



1° CORSO NAZIONALE DI AGGIORNAMENTO I PER[CORSI] AME



Roma,
9-11 novembre 2012

**Terapie ipolipemizzanti nel Diabete Mellito tipo 2:
fra evidenze di efficacia e vincoli normativi**

Dieta e Integratori

Massimo Procopio

SCDU Endocrinologia, Diabetologia e Metabolismo

Azienda Ospedaliera Città della Salute e della Scienza

Torino



Roma,
9-11 novembre 2012

Comorbidità nel Diabete Mellito tipo 2 (DM2)

Dislipidemia

Ipertensione arteriosa

Obesità



Aumentata morbilità e
mortalità cardiovascolare

Terapie ipolipemizzanti nel DM 2: fra evidenze di efficacia e vincoli normativi

Comprehensive Diabetes Care Treatment Goals

Parameter	Treatment Goal
Glucose	
Hemoglobin A _{1c} , %	Individualize on the basis of age, comorbidities, duration of disease; in general ≤ 6.5 for most; closer to normal for healthy; less stringent for "less healthy"
Fasting plasma glucose, mg/dL	<110
2-Hour postprandial glucose, mg/dL	<140
Inpatient hyperglycemia: glucose, mg/dL	140-180
Lipids	
Low-density lipoprotein cholesterol, mg/dL	≤ 70 highest risk; <100 high risk
Non-high-density lipoprotein cholesterol, mg/dL	<100 highest risk; <130 high risk
Apolipoprotein B, mg/dL	<80 highest risk; <90 high risk
High-density lipoprotein cholesterol, mg/dL	>40 in men; >50 in women
Triglycerides, mg/dL	<150
Blood pressure	
Systolic, mm Hg	<130
Diastolic, mm Hg	<80
Weight	
Weight loss	Reduce weight by at least 5%-10%; avoid weight gain
Anticoagulant Therapy	
Aspirin	For secondary cardiovascular disease prevention or primary prevention for patients at very high risk ^a

Terapia Ipolipemizzante nel DM 2

Indicazioni alla terapia dietetica o nutrizionale

- Solo dieta: in pazienti senza CVD, di età < 40 aa e senza altri fattori di rischio CV che mantengono livelli di colesterolo LDL (col LDL)<100 mg/dl
- Dieta+Statine indipendentemente dai livelli di col LDL :
 1. in pazienti con CVD
 2. in pazienti senza CVD di età >40 aa e con ulteriori (uno o più) fattori di rischio CV

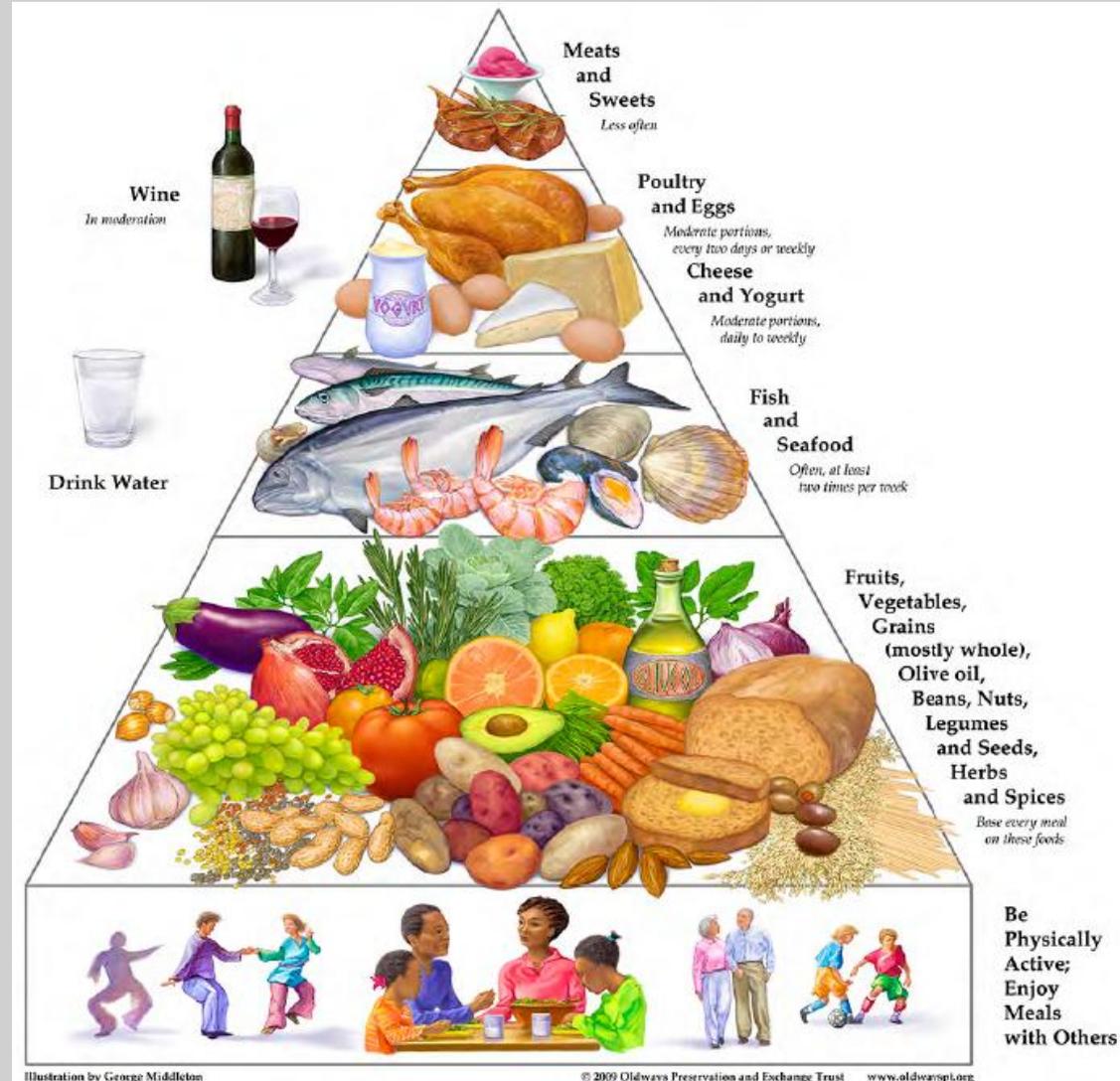
Terapia Ipolipemizzante nel DM 2

Quale dieta ?

- Dieta ipocalorica (isocalorica)
 - Caratteristiche quantitative
 - Caratteristiche qualitative
 - Compliance e mantenimento a lungo termine:
 1. Preferenze alimentari individuali
 2. Esercizio fisico
 3. Terapia comportamentale
- Dieta mediterranea
 - Dieta ipolipidica
 - Dieta ipoglicidica
 - Dieta portfolio

Dieta Mediterranea

A high consumption of foods of vegetable origin, such as fruits, vegetables, legumes, nuts, cereals and whole-grains; olive oil as the principal source of fat; fish and poultry consumed in low-to-moderate amounts; relatively low consumption of red meat; and moderate consumption of wine, normally with meals, could be considered important characteristics of this dietary pattern



Weight Loss with a Low-Carbohydrate, Mediterranean, or Low-Fat Diet

n=322 obese pts including pts with type 2 DM

- Low-fat restricted-calorie diet: 30% fat, 10% saturated fat, 300 mg of cholesterol per day.
- Mediterranean moderate fat restricted-calorie diet: 35% fat, including 30-45 g olive oil and <20 g of nuts per day)
- Low-carbohydrate, non-restricted-calorie diet: from 20 g (2-month induction phase) to 120 g per day to maintain the weight loss

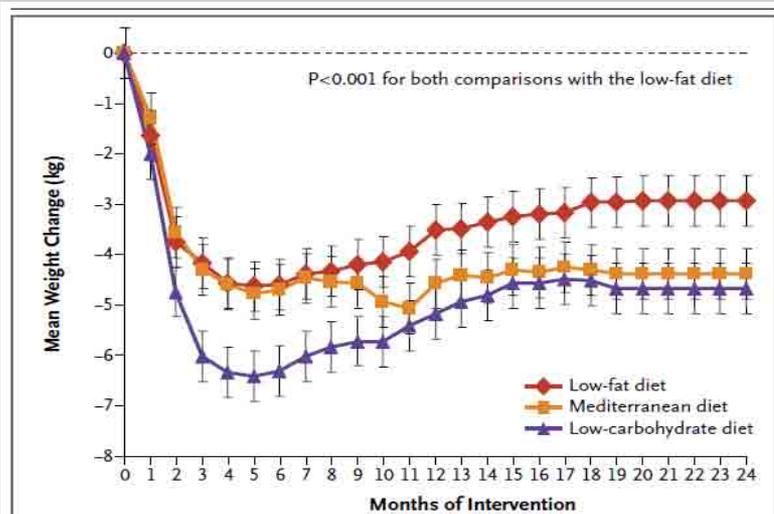


Figure 2. Weight Changes during 2 Years According to Diet Group.

Vertical bars indicate standard errors. To statistically evaluate the changes in weight measurements over time, generalized estimating equations were used, with the low-fat group as the reference group. The explanatory variables were age, sex, time point, and diet group.

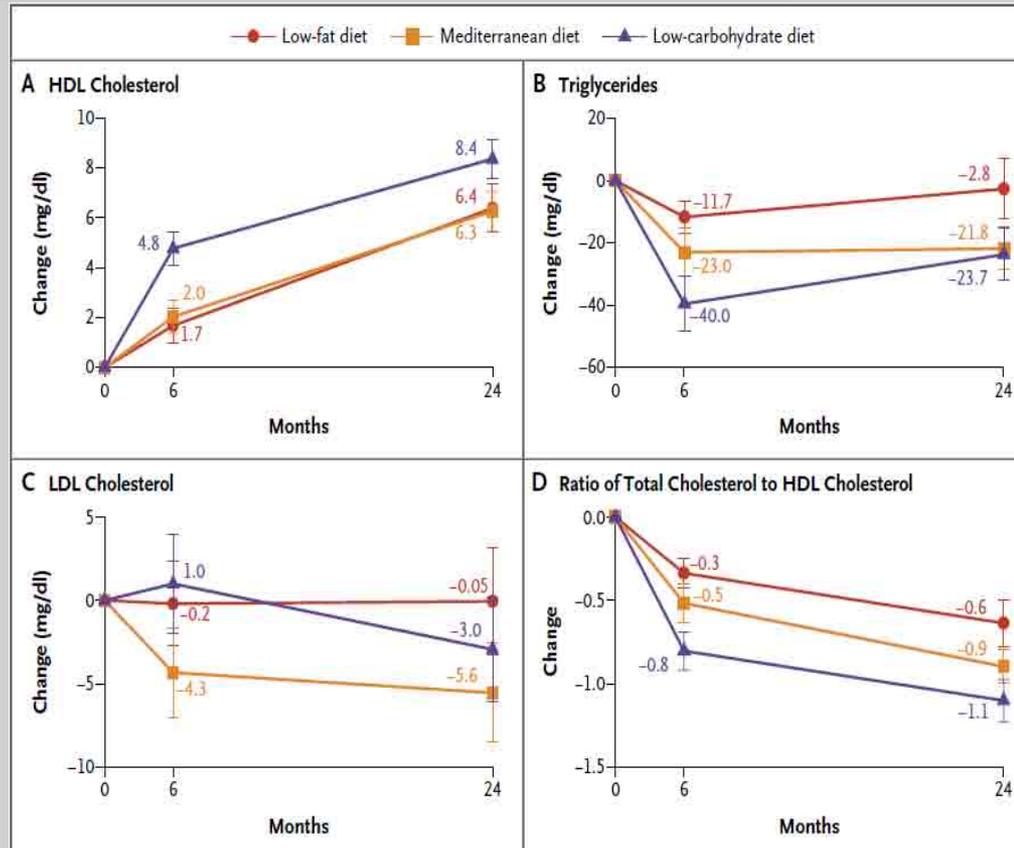


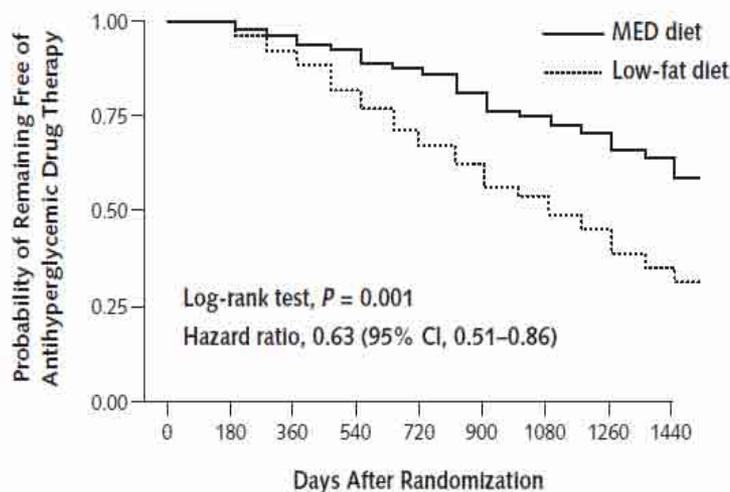
Figure 3. Changes in Cholesterol and Triglyceride Biomarkers According to Diet Group during the Maximum Weight-Loss Phase (1 to 6 Months) and the Weight-Loss Maintenance Phase (7 to 24 Months) of the 2-Year Intervention.

Effects of a Mediterranean-Style Diet on the Need for Antihyperglycemic Drug Therapy in Patients With Newly Diagnosed Type 2 Diabetes

A Randomized Trial

Katherine Esposito, MD, PhD; Maria Ida Malorino, MD; Miryam Ciotola, MD; Carmen Di Palo, MD; Paola Scognamiglio, MD; Maurizio Gicchino, MD; Michela Petrizzo, MD; Franco Saccomanno, MD; Flora Beneduce, MD; Antonio Ceriello, MD; and Dario Giugliano, MD, PhD

Figure 2. Probability of remaining free of antihyperglycemic drug therapy.



At risk, n	0	180	360	540	720	900	1080	1260	1440	
MED diet	108	108	105	101	89	80	77	66	52	49
Low-fat diet	107	107	98	87	72	64	54	45	35	29

MED = low-carbohydrate, Mediterranean-style.

Table 2. Trial Outcomes at 1 Year and End of Trial (4 Years)*

Variable	MED Diet	Low-Fat Diet	Difference (95% CI)
Coronary risk factors			
Total cholesterol level, mmol/L			
Year 1	-0.39 (0.38)	-0.15 (0.17)	-0.24 (-0.36 to -0.12)
Year 4	-0.25 (0.20)	-0.10 (0.18)	-0.15 (-0.39 to 0.05)
HDL cholesterol level, mmol/L			
Year 1	0.10 (0.12)	0.025 (0.02)	0.08 (0.04 to 0.12)
Year 4	0.09 (0.08)	0.02 (0.02)	0.07 (0.02 to 0.14)
Triglyceride level, mmol/L			
Year 1	-0.44 (0.57)	-0.22 (0.45)	-0.22 (-0.32 to -0.10)
Year 4	-0.28 (0.28)	-0.07 (0.10)	-0.21 (-0.36 to -0.02)

Patients: 215 overweight people with newly diagnosed type 2 diabetes who were never treated with antihyperglycemic drugs and had hemoglobin A_{1c} (HbA_{1c}) levels less than 11%.

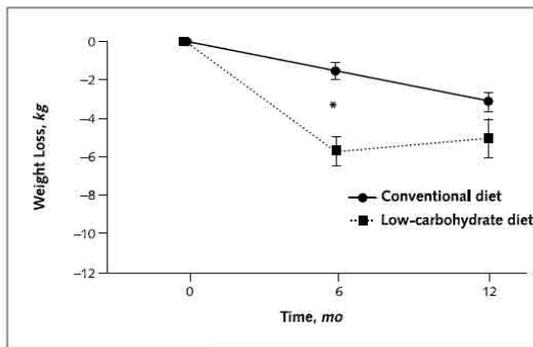
Intervention: Mediterranean-style diet (<50% of daily calories from carbohydrates) (*n* = 108) or a low-fat diet (<30% of daily calories from fat) (*n* = 107).

The Effects of Low-Carbohydrate versus Conventional Weight Loss Diets in Severely Obese Adults: One-Year Follow-up of a Randomized Trial

Linda Stern, MD; Nayyar Iqbal, MD; Prakash Seshadri, MD; Kathryn L. Chicano, CRNP; Denise A. Daily, RD; Joyce McGrory, CRNP; Monica Williams, BS; Edward J. Gracely, PhD; and Frederick F. Samaha, MD

- n=132 obese pts, 83% with type 2 DM or MS
- Low-carbohydrate diet: <30 g per day
- Conventional diet low in fat: <30% of calories from fat, deficit of 500 calories per day

Figure. Comparison of mean weight loss in kg between participants on the conventional diet and participants on the low-carbohydrate diet at 6 months (n = 118) and at 1 year (n = 126).



*P = 0.003 for comparisons between diet groups by random-coefficient analysis. The difference in weight loss was not significant between the 2 diet groups by 1 year (P = 0.195 before and P > 0.2 after adjustment for baseline variables, by random-coefficient analysis). Error bars represent SDs.

Table 3. Change in Serum Lipids, Glycemic Indices, Creatinine Levels, and Uric Acid Levels at 1 Year*

Variable	Baseline (n = 87)	1 Year (n = 87)	Change (n = 87)	Mean Difference (95% CI)†	P Value‡	Adjusted P Value§
Triglyceride level, mmol/L (mg/dL)				-0.62 (-1.09 to -0.15) [-55 (-96 to -13)]	0.044	0.041
Conventional diet	1.83 ± 0.88 (162 ± 78)	1.88 ± 1.15 (166 ± 102)	0.05 ± 0.96 (4 ± 85)			
Low-carbohydrate diet	2.27 ± 2.31 (201 ± 204)	1.63 ± 1.09 (144 ± 96)	-0.65 ± 1.78 (-58 ± 158)			
Cholesterol level, mmol/L (mg/dL)				0.31 (-0.10 to 0.73) [12 (-4 to 28)]	0.143	0.133
Conventional diet	5.03 ± 0.75 (194 ± 29)	4.84 ± 0.88 (187 ± 34)	-0.21 ± 0.91 (-8 ± 35)			
Low-carbohydrate diet	4.71 ± 1.24 (182 ± 48)	4.87 ± 1.14 (188 ± 44)	0.16 ± 1.11 (6 ± 43)			
HDL cholesterol level, mmol/L (mg/dL)				0.08 (0.01 to 0.16) [3 (0 to 6)]	0.028	0.014
Conventional diet	1.06 ± 0.23 (41 ± 9)	0.93 ± 0.21 (36 ± 8)	-0.13 ± 0.16 (-5 ± 6)			
Low-carbohydrate diet	1.06 ± 0.26 (41 ± 10)	1.04 ± 0.23 (40 ± 9)	-0.03 ± 0.18 (-1 ± 7)			
LDL cholesterol level, mmol/L (mg/dL)				0.23 (-0.13 to 0.57) [9 (-5 to 22)]	0.191	0.341
Conventional diet	3.13 ± 0.73 (121 ± 28)	3.06 ± 0.70 (118 ± 27)	-0.10 ± 0.75 (-4 ± 29)			
Low-carbohydrate diet	2.90 ± 0.83 (112 ± 32)	3.11 ± 1.01 (120 ± 39)	0.18 ± 0.91 (7 ± 35)			
Glucose level for persons without diabetes, mmol/L (mg/dL) (n = 78)				-0.06 (-0.39 to 0.33) [-1 (-7 to 6)]	0.693	0.948
Conventional diet	5.66 ± 0.72 (100 ± 11)	5.72 ± 0.61 (103 ± 11)	0.17 ± 0.67 (3 ± 12)			
Low-carbohydrate diet	5.61 ± 0.72 (99 ± 14)	5.66 ± 0.56 (102 ± 10)	0.17 ± 0.61 (3 ± 11)			
Glucose level for persons with diabetes, mmol/L (mg/dL) (n = 54)				-0.28 (-2.33 to 1.72) [-5 (-42 to 31)]	0.800	0.674
Conventional diet	8.55 ± 2.78 (154 ± 50)	7.44 ± 3.44 (134 ± 62)	-1.17 ± 3.66 (-21 ± 66)			
Low-carbohydrate diet	9.21 ± 3.66 (166 ± 66)	7.66 ± 3.39 (138 ± 61)	-1.55 ± 2.16 (-28 ± 39)			
HBA_{1c} level for persons with diabetes, % (n = 54)				-0.7 (-1.6 to 0.2)	0.102	0.019
Conventional diet	7.3 ± 1.1	7.2 ± 1.9	-0.1 ± 1.6			
Low-carbohydrate diet	7.4 ± 1.6	6.6 ± 1.4	-0.7 ± 1.0			

Effects of Low-Carbohydrate vs Low-Fat Diets on Weight Loss and Cardiovascular Risk Factors

A Meta-analysis of Randomized Controlled Trials

Alain J. Nordmann, MD, MSc; Abigail Nordmann, BS; Matthias Briel, MD; Ulrich Keller, MD; William S. Yancy, Jr, MD, MSH; Bonnie J. Brehm, PhD; Heiner C. Bucher, MD, MPH

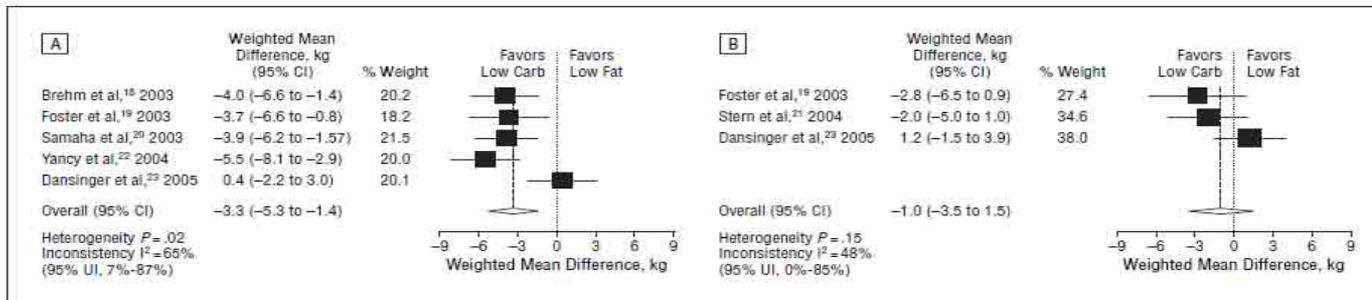


Figure 2. Weighted mean differences in weight loss after 6 (A) and 12 (B) months of follow-up. Carb indicates carbohydrates; CI, confidence interval; UI, uncertainty interval.

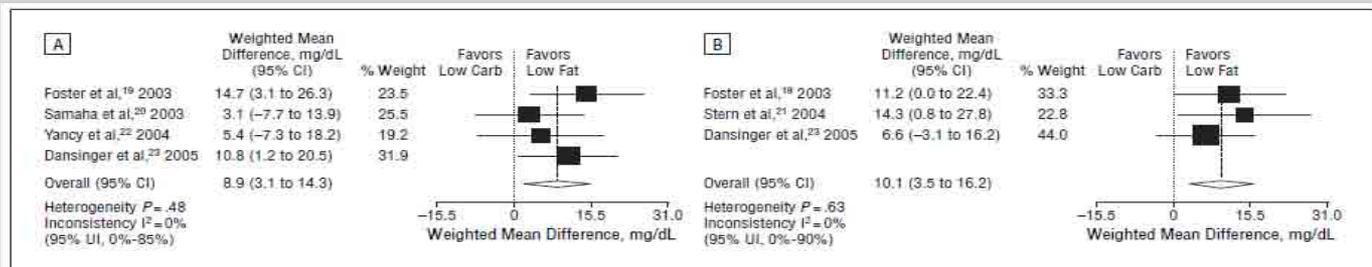


Figure 4. Weighted mean differences in total cholesterol level after 6 (A) and 12 (B) months of follow-up. Carb indicates carbohydrates; CI, confidence interval; UI, uncertainty interval. To convert cholesterol levels to millimoles per liter, multiply by 0.0259.

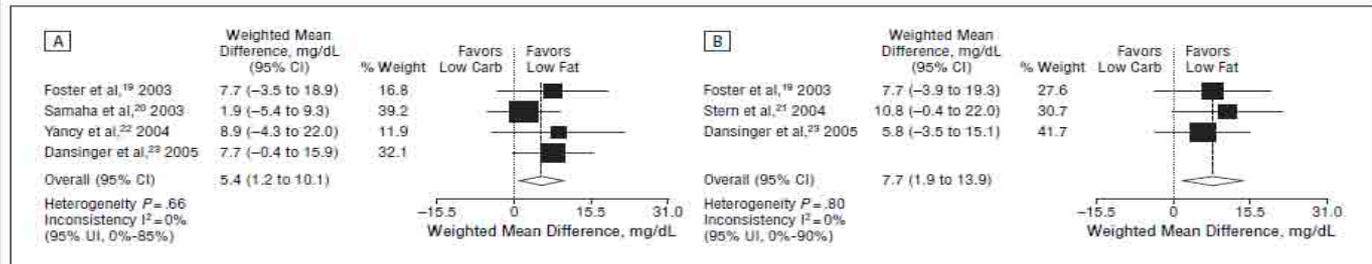


Figure 5. Weighted mean differences in low-density lipoprotein cholesterol level after 6 (A) and 12 (B) months of follow-up. Carb indicates carbohydrates; CI, confidence interval; UI, uncertainty interval. To convert cholesterol levels to millimoles per liter, multiply by 0.0259.

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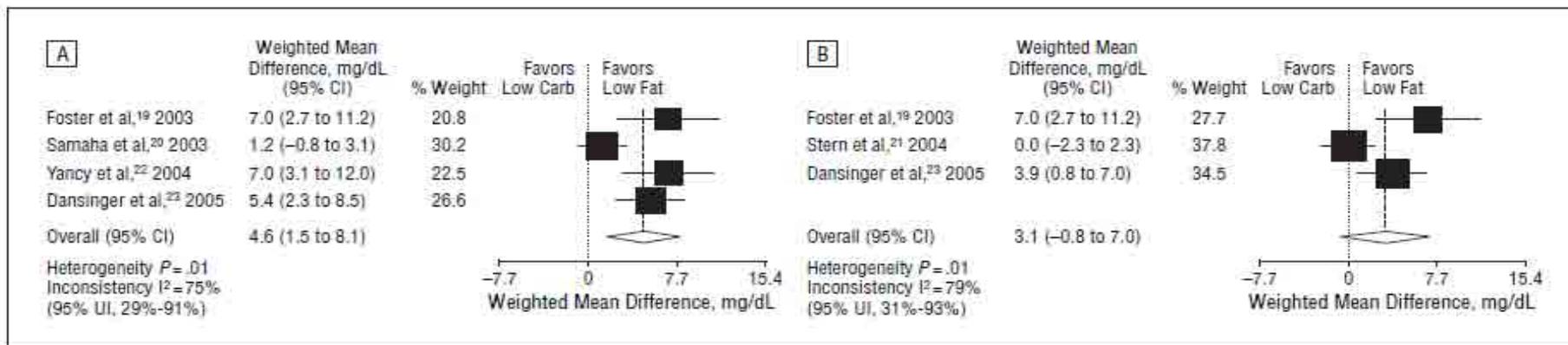


Figure 6. Weighted mean differences in high-density lipoprotein level after 6 (A) and 12 (B) months of follow-up. Carb indicates carbohydrates; CI, confidence interval; UI, uncertainty interval. To convert cholesterol levels to millimoles per liter, multiply by 0.0259.

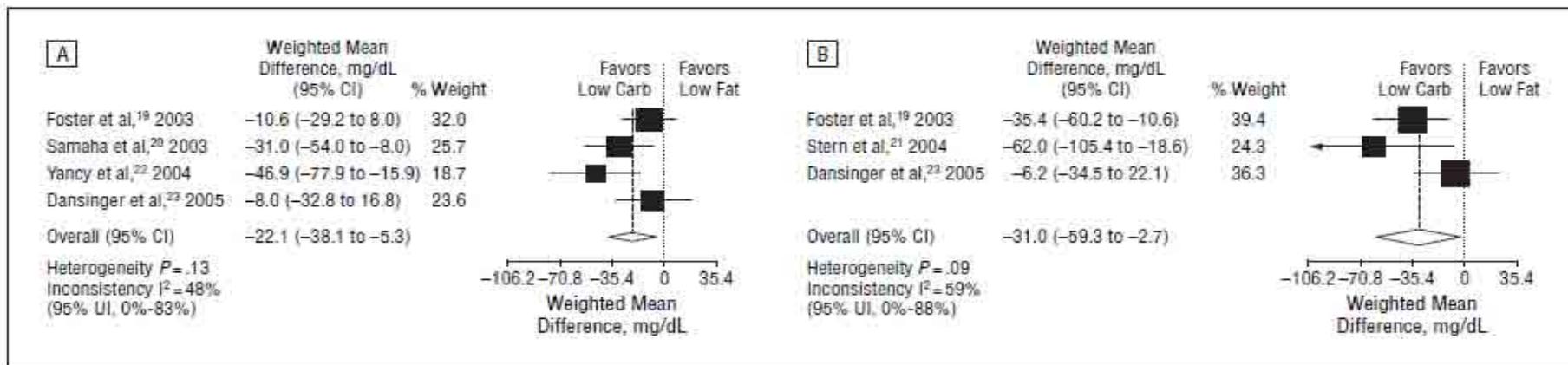


Figure 7. Weighted mean differences in triglyceride level after 6 (A) and 12 (B) months of follow-up. Carb indicates carbohydrates; CI, confidence interval; UI, uncertainty interval. To convert triglyceride levels to millimoles per liter, multiply by 0.0113.



Long-term Effects of a Lifestyle Intervention on Weight and Cardiovascular Risk Factors in Individuals With Type 2 Diabetes Mellitus

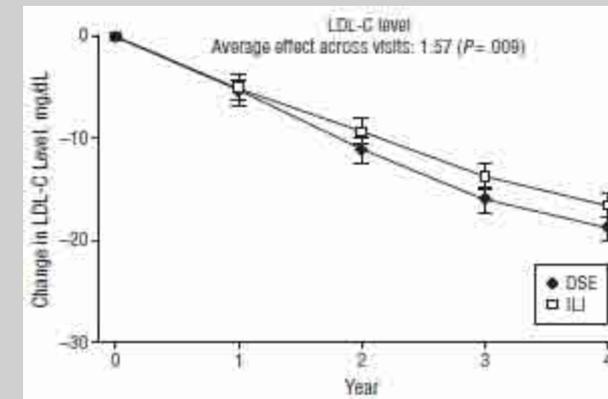
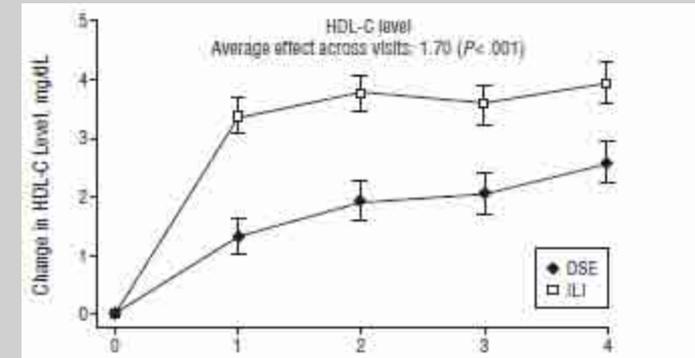
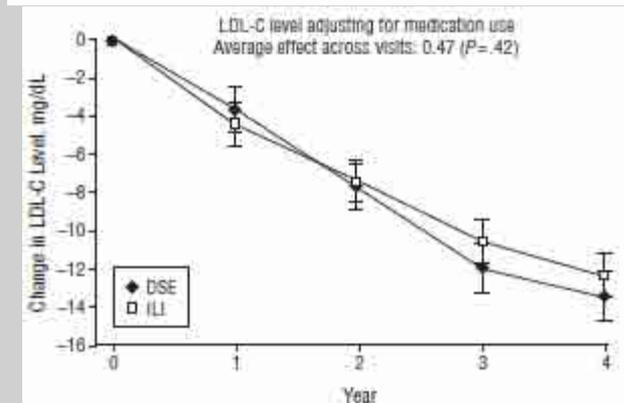
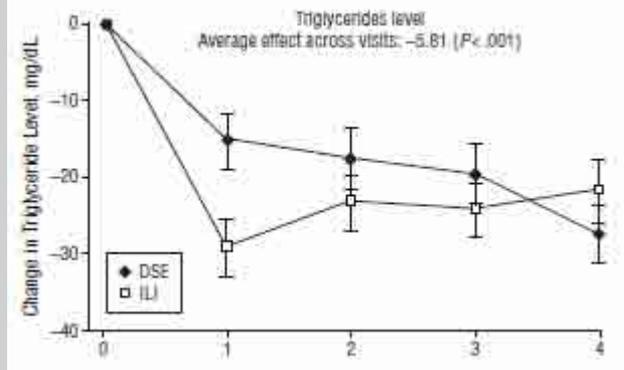
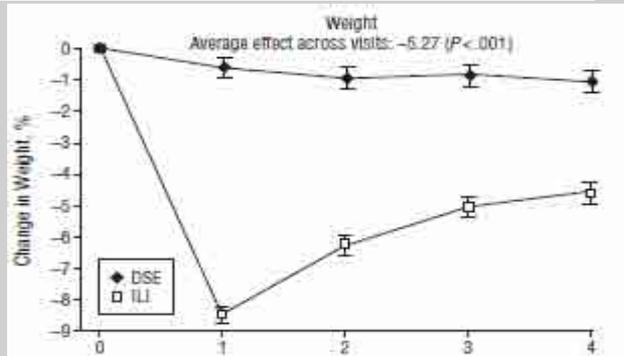


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Four-Year Results of the Look AHEAD Trial *The Look AHEAD Research Group*

n=5145 overweight or obese pts with type 2 DM

- ILI group: <30% of total calorie from fat (<10% from saturated fat) and a minimum of 15% of total calories from protein; 175 min of physical activity per week; behavioral strategies.
- DSE group: routine information on diet and physical activity





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REVIEW

Low glycaemic index diets and blood lipids: A systematic review and meta-analysis of randomised controlled trials

L.M. Goff^{a,*}, D.E. Cowland^a, L. Hooper^b, G.S. Frost^c

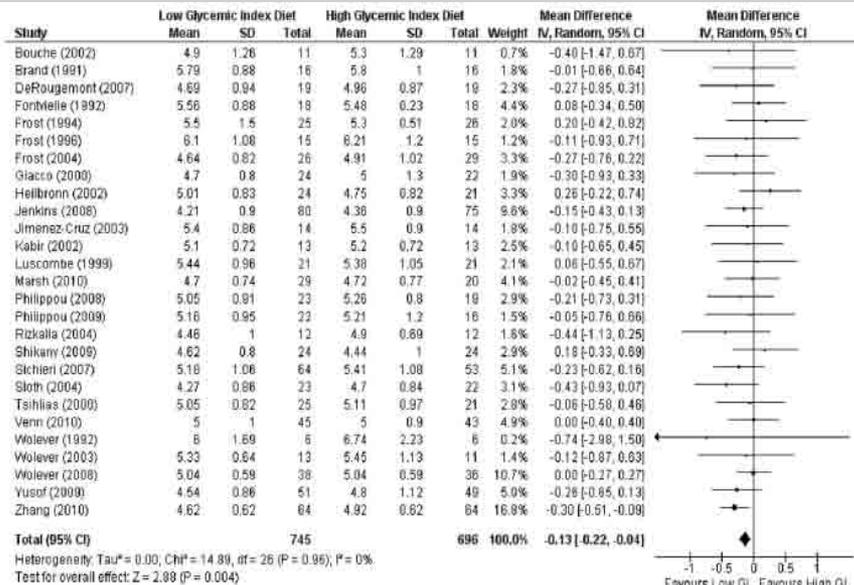


Figure 1 Effects of low and high glycaemic index dietary interventions on total cholesterol concentrations (mmol/L). Analysis includes all studies which assessed total cholesterol. ., effect estimate of each study, horizontal line denote the 95%CI; ♦, combined overall effect; CI, confidence interval; GI, glycaemic index; random, random effects model; mean difference, mean of difference in post-intervention cholesterol/LDL-C concentrations between low GI and high GI groups; SD, standard deviation.

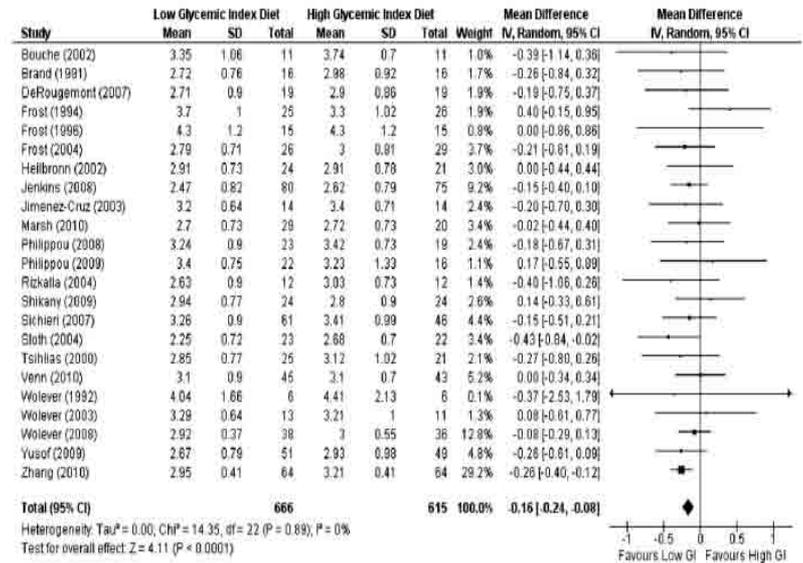


Figure 2 Effects of low and high glycaemic index dietary interventions LDL-cholesterol (mmol/L). Analysis includes all studies which assessed LDL-cholesterol. ., effect estimate of each study, horizontal line denote the 95%CI; ♦, combined overall effect; CI, confidence interval; GI, glycaemic index; random, random effects model; mean difference, mean of difference in post-intervention cholesterol/LDL-C concentrations between low GI and high GI groups; SD, standard deviation.

Integratori alimentari: definizione

Gli integratori alimentari sono definiti come:

“prodotti alimentari destinati ad integrare la comune dieta e che costituiscono una fonte concentrata di sostanze nutritive, quali le vitamine e i minerali, o di altre sostanze aventi un effetto nutritivo o fisiologico, in particolare, ma non in via esclusiva, aminoacidi, acidi grassi essenziali, fibre ed estratti di origine vegetale, sia monocomposti che pluricomposti, in forme predosate”.

Sono solitamente presentati in capsule, compresse, bustine, flaconcini e simili, e possono contribuire al benessere dell'organismo ottimizzando lo stato nutrizionale oppure contribuendo al benessere con l'apporto di nutrienti o sostanze di altro tipo.

Direttiva 2002/46/CE, attuata con il decreto legislativo 21 maggio 2004, n. 169

Integratori alimentari nel DM 2



- Fibre idrosolubili
- Acidi grassi poli-insaturi (omega 3) e mono-insaturi
- Fitosteroli e Fitostanoli
- Proteine di soia
- Isoflavoni

- Policosanoli
- Estratti di riso rosso fermentato

Possono essere usati da soli o in associazione ai farmaci ipolipemizzanti per raggiungere gli obiettivi terapeutici.

Nei pazienti intolleranti alle statine o fibrati.



Systematic Review/Meta-analysis

The Impact of Dietary Changes and Dietary Supplements on Lipid Profile

Jingbo Huang, MD, PhD,^a Jiri Frohlich, MD, FRCPC,^{a,b} and
Andrew P. Ignaszewski, MD, FRCPC, FACC^{a,c}

Table 11. Level of evidence and size of treatment effect for dietary interventions

Level of Evidence	Size of treatment effect			
	Class I	Class IIa	Class IIb	Class III
	Benefit >>>> risk Little or no conflicting evidence	Benefit >> risk Some conflicting evidence; additional studies with focused objectives needed	Benefit ≥ risk More conflicting evidence; additional studies with broad objectives needed	Risk ≥ benefit No additional studies needed
Level A Multiple populations (3–5) evaluated Data derived from multiple RCTs or meta-analyses	Fully recommend Soy protein High-fibre diet Phytosterols Whole grain foods Low-fat diet Mediterranean diet Portfolio diet Omega-3 fatty acids	Reasonable to recommend Policosanol Red yeast rice extract	Probably not recommend Guggulipid	Cannot recommend Garlic
Level B Limited populations evaluated Data derived from single RCT or nonrandomized studies	Might be useful Nuts Green tea Red wine High-carbohydrate diet High-protein diet	Might be useful	Not recommended	Not recommended Chromium MPPG Vitamin C Tocotrienols Absorbitol
Level C Very limited population evaluated Only consensus opinion of experts, case studies, or standard of care	Might be useful	Not recommended	Not recommended	Not recommended

Summary of dietary interventions' daily dose, effects on lipid profile, side effects, level of evidence, and size of treatment effect derived from the reviewed studies

Dietary intervention	Daily dose	Effects on lipid levels	Side effects	Level of evidence	Size of treatment effect
Soy protein powder	30-50 g	↓ TC by 2%-10%	None	Level A	Class I
Isoflavones	50-100 mg	↓ TC by 2%-10%	None	Level A	Class I
		↓ LDL-C by 3%-11%			
Soluble fibre	5-15 g	↓ TC and by 2%-12%	None	Level A	Class I
		↓ LDL-C by 5%-20%			
Uncooked oatmeal	60 g	↓ TC by 4%-6%	None	Level A	Class I
		↓ LDL-C by 2%-6%			
Plant sterols	1-3 g	↓ TC by 2%-13%	None	Level A	Class I
		↓ LDL-C by 4%-13%			
AHA Step I and Step II diets		↓ TC and LDL-C by 5%-10%	None	Level A	Class I
Mediterranean diet		↓ TC and LDL-C by 5%-15%	None	Level A	Class I
		↑ HDL-C by 3%-15%			
Portfolio diet		↓ TC and LDL-C by 10%-20%	None	Level A	Class I
Omega-3 fatty acids	1-2 g	↓ TG level by 3%-9%	GI symptoms, skin rash/itching	Level A	Class I
Nuts	50-80 g	↓ LDL-C by 5%	None	Level B	Class I
Green tea extract	1.2 g	↓ TC by 2.3%	None	Level B	Class I
		↓ LDL-C by 10%			
		↓ TG by 6%			
Red wine	300 mL for men 200 mL for women	↑ HDL-C by 13%	None	Level B	Class I
High-carbohydrate diet	50%-60% of total energy (not > 60%)	↓ TC, LDL and TGs by 5%-10%	None	Level B	Class I
High-protein diet	25% of total energy	↓ TC, LDL, and TGs by 5%-10%	None	Level B	Class I
Policosanol	5-20 mg	↓ TC by 12%-20%	Polyuria, polyphagia, insomnia, headache	Level A	Class IIa
		↓ LDL-C by 15%-25%			
		↑ HDL-C by 8%-30%			
Red yeast rice extract capsule	1-2 g	↓ TC by 44%	GI symptoms, myalgias, elevation of AKP and ALT	Level A	Class IIa
		↓ LDL-C by 7%-25%			
		↓ TGs by 7%-44%			
		↑ HDL-C by 0%-17%			
Guggulipid	100 mg	↓ TC by 11.7%	Headache, GI symptoms, skin hypersensitivity reaction	Level A	Class IIb
		↓ LDL-C by 12.5%			
Garlic powder/tablet/extract	600-1000 mg	None	GI symptoms, headaches, smell	Level A	Class III

Current Nutritional Recommendations of Health Diabetes Organizations

Organization	Weight management	Macronutrients % of total daily energy	Source of carbohydrates	Source of fat % of total daily energy
American Diabetes Association (ADA) [16]	In overweight and obese insulin resistant individuals, modest weight loss may improve insulin resistance. For weight loss, either low-carbohydrate or low-fat calorie-restricted diets may be effective in the short term (up to 1 year).	Protein – 15–20%. The best mix of carbohydrate, protein, and fat appears to vary depending on individual circumstances. Total caloric intake must be appropriate to weight management goals.	Carbohydrate from fruits, vegetables, whole grains, legumes, and low-fat milk is encouraged for good health. The use of glycemic index and load may provide a modest additional benefit.	Saturated fat to <7% Minimize Intake of trans fat. Limit cholesterol to <200 mg/day. 2+ servings of fish per week to provide n-3 polyunsaturated fatty acids
European Association for the Study of Diabetes (EASD) [17]	For BMI >25 kg/m ² , reduce caloric intake and increase energy expenditure.	Protein – 10–20%. Fat – up to 35%. Carbohydrates – the remainder 45–60%.	Vegetables, legumes, fruits and wholegrain cereals. Dietary fiber and low glycemic index particularly important to individuals in the upper end of recommended range.	Saturated and trans-unsaturated fats <8–10%, monounsaturated fat 10–20% of daily energy, polyunsaturated fatty acids up to 10% 2–3 servings of fish a week and plant sources of n-3 fatty acids.



Dietary recommendations from the NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults



Roma,
9-11 novembre 2012

Nutrient	Recommended intake
Saturated fat*†	<7% of total calories
Monounsaturated fat	Up to 20% total calories
Polyunsaturated fat	Up to 10% total calories
Total fat	25–35% or less of total calories
Carbohydrate‡	50–60% or more of total calories
Fiber	20–30 g/day
Protein	Approximately 15% of total calories
Cholesterol†	<200 mg/day

*The combination of *trans* fatty acids and saturated fat <7%. †If LDL cholesterol is not elevated and there is no preexisting cardiovascular disease, saturated and *trans* fat intake of <10% of total calories; cholesterol <300 mg/day. ‡Complex carbohydrates from a variety of vegetables, fruits, and whole grains. Adapted from 76.

Terapia dietetica della dislipidemia nel DM 2

- Dieta ipocalorica se paziente sovrappeso od obeso (80-90% dei casi) (deficit di 500-1000 Kcal/die rispetto al fabbisogno calorico)+ esercizio fisico (150 -180 min/settimana)
- Apporto qualitativo dei macronutrienti (% intake calorico totale giornaliero):
 1. 45-60% carboidrati complessi
 2. 15-20% proteine
 3. <30% lipidi (acidi grassi saturi<7%, monoinsaturi 10-20%, poli-insaturi<10%)
- Colesterolo <200 mg/die
- Fibre 20-30 g die
- Eventuale apporto di integratori: fibre idrosolubili, omega-3, fitosteroli, proteine di soia, isoflavoni

Conclusioni I

Dieta

- La terapia dietetica/nutrizionale è un presidio terapeutico fondamentale nella dislipidemia del diabete tipo 2.
- Evidenze a favore di dieta mediterranea, ipolipidica e portfolio
- L'effetto ipolipemizzante è generalmente modesto (5-15%) ma può consentire il raggiungimento degli obiettivi terapeutici lipemici
- Il beneficio terapeutico della dieta va oltre l'effetto ipolipemizzante e si traduce in un migliore compenso glicemico e pressorio.

Conclusioni II

Integratori dietetici

- Gli integratori alimentari rappresentano un ausilio nella terapia ipolipemizzante del diabete tipo 2 nei casi di intolleranza/inefficacia della terapia dietetica e farmacologica
- Evidenze a favore di fibre idrosolubili, omega 3, fitosteroli/stanoli, proteine di soia, isoflavoni
- L'effetto ipolipemizzante è generalmente modesto (5-15%)



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grazie dell'attenzione