Effectiveness of a Hypocaloric and Low-Carbohydrate Diet on Visceral Adipose Tissue and Glycemic Control in Overweight and Obese Patients with Type 2 Diabetes

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Objective: To assesses the efficacy of a hypocaloric low-carbohydrate diet in overweight and obese patients with type 2 diabetes.

Design: A Randomized Controlled Trial.

Setting: Istituto Santa Margherita, University of Pavia, Italy.

Method: Patients were enrolled based on the following criteria: both genders, age 30–85, Caucasian origin, BMI between 24.9 and 34.9 kg/m^2 (overweight and obese), glycated hemoglobin ≤7.5%, glomerular filtration rate ≥60 ml/min/1.73m^2 (CDK-EPI), on a free diet and only treated with metformin. Patients were evaluated before and after the intervention. They were randomly allocated to receive metformin with either a low-carbohydrate or a standard diet (control group) for 90 days. At the end of each dietary period, anthropometric and biochemical assessments, and Dual-energy X-ray absorptiometry (DXA) measurements were documented.

Result: Seventeen type 2 diabetic patients with an average age of 67 years and a BMI of 31 kg/m^2 were included in the study. Eleven (64%) were females and 6 (35.3%) were males. Patients on the low-carbohydrate diet showed reduced values of glycated hemoglobin (-0.43%; -5 mmol/mol; P<0, 05) both within the treated group and the control group. The preliminary data showed maintenance of fat-free mass (FFM) (-0.24 kg; p=0.862) a decrease in gynoid fat mass (FM) (-2.18 kg; P<0, 05), with a decrease in visceral adipose tissue (-0.20 kg; p=0-108).

Conclusion: A low-carbohydrate low-calorie diet has a short-term effect on the assessment of blood glucose and glycated hemoglobin values. It also shows promising results in the reduction of gynoid fat and visceral fat among type 2 diabetic patients.

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Type 2 diabetes, or non-insulin-dependent diabetes mellitus (DM), occurs in 90% to 95% of all diagnosed diabetic cases. This type of diabetes affects individuals with relative insulin deficiency and insulin resistance in the peripheral tissue[1]. There are several risk factors associated with the onset of type 2 diabetes: genetic predisposition, overweight and obesity (with BMI >25 kg/m^2), age, race/ethnicity, impaired fasting glucose or impaired glucose tolerance, gestational diabetes, hypertension 140/90 mmHg, HDL cholesterol below 35 mg/dl and/or >250 mg/dl triglycerides (TRG)[2].

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The nutritional therapy aims to lower glycemia, blood pressure and maintain a good lipid profile, reduce the cardiovascular risk, coronary heart disease and heart attack. According to current knowledge, there is no ideal percentage of calories from carbohydrates, fats, and proteins for people with type 2 diabetes[3]. Nevertheless, a wide variety of nutritional therapies have been accepted for diabetes management to promote patient health and prevent disease[2].

The energy intake must be adequate for the patient to achieve or maintain the correct weight[2]. For example, the American Diabetes Association (ADA) has traditionally advocated against the use of low-carbohydrate diets (less than 130 g/day or <26% of total energy), while in the most recent guidelines this dietary approach is now accepted[3]. The diet model is based on scientific mechanisms.

Carbohydrate restriction improves glycemic control, reducing insulin fluctuations, thus improving glycated hemoglobin as observed in numerous studies[4-5]. Studies revealed that a low-carbohydrate diet resulted in a decrease of TRG and low-density lipoproteins (LDL) cholesterol and an increase of high-density lipoprotein (HDL) cholesterol[6,7].

The weight loss results were mainly dependent on the calorie deficit as the reduction in body weight reported with either a low-carbohydrate or a low-fat diet were similar[8-9]. Similar results were reported by several studies on the beneficial effect of carbohydrate restriction on lipid profile[12-14].

A study has verified a correlation between the decrease in carbohydrate intake and the decrease in abdominal fat, independent of caloric reduction[15].

Low-carbohydrate diets were previously related to an increase in endothelial function impairment[16-17]. A low-carbohydrate diet, high in unsaturated fats and controlled in saturated fats had no adverse effects on endothelial function in type 2 diabetic patients[18]. A high-carbohydrate intake was negatively correlated with mortality in general, while saturated and unsaturated fats were associated with a lower risk of mortality and stroke[19]. Densitometry using dual-energy X-ray absorptiometry (DXA) is considered the gold standard method for assessment of bone density and body composition[20].

The aim of this study was to evaluate the effectiveness of a hypocaloric low-carbohydrate diet on the values of glycated hemoglobin in overweight and obese type 2 diabetic patients.

METHOD

A randomized, controlled two-arm study was conducted among diabetic patients. Patients in the experimental group were treated with metformin and a low-carbohydrate diet, while those in the control group received metformin with a balanced standard diet. All the patients involved in the study were selected according to the following criteria: both genders, age 30–85, Caucasian origin, BMI between 24.9 and 34.9 kg/m^2 (overweight and obese), glycated hemoglobin ≤7.5%, glomerular filtration rate ≥60 ml/min/1.73m^2 (CDK-EPI), on a free diet and only treated with metformin.

Patients with major morbidity (arterial hypertension not compensated by drug therapy, heart failure, hepatopathy, kidney disease, tumors, acute and chronic gastrointestinal diseases, etc.) were excluded from this study.

Body weight (kg), height (cm) and BMI were calculated, as well as the waist circumference (WC; cm).

The following hematochemical parameters were assessed: glycemia, C-peptide, lipid profile (total cholesterol, TRG, HDL cholesterol, and LDL cholesterol), creatinine, aspartate aminotransferase (AST) and alanine aminotransferase (ALT).

Statistical analyses were performed using SPSS 21. Frequency analysis assessed the number of subjects within each sample and the frequency per gender. Differences by gender between the two groups were assessed through the Chi-square test. Significance has been established to consider the null hypothesis below 0.05%.

RESULT

A moderately low-calorie and low-carbohydrate diet (<125g/day) was used for a period of 90 days. Two different diets were prepared according to gender: one that provided approximately 1,600 kcal/day for females and the other that provided approximately 1,800 kcal/day for males, see tables 1 and 2.

Table 1: Energy Composition of the Low-Carbohydrate Diet of 1,600 Kcal/day

Nutrient	g	Total	% kcal
Protein (4 kcal/g)	87.1	348	22.1**%**
Carbohydrate (4 kcal/g)	125.1	500	31.7**%**
Fat (9 kcal/g)	81.4	729	46.2**%**
Total Energy		1,577	100**%**

Table 2: Energy Composition of the Low-Carbohydrate Diet of 1,800 Kcal/day

Nutrient	g	Total	% kcal
Protein (4 kcal/g)	101.5	406	22.3**%**
Carbohydrate (4 kcal/g)	124.6	498.4	27.4**%**
Fat (9 kcal/g)	101.5	913.5	50.2**%**
Total Energy		1,818	100**%**

The control group followed a low-calorie diet, iso-caloric to a low-carbohydrate diet, and balanced (carbohydrates 55-60%, lipids 25-30%, proteins 15-20%) to meet the different habits of the patients. Two different standard diets were prepared according to gender: one provided approximately 1,600 kcal/day for females and the other provided approximately 1,800 kcal/day for males, see tables 3 and 4.

Table 3: Energy Composition of the Standard Diet of 1,600 Kcal/day

Nutrient	g	Total	% kcal
Protein (4 kcal/g)	74.3	297.2	18.1**%**
Carbohydrate (4 kcal/g)	241.0	964	58.7**%**
Fat (9 kcal/g)	42.3	380.7	23.2**%**
Total Energy		1,642	**100%**

Table 4: Energy Composition of the Standard Diet of 1,800 Kcal/day

Nutrient	g	Total	% kcal
Protein (4 kcal/g)	77.3	309.2	16.3%
Carbohydrate (4 kcal/g)	264.0	1,056	55.8%
Fat (9 kcal/g)	58.7	528.3	27.9%
Total Energy		1,894	**100%**

Seventeen patients (11 females and 6 males) were enrolled in the study, see table 5. Their mean age was 67 years **(±8.65)**; they were classified as overweight or obese with an average BMI of 31 kg/m^2 (±2.72).

Table 5: Number of Subjects Enrolled and Subdivided by Gender

	Frequency (n.)	(%)
Women	11	64.7%
Men	6	35.3%
Total	**17**	**100.0%**

All patients met the inclusion criteria, see table 6. No other abnormalities in blood chemistry were detected and all were subjected to pharmacological treatment with metformin. The possible significant differences between the two groups were highlighted. There were differences in the WC (baseline WC in the control group greater than that of the experimental group) and in the VAT (initial values of the control group were also higher). As for the other variables (gender, age, blood values, etc.), no significant differences were observed between groups. Because of the two significant variables, the results were then corrected, as well as for gender and age, for the WC and for the VAT, see table 7.

Patients in the experimental group had decreased body weight (-2.5 kg), BMI (-0.8 kg/h^2) and WC (-1.45 cm), see table 7. The experimental group had decreased levels of creatinine, cholesterol (total and LDL), TRG and inflammatory markers (AST and ALT), and a significant decrease of glycated hemoglobin (-3.7 mmol; P<0.05).

The main trends showed an increase in the values of some tests such as the glomerular filtrate rate (eGFR CKD-EPI), HDL cholesterol and C-peptide. DXA evaluation of body composition revealed the following: 1) the loss of fat free mass (FFM), though significantly, lower than that of fat mass (FM); 2) loss of gynoid mass, VAT, subcutaneous fat (SAT), sarcopenia index (ALM/h^2) and appendicular lean mass (ALM); 3) a significant decrease in the percentage loss of android mass (-3.2%). In addition to the loss of fat-free mass of legs (FFM legs; -1.1 kg; P<0.05); 4) the increase in SAT, ALM standardized for BMI and fat-free mass of arms (FFM arms), see table 7.

There were significant differences in glycated hemoglobin between the experimental and the control group (-0.43%; -5 mmol; P<0.05), and the gynoid mass (-2, 18%; P<0.05). No statistical variations were observed for the anthropometric, hematochemical and body composition values, see table 8.

Table 6: Baseline Characteristics of the Sample

Variable	Standard Diet Media; Deviazione Standard	Low-Carb Diet Media; Deviazione Standard	Total Sample Media Deviazione Standard	P-value
Gender				
Male	4 (23.5%)	2 (11.8%)	17 (100%)	X^2:0.701; p=0.402
Female	5 (29.4%)	6 (35.9%)		
Age (years)	67.78 ±5.87	59.50±9.48	63.88±8.65	0.056
Height (m)	1.65±0.10	1.64±0.08	1.64±0.92	0.809
Weight (kg)	88.52±13.78	81.56±9.91	85.25±12.27	0.248
BMI (kg/h^2)	32.41±2.91	30.30±2.13	31.42±2.72	0.106
WC (cm)	112.44±7.38	98.00±6.76	105.65±10.12	**0.001**
Glycaemia(mg/dl)	109.44±14.79	107.50±27.17	108.53±20.82	0.860
Glycated (%)	5.99±0.22	5.90±0.74	5.95±0.51	0.751
Glycated (mmol/mol)	41.89±2.15	40.63±8.09	41.29±5.60	0.680
C-peptide (ng/ml)	4.66±2.50	3.39±0.83	4.06±1.97	0.182
Creatinine (mg/dL)	0.78±0.15	0.82±0.08	0.80±0.12	0.509
eGFR CKD-EPI (mL/min)	85.86±12.04	81.26±8.02	83.69±10.31	0.366
Chol tot (mg/dl)	174.67±34.42	183.75±24.52	178.94±29.62	0.538
Chol LDL (mg/dL)	97.42±30.31	103.23±20.86	100.15±25.67	0.650
Chol HDL (mg/dL)	46.44±6.52	48.50±10.62	47.41±8.47	0.645
TRG (mg/dl)	154.00±44.79	159.38±96.93	156.53±71.56	0.889
AST (I.U./l)	21.11±3.76	19.75±5.31	20.47±4.46	0.557
ALT (I.U./I)	31.67±14.69	25.13±10.95	28.59±13.16	0.314
FFM (kg)	50.16±12.05	45.91±10.31	48.16±11.13	0.446
FM (kg)	35.71±5.01	33.09±7.70	34.48±6.35	0.427
Fat tissue (%)	42.07±6.46	42.10±8.64	42.08±7.32	0.993
Android (kg)	7.46±1.67	6.03±0.95	6.78±1.53	**0.05**
Android (%)	50.07±5.70	49.11±7.96	49.62±6.65	0.783
Gynoid (%)	42.39±10.10	41.58±9.46	42.01±9.50	0.866
VAT (kg)	2.34±0.82	1.57±0.60	1.98±0.81	**0.05**
SAT (kg)	5.12±1.02	4.46±0.67	4.81±0.91	0.132
SAT FM (kg)	0.15±0.03	0.14±0.04	0.14±0.04	0.865
SAT BMI (kg)	0.16±0.03	0.15±0.02	0.15±0.03	0.409
VAT FM (kg)	0.07±0.02	0.05±0.02	0.06±0.02	0.075
VAT BMI (kg)	0.07±0.02	0.05±0.02	0.06±0.02	0.054
ALM/h^2	8.42±1.25	8.18±1.21	8.31±1.20	0.690
ALM BMI (kg)	0.72±0.17	0.73±0.17	0.73±0.16	0.833
ALM	23.25±6.01	22.18±5.01	22.75±5.42	0.695
FFM legs (kg)	18.01±4.32	17.50±3.59	17.76±3.88	0.790
FFM arms (kg)	5.25±1.84	4.70±1.61	4.99±1.70	0.521

Table 7: Intra-Group Analysis of Changes in Averages

Variables	Δ (t1-t0)	CI 95%	P-value	Δ (t1-t0)	CI 95%	P-value
	Standard diet			Low-carb diet		
Weight (kg)	-0.70	-3.08;2.94	NS	-2.53	-5.81;0.74	NS
BMI (kg/h²)	-0.025	-1.15;1.10	NS	-0.81	-2.04;0.42	NS
WC (cm)	-2.27	-5.04;0.50	NS	-1.45	-4.46;1.57	NS
Glycaemia (mg/dL)	4.49	-8.32;17.29	NS	0.088	-15.14;15.31	NS
Glycated (%)	0.11	-0.11;0.33	NS	-0.32	-0.56;-0.084	**0.05**
Glycated (mmol/mol)	1.30	-1.17;3.77	NS	-3.71	-6.40;-1.03	**0.05**
C-peptide (ng/mL)	-1.35	-2.98;0.28	NS	0.64	-1.12;2.41	NS
Creatinine (mg/dL)	0.029	-0.07;0.12	NS	-0.005	-0.11;0.10	NS
eGFR CKD-EPI (mL/min)	-1.80	-11.05;7.45	NS	2.05	-7.99;12.10	NS
Chol tot (mg/dL)	-2.44	-22.60;17.71	NS	-6.25	-28.15;15.65	NS
Chol LDL (mg/dL)	4.33	-8.93;17.58	NS	-3.09	-17.49;11.31	NS
Chol HDL (mg/dL)	-1.88	-7.72;3.96	NS	0.61	-5.73;6.96	NS
TRG (mg/dL)	-23.32	-51.36;4.71	NS	-23.51	-53.97;6.94	NS
AST (I.U./I)	2.51	-6.37;11.38	NS	-2.32	-11.96;7.32	NS
ALT (I.U./I)	2.62	-10.24;15.49	NS	-4.33	-18.30;9.65	NS
FFM (kg)	-0.32	-2.03;1.39	NS	-0.56	-2.41;1.30	NS
FM (kg)	0.33	-1.43;2.09	NS	-2.10	-4.01;-0.19	**0.05**
Fat tissue (%)	0.36	-0.74;1.45	NS	-1.16	-2.35;0.025	NS
Android (Kg)	-0.29	-0.73;0.160	NS	-0.12	-0.60;0.36	NS
Android (%)	-0.24	-2.89;2.41	NS	-3.22	-6.10;-0.34	**0.05**
Gynoid (%)	1.36	0.34;2.39	P<0.05	-0.82	-1.93;0.29	NS
VAT (kg)	-0.039	-0.28;0.20	NS	-0.24	-0.49;0.026	NS
SAT (kg)	-0.21	-0.57;0.14	NS	0.08	-0.31;0.47	NS
SAT FM (Kg)	-0.006	-0.016;0.003	NS	0.01	0.00;0.02	**0.05**
SAT BMI (Kg)	-0.006	-0.02;0.004	NS	0.006	-0.005;0.02	NS
VAT FM (Kg)	-0.003	-0.01;0.005	NS	-0.003	-0.01;0.006	NS
VAT BMI (Kg)	-0.003	-0.01;0.006	NS	-0.004	-0.014;0.005	NS
ALM h²	0.202	-0.29;0.70	NS	-0.22	-0.76;0.32	NS
ALM BMI (Kg)	0.02	-0.014;0.052	NS	0.003	-0.033;0.039	NS
ALM	0.556	-0.847;1.96	NS	-0.65	-2.17;0.879	NS
FFM legs (Kg)	0.259	-0.551;1.07	NS	-1.10	-1.98;-0.22	**0.05**
FFM arms (Kg)	0.291	-0.62;1.20	NS	0.456	-0.531;1.44	NS

NS = not significant

Table 8: Analysis of the Two Groups

Variable	Δ change; CI 95% (Low-carbohydrate minus standard diet)	P-value
Weight (kg)	-2.46 (-7.74;2.81)	0.322
BMI (kg/h²)	-0.78 (-2.76;1.19)	0.397
WC (cm)	0.82 (-4.03;5.68)	0.713
Glycemia (mg/dl)	-4.40 (-27.69;18.89)	0.679
Glycated (%)	-0.43 (-0.82;-0.05)	**0.05**
Glycated (mmol/mol)	-5.02 (-9.34;-0.69)	**0.05**
c-peptide (ng/ml)	1.99 (-0.85;4.85)	0.149
Creatinine (mg/dl)	-0.03 (-0.20;0.13)	0.654
eGFR CKD-EPI (ml/min)	3.85 (-12.34;20.04)	0.608
Chol tot (mg/dl)	-3.81 (-39.08;31.47)	0.815
Chol LDL (mg/dl)	-7.42 (-30.62;15.78)	0.493
Chol HDL (mg/dl)	2.49 (-7.72;12.71)	0.599
TRG (mg/dl)	-0.19 (-49.26;48.87)	0.993
AST (I.U./I)	-4.83 (-20.36;10.71)	0.504
ALT (I.U./I)	-6.95 (-29.46;15.56)	0.507
FFM (kg)	-0.24 (-3.23;2.75)	0.862
FM (kg)	-2.44 (-5.51;0.64)	0.108
Fat tissue (%)	-1.52 (-3.44;0.40)	0.107
Android (kg)	0.17 (-0.61;0.94)	0.640
Android (%)	-2.98 (-7.62;1.66)	0.183
Gynoid (%)	-2.18 (-3.97;-0.39)	**0.05**
VAT (kg)	-0,20 (-0.62;0.22)	0.321
SAT (kg)	0.29 (-0.33;0.92)	0.322
SAT FM (kg)	0.017 (-0.001;0.034)	0.056
SAT BMI (kg)	0.013 (-0.005;0.030)	0.145
VAT FM (kg)	0.00 (-0.014;0.014)	0.960
VAT BMI (kg)	-0.002 (-0.016;0.013)	0.814
ALM h²	-0.42 (-1.30;0.46)	0.312
ALM BMI (kg)	-0.016 (-0.074;0.042)	0.552
ALM	-1.20 (-3.67;1.27)	0.303
FFM legs (kg)	-1.36 (-2.79;0.07)	0.060
FFM arms (kg)	0.17 (-1.43;1.77)	0.822

Table 9: Nutritional Values on a Typical Day of 1,600 Kcal, Low-Carbohydrate Compared to a Standard Diet

Nutrient	Low-carbohydrate		Standard	
	(g)	(%)	(g)	(%)
Protein	87.1	22.5	74.3	18.8
Fat	81.4	47.2	42.3	24.3
Saturated fat	22.4	12.9	10.3	5.9
Available carbohydrates	125.0	30.2	241.0	57.7
Simple carbohydrates	62.8	15.2	52.2	12.5
Fiber	22.0		26.0	
Calcium	748 mg		712 mg	
Sodium	925 mg		1537 mg	
Iron	10.3 mg		11.7 mg	
Total Energy	**1,570**		**1,566**	

Table 10: Comparison between a Low-Carbohydrate and Standard Diet of 1,600 kcal/day

	Low-carbohydrate	Standard
Breakfast	• 200 g whole milk • 30 g biscuits	• 200 g partially skimmed milk • 30 g biscuits
Lunch	• 50 g pasta • 100 g ricotta cheese 200 g vegetables • 150 g fruit	• 80 g pasta • 100 g ricotta cheese • 200gr vegetables • 150 gr fruit
Snack	• Whole yogurt	• Partially skimmed yogurt • 1 pack of cracker
Dinner	• 250 g swordfish • 200 g vegetables • 150 g fruit	• 80 g white bread • 120 g swordfish • 200 g vegetables • 150 g fruit
Condiments	• 50 g oil EVO (extra virgin oil)	• 20 g oil EVO

DISCUSSION

Patients on the low-carbohydrate diet showed a significant improvement in the values of both blood glucose (-4.4 mg/dl) and glycated hemoglobin (-0.43%; -5 mmol/mol; $P<0.05$), both within the treated group and the control group. This study also confirmed the preliminary data of Westman et al who found an improvement in glycated hemoglobin from 7.4% to 6.3% within 16 weeks among overweight patients[21]. In another study, long-term consumption of a low-carbohydrate diet was related to a marked reduction of glycated hemoglobin levels in overweight type 2 diabetic patients[4]. Furthermore, the results of this study demonstrate that the beneficial effects of a low-carbohydrate diet did not necessarily accompany a decrease in body weight, as previously demonstrated by other studies[10,11]. In both those studies, improved glucoregulation and lipid profile without weight loss were reported in diabetic patients who were on a low-carbohydrate diet. In addition, this study shows promising but non-significant improvement in body composition. The preliminary data show maintenance of FFM (-0.24 kg) at the same time of a decrease in FM (-2.44 kg), with a particular focus on VAT. This type of diet could play a greater role in maintaining free fat mass than fat mass during a weight loss program.

Boyko et al indicated that a smaller amount of visceral adipose tissue prevented the development of type 2 diabetes[22]. Similarly, another study found a correlation between the decrease in carbohydrate intake (regardless of caloric reduction) and the significant decrease in abdominal fat in non-obese diabetic type 2 patients[15].

In addition, this study highlights that increasing the percentage of fat in the diet to approximately 50% of total energy did not result in adverse changes in lipid profile. Few studies have investigated this association in diabetic patients, with encouraging results reported a decrease in TRG and cholesterol levels, with an increase in HDL cholesterol[6,7]. Brouns et al demonstrated that not only did low-carbohydrate diets in obese subjects with type 2 diabetes lead to improvements in body mass indices but also improved glycemic control and reduce TRG levels[23]. These findings are similar with our study, which showed reductions in LDL cholesterol (-7.42 mg/dl), total cholesterol (-3.81 mg/dl) and TRG (-0.2 mg/dl) and increase in HDL cholesterol (+2.49 mg/dl).

Previous studies revealed that diabetic type 2 patients were likely to have a greater disposition to develop liver diseases, particularly the amount of fat in the liver[23-24]. In this study, a reduction in transaminases (AST -4.83 I.U./I; ALT -6.95 I.U./I) was observed. Although the differences were not significantly different, the causes for such an improvement should be further studied.

The study has some limitations that should be considered. The study had a small sample size, and the relatively short intervention period of only 12 weeks, which emphasizes the need for conducting medium-long term interventions.

CONCLUSION

A low-carbohydrate, low-calorie diet has a short-term effect on reducing levels of glycemia and glycated hemoglobin. It also appears to be promising, particularly if protracted for a long period of time, in the reduction of visceral and intrahepatic fat, with consequent improvement of ALT and AST levels and the reduction of vascular complications. A potential benefit is the reduction of TRG levels and a stabilization of total cholesterol, with improvement of HDL cholesterol.

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