88 (71.0)	113 (91.1)	0.000
BMI (kg/m^2)	<27	61 (49.2)	76 (61.3)	0.000
Body fat (%)	Men < 20 Women < 25	12 (9.7)	14 (11.3)	0.250

LDL, low-density lipoprotein; HDL, high-density lipoprotein; BMI, body mass index.
*McNemar test

breakfast and 91.1% ($R^2 = 0.911$) of the variance for 2 h after lunch, is explained by the diet.

The total global effect of the Ma-Pi 2 diet, which includes the effect of all variables of the studies, was Italy (1.96), China (1.79), Cuba (1.38) and Ghana (0.98). The global effect of all studies was high (1.20). The Italian study, with better conditions during the study such as lodging and feeding, showed the highest effect values, whereas the Ghanaian study showed the lowest.

One-way analysis of variance of the global effect did not show significant differences ($p = 0.300$) suggesting that the effect of the Ma-Pi 2 diet was similar in all studies in every country. The analysis of the effect size, according to the Principal Components, demonstrated that the PC2 (glycemia) was associated with the highest effect, $d = 2.44$ (95% confidence interval 2.77–2.11). The individual effect size for each variable by each study observed was independent of the study's sample size and of the global effect of all variables ($p > 0.05$ for all comparisons).

The positive effect of the Ma-Pi 2 diet on the glycemic profile and on venous glucose was independent of hypoglycemic drug consumption. Overall, insulin had to be reduced by 50% in all 91 insulin-treated subjects to avoid hypoglycemia: from 2.666 units at onset (29.3 units per person) to 1.335 units at t21 (14.67 units per person). Analysis by country showed that in Cuba, China and Ghana, a similar percentage reduction in insulin was observed (45%), whereas a greater reduction (82%) was

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Table 3a. Measured indicators of metabolic control with very high effect size ($d \geq 1.30$).

Variable	Effect size	All countries ($n = 124$)	China ($n = 16$)	Italy ($n = 24$)	Cuba ($n = 61$)	Ghana ($n = 23$)
Glycemia	d*	−1.83	−2.10	−3.16	−1.15	−3.80
	(LL; UL)**	(−2.13; −1.53)	(−2.97; −1.24)	(−4.01; −2.31)	(−1.53; −0.77)	(−4.77; −2.83)
	R^2	0.456	0.525	0.714	0.249	0.783
Capillary fasting glycemia	d*	−2.86	−3.37	−3.54	−2.51	−3.80
	(LL; UL)**	(−3.21; −2.5)	(−4.45; −2.29)	(−4.45; −2.64)	(−2.99; −2.04)	(−4.77; −2.83)
	R^2	0.671	0.739	0.759	0.612	0.783
Capillary glycemia 2 h after breakfast	d*	−2.82	−7.00	−4.44	−2.77	−1.91
	(LL; UL)**	(−3.17; −2.46)	(−8.86; −5.15)	(−5.50; −3.39)	(−3.26; −2.27)	(−2.61; −1.22)
	R^2	0.665	0.925	0.831	0.657	0.478
Capillary glycemia 2 h after lunch	d*	−2.24	−6.42	−8.27	−2.12	−1.47
	(LL; UL)**	(−2.56; −1.93)	(−8.13; −4.70)	(−10.02; −6.52)	(−2.56; −1.67)	(−2.13; −0.82)
	R^2	0.557	0.911	0.945	0.528	0.352
Total cholesterol	d*	−1.35	−1.51	−1.24	−2.13	0.57
	(LL; UL)**	(−1.62; −1.07)	(−2.30; −0.73)	(−1.86; −0.63)	(−2.57; −1.68)	(−0.02; 1.16)
	R^2	0.312	0.364	0.279	0.530	0.075
Triglycerides	d*	−1.59	−0.49	−3.37	−2.14	0.18
	(LL; UL)**	(−1.88; −1.31)	(−1.20; 0.21)	(−4.25; −2.49)	(−2.58; −1.69)	(−0.39; 0.76)
	R^2	0.388	0.057	0.740	0.534	0.008
Urinary pH	d*	1.47	1.01	1.06	1.74	1.84
	(LL; UL)**	(1.19; 1.75)	(0.28; 1.75)	(0.45; 1.66)	(1.32; 2.16)	(1.15; 2.52)
	R^2	0.351	0.204	0.218	0.431	0.457

LL, lower limit; UL, upper limit.
*Cohen's *d* value
**95% Confidence Interval of *d* (LL; UL)

Table 3b. Measured indicators of metabolic control with high effect size ($d = 0.80–1.29$).

Variable	Effect size	All countries ($n = 124$)	China ($n = 16$)	Italy ($n = 24$)	Cuba ($n = 61$)	Ghana ($n = 23$)
LDL cholesterol	d*	−1.03	−1.43	−1.01	−1.49	0.20
	(LL; UL)**	(−1.29; −0.76)	(−2.21; −0.65)	(−1.61; −0.41)	(−1.89; −1.09)	(−0.38; 0.78)
	R^2	0.209	0.338	0.202	0.358	0.010
LDL/HDL ratio	d*	−0.88	−0.80	−0.57	−1.30	−0.29
	(LL; UL)**	(−1.15; −0.62)	(−1.51; −0.08)	(−1.14; 0.01)	(−1.69; −0.91)	(−0.87; 0.29)
	R^2	0.164	0.136	0.074	0.298	0.021
Total cholesterol/HDL cholesterol	d*	−1.05	−0.63	−0.68	−1.62	−0.31
	(LL; UL)**	(−1.31; −0.78)	(−1.34; 0.08)	(−1.26; −0.09)	(−2.03; −1.21)	(−0.89; 0.27)
	R^2	0.214	0.089	0.102	0.397	0.024
Urea	d*	−1.24	−2.43	−1.98	−1.85	−1.08
	(LL; UL)**	(−1.51; −0.96)	(−3.34; −1.52)	(−2.67; −1.29)	(−2.27; −1.42)	(−1.70; −0.47)
	R^2	0.276	0.596	0.496	0.460	0.227

LDL, low-density lipoprotein; HDL, high-density lipoprotein; LL, lower limit; UL, upper limit.
*Cohen's *d* value
**95% Confidence Interval of *d* (LL; UL)

demonstrated in the Italian study. The use of hypoglycemic drugs decreased by 39% in Italian patients; in Ghana, only one patient decreased the consumption of these drugs, and in China and Cuba, there were no changes in hypoglycemic drug intake during the study period.

Discussion

This study confirms the beneficial effect of the Ma-Pi 2 diet; multivariate analysis of results obtained in each individual study [64–67] illustrate the ability of this diet to achieve relatively fast metabolic and blood pressure control in adults with T2DM. Independent of location, climate, genotype or physical activity levels of individuals, the Ma-Pi 2 diet demonstrated a very high or high positive effect, according to Cohen's d values. These effects were reproduced with similar results on both the capillary or venous glucose levels in the four studies, independent of the sample size.

The greatest global effect of the diet was observed in the Italian study and could be explained by the better conditions experienced during the study: patients were located in a hotel close to the sea, had strict controls on food consumption, better food preparation and cooking methods, and a higher level of physical activity compared with the conditions of the other three studies. Physical activity is essential to the management of T2DM and helps

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Table 3c. Measured indicators of metabolic control with moderate (d = 0.50–0.79) and small (d = 0.20 a 0.49) effect size.

Variable	Effect size	All countries (n = 124)	China (n = 16)	Italy (n = 24)	Cuba (n = 61)	Ghana (n = 23)
Systolic blood pressure	d*	−0.79	−0.93	−0.98	−1.16	0.00
	(LL; UL)**	(−1.05; −0.53)	(−1.66; −0.20)	(−1.57; −0.38)	(−1.54; −0.78)	(−0.58; 0.58)
	R^2	0.135	0.178	0.192	0.251	0.000
Diastolic blood pressure	d*	−0.65	−0.62	−1.16	−0.82	−0.24
	(LL; UL)**	(−0.91; −0.4)	(−1.33; 0.09)	(−1.77; −0.55)	(−1.19; −0.45)	(−0.82; 0.34)
	R^2	0.096	0.088	0.252	0.143	0.014
Weight	d*	−0.17	−0.17	−0.38	−0.16	0.00
	(LL; UL)**	(−0.42; 0.08)	(−0.87; 0.52)	(−0.95; 0.19)	(−0.51; 0.20)	(−0.58; 0.57)
	R^2	0.007	0.008	0.035	0.006	0.000
BMI	d*	−0.2	−0.25	−0.42	−0.20	−0.02
	(LL; UL)**	(−0.45; 0.05)	(−0.94; 0.45)	(−0.99; 0.15)	(−0.55; 0.16)	(−0.60; 0.55)
	R^2	0.010	0.015	0.042	0.010	0.000
Body fat	d*	−0.2	−0.18	−0.30	−0.31	−0.03
	(LL; UL)**	(−0.45; 0.05)	(−0.87; 0.52)	(−0.87; 0.27)	(−0.66; 0.05)	(−0.61; 0.55)
	R^2	0.010	0.008	0.022	0.023	0.000

*Cohen's d value
**95% Confidence Interval of d (LL; UL)

to achieve and maintain therapeutic goals and improve quality of life [70–73]. In Cuba and China, full compliance with the diet was less likely because patients were only monitored during the day at health centres; these patients also had fewer opportunities for physical activity than the Italian patients. The Ghanaian patients had the worst study conditions; they were confined to their hospital beds, had low food accessibility (mainly to vegetables) and little chance of physical activity. In spite of all of these limitations, results from Ghanaian patients showed the diet had a high effect on venous glucose levels, which indicates that a Ma-Pi 2 diet, independent of physical activity, has a high regulating effect on carbohydrate metabolism. The Ghanaian patients had a greater lack of glycemic metabolic control at onset (Figure 1), but also had the lowest levels of serum lipids, blood pressure and body weight at baseline. This may explain why these subjects showed the lowest global effect of the Ma-Pi 2 diet; however, the results suggest that the diet has a rapid effect on carbohydrate metabolism, before body weight reduction is observed. This diet could therefore constitute an appropriated therapeutic alternative for uncontrolled diabetic patients who need to be institutionally treated. The individual influence of physical activity on weight, blood pressure and serum lipids should also be taken into consideration in the interpretation of these results. The effect of physical activity on blood pressure in patients with T2DM has been well documented [71,74]; a moderate loss of 5% of body weight has been associated with decreased insulin resistance, improved measures of glycemia and lipidemia and reduced blood pressure [74]. In the four studies analyzed, a similar 5.4% weight loss was documented in the Cuban, Chinese and Italian subjects.

Although numerous reviews and guidelines on the management of T2DM have been published [75–77], achieving optimal care for the growing number of patients with this disease has been, and will remain, a complex and difficult task. In particular, practitioners lack clear, scientifically-supported dietary recommendations. The scientific community needs to improve its strategic approach to combating this increasing epidemic, especially with regard to dietary/lifestyle changes [78]. The results of this study support recommendations for a diet that is rich in fibre, complex carbohydrates, whole-grain, vegetables and legumes for T2DM. Such diets can achieve good glycemia control, lower insulin requirements, slow glucose absorption, increase peripheral tissue sensitivity to insulin, reduce cholesterol and serum triglyceride levels, control body weight and lower blood pressure [79].

One criticism of the Ma-Pi 2 diet could be the contribution of macronutrients to the total energy intake (12% protein, 18% fat and 70% carbohydrate), which is quite different to recommended values (20% protein, 30% fat and 50% of carbohydrate). Although numerous studies have attempted to identify the optimal mix of macronutrients for meal plans for people with diabetes, a recent systematic review [80] confirms the lack of a single effective mix of macronutrients and suggests that macronutrient proportions should be individualized. In 2013, the American Diabetes Association recognized that the most important goal in T2DM management should be to offer a total calorie intake appropriate to weight management and control. Further individualization of the macronutrient composition may then depend on the metabolic status of the individual patient (lipid profile, renal function and food preferences) [3].

A variety of diets can be effective for managing diabetes including, the Mediterranean-style, plant-based (vegan or vegetarian), low-fat and low-carbohydrate diets [5–9,81–83]. However, the speed of metabolic control achieved with the Ma-Pi 2 diet appears not to have been shown in other diets found in the available literature. The overall results together with the remarkable reduction in

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insulin consumption (50% in only 21 days), illustrate the key feature of the diet in the diabetic management of these patients. Although these studies had several limitations (small and non-random selected samples, the use of non-habitual foodstuffs or physical inactivity), this pooled analysis has accomplished a fundamental goal outlined by expert recommendations for the management of T2DM [3].

The main function of foods is to supply energy and nutrients to satisfy metabolic requirements and generate wellbeing. However, some foodstuffs may have physiological effects in addition to their accepted nutritional benefits, and these have been defined as 'functional foods'. The foods used in the Ma-Pi 2 diet, such as whole-grain cereals, dietary fibres, vegetables, fermented products, seaweeds and green tea, are classified as functional foods and exhibit high antioxidant properties and prebiotic or probiotic effects, which can make an essential contribution to the overall effects of the diet. The total antioxidant capacity of the Ma-Pi 2 diet, measured by the Modified 2,2-Azino-bis-3-ethylbenzothiazoline-6-sulfonic Acid and Ferric Reducing Antioxidant Power methods, generates high values (8378 and 1571 mg ascorbic acid, respectively); the main contributing foods to these values were vegetables 36%, and Bancha tea, 31% [84]. These values were higher than those the reported for the Spanish Mediterranean Diet (1046 and 370 mg ascorbic acid, respectively), in which beverages (wine, coffee and tea) are the main contributors with 65% [85]. The polyphenol content of the Ma-Pi 2 diet was 2664 mg gallic acid, and the main contributors to this value were cereals 43%, vegetables 30%, legumes 11% and sesame seeds 8% [84]. The corresponding value for the Spanish Mediterranean Diet was 1171 mg gallic acid, with beverages as the main contributors, at 50% [85]. Additionally, the Ma-Pi 2 diet may also modify and improve the intestinal microbiota, rebalancing the gut flora and so reducing the risk of inflammatory changes seen in diabetes mellitus. The modern Western diet is associated with dysbiosis, which can result in enhanced permeability of the intestinal epithelium and eventual endotoxemia. The enhanced permeability induces lipopolysaccharide or whole microorganism translocations through the intestinal epithelial barrier. As a result, the immune system in the gastrointestinal tract experiences an antigen overload, which leads to inflammation [86]. Chronic inflammation is known to be associated with many chronic diseases including T2DM [87], whereas changes in the composition and diversity of the intestinal microbiota are related to obesity and obesity-associated metabolic disorders, such as T2DM and metabolic syndrome [88,89]. The gut microbiota composition can be optimized through dietary interventions with prebiotic or probiotic food sources [90,91]. Bancha tea, rich in polyphenols such as epigallocatequinegalate, is a source of liquid (around 2 L per day) in the Ma-Pi 2 diet. The green tea can result in a 15% increase in insulin activity in vitro [92], protect against oxidative damage, and inhibit the LDL cholesterol oxidation, which is associated with atherosclerosis risk, heart disease and also with the formation of reactive oxygen specimens and free radicals [93].

Conclusion

This pooled analysis shows that short-term (21 days) Ma-Pi 2 diet interventions can significantly reduce glucose, cholesterol, triglycerides, urea serum levels and cardiovascular risk in adults with T2DM. This effect was independent of hypoglycemic drug consumption, although this should be reduced while patients are on the diet to avoid hypoglycemia. The results suggest that the Ma-Pi 2 diet could be considered a valid additional treatment for T2DM, particularly when carbohydrate metabolism needs to be rapidly controlled. Nutritional characterization of the Ma-Pi 2 diet suggests it can be classified as a functional diet. Additional research is now needed to describe the specific biochemical and physiological mechanisms that explain these preliminary results. A randomized controlled clinical trial (with a control group receiving the standard medical diet for diabetes) is recommended.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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