

Rediscovery of Hydroxycitric Acid a Versatile Nutraceutical

by Vladimir Badmaev MD, PhD

- *Potassium Hydroxycitrate for the Suppression of Appetite and Induction of Weight Loss. United States Patent 5,783,603 (1998)
- * Process for the Production of Potassium HCA, and Composition Containing HCA. United States Patent 6,770,782 B1 (2004)
- * Bioavailable composition of Natural and Synthetic HCA. Patent (AU) 773081 (2004) - Garcitrin ®
- * Bioavailable composition of Natural and Synthetic HCA. Patent (NZ) Patent No. 518116 (2005) - Garcitrin ®
- * Bioavailable composition of Natural and Synthetic HCA. United States Patent 7,063,861 (2006) - Garcitrin ®
- * Bioavailable composition of Natural and Synthetic HCA. Europe (EC). Patent No. 1 254 209 (2007) - Garcitrin ®
- * Bioavailable composition for reduction of body fat Japanese Patent Office JP,2008-110996,A (2008) - Garcitrin ®



SABINSA CORPORATION

Citrin®



- Source
 - *Garcinia cambogia* (fam. Clusiaceae)
- Plant Part Used
 - Fruits
- Active Constituents
 - (-) Hydroxycitric acid
 - (-) HCA

Salient Features of HCA and Citrin Products:

- Safe in preclinical and clinical studies; time proven food derived (Citrin[®] , Citrin[®]K , GarCitrin[®])
- Cardiovascular and metabolic benefits (Citrin[®])
- Improvement in aerobic exercise (application in sports nutrition) (Citrin[®]K , GarCitrin[®])
- Prevention and treatment of urinary stones (Citrin[®]K)
- Increases Fat Utilization (Citrin[®] , Citrin[®]K , GarCitrin[®])
- Citrin[®]K has potential as a food supplement in cancer prevention and cancer therapy

Safety

- The LD50 value established by Hoffman LaRoche for HCA is 4000mg/kg (comparable to the value for a known GRAS [Generally Recommended As Safe] item, citric acid)
 - One may compare this value with a daily recommended dose of HCA established through our clinical studies to be 750 mg/person/day

Safety

- One of the key nutraceutical products developed by Sabinsa is a brand of natural hydroxycitric (HCA) acid, Citrin[®], present on the nutritional market in the US, Europe, Japan and Australia for more than a decade now
- Based on our extensive experience with HCA we recommend use of this product in the USA as a category of Food for Special Dietary Use (FSDU), or as a Dietary Supplement under the new Dietary Supplement Health and Education Act of 1994 (DSHEA)

Safety

- Based on our 8 weeks and up to 36 months clinical study of Citrin® in overweight patients, some of which had poor glucose tolerance, we can report that Citrin® in a dose of 1500 mg [calculated as 750 mg of pure HCA] did not affect the overall clinical status of the patients and did not alter blood biochemistry in a detrimental way

Safety

- In addition, the blood chemistry parameters like blood electrolytes, in particular sodium, potassium, chloride, calcium and phosphorus, blood urea nitrogen [BUN], creatinine, plasma proteins and liver enzymes were not altered even after several months administration of Citrin®

Safety

- In a subchronic study, the gavage administration of proprietary preparation calculated as 1250 mg/kg/day of pure HCA for a period of 90 days caused a significant decrease in body weight and reduction in feed consumption without any adverse effects
- The structure, mechanism of action, long history of use of HCA and other toxicity studies indicate that HCA is unlikely to cause reproductive or developmental effects

Soni MG, Burdock GA, Preuss HG, Stohs SJ, Ohia SE, Bagchi
DFood Chem Toxicol. 2004 Sep;42(9):1513-29

Safety

- HCA derived from proprietary preparation was not mutagenic in the presence or absence of metabolic activation in Ames genotoxicity assays in strains TA98 and TA102
- There is sufficient qualitative and quantitative scientific evidence, including animal and human data suggesting that intake of HCA at levels up to 2800 mg/day is safe for human consumption

Soni MG, Burdock GA, Preuss HG, Stohs SJ, Ohia SE, Bagchi
DFood Chem Toxicol. 2004 Sep;42(9):1513-29

Safety

- 51 mmol HCA/kg diet (389 mg HCA/kg BW/d) was deemed to be the no observed adverse effect level (NOAEL)

[Saito M](#), [Ueno M](#), [Ogino S](#), [Kubo K](#), [Nagata J](#), [Takeuchi M](#). Food Chem Toxicol. 2005 Mar;43(3):411-9.

Clinical Studies

Chronological list of research and/or publications of clinical and preclinical studies of HCA sponsored by Sabinsa.

1. Conte AA (1993 Summer) A Non-Prescription Alternative in Weight Reduction Therapy. The Bariatrician: 17-19.
2. AA (October 1994) The effects of (-) - Hydroxycitrate And Chromium (GTF) On Obesity. J Amer Coll Nutr. 13 (5): 535 [Abstract 60].
3. Katts GR, Pullin D, Parker LK, Keith PL, Keith S (March 1995) Reduction Of Body Fat As A Function Of Taking A Dietary Supplement Containing Garcinia Cambogia Extract, Chromium Picolinate And L-Carnitine - A Double Blind Placebo Controlled Study. Abstract/Poster presented at a symposium on obesity organized by the Mexican Sociedad Medical del Sureste para el Estudio de la Obesidad, March 4, 1995, Merida, Yucatan, Mexico.
4. Conte AA (June/July 1995) Effective Natural Weight Loss Techniques. Alternative Complementary Therapies. 1 (4): 212-215.
5. Badmaev V, Majeed M (July 1995) Open Field, Physician Controlled, Clinical Evaluation Of Botanical Weight Loss Formula Citrin ®. Nutracon 95: Nutraceuticals, Dietary Supplements And Functional Foods. Day One (Sponsored by Global Business Research LTD). Published in the symposium book.



Clinical Studies

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6. Thom E (May 1996) Hydroxycitrate (HCA) In The Treatment Of Obesity. Int J Obesity. 20 (4): 75 [Abstract /Poster 08-193-WP1 at 7th European Congress on Obesity in Barcelona, Spain 14-17 May, 1996].
7. Krishna Puttaparthi, Thomas Rogers, Nabil A Eishourbagy, Moshe Levi, and Joel Z. Melnick, Renal ATP Citrate Lyase (ATP CL) Protein Localizes Throughout the Nephron and Increases Only in the Proximal Tubule with Chronic Metabolic Acidosis (CMA) Northwestern University Medical School, Chicago, IL.
8. [Heymsfield SB](#), [Allison DB](#), [Vasselli JR](#), [Pietrobelli A](#), [Greenfield D](#), [Nunez C](#). Garcinia cambogia (hydroxycitric acid) as a potential antiobesity agent: a randomized controlled trial. Department of Medicine, Obesity Research Center, St Luke's-Roosevelt Hospital, Columbia University. JAMA. 1998 Nov 11;280(18):1596-600.
9. [Badmaev V](#), [Majeed M](#), [Conte AA](#). Garcinia cambogia for weight loss. JAMA. 1999 Jul 21;282(3):233-4;
10. Badmaev V, Majeed M, Conte AA. Open field, physician controlled clinical evaluation of a botanical weight loss formula based on Garcinia cambogia derived (-)hydroxycitric acid. NutraCos Vol. 1, No. 1 (Jan/Feb);2002.
11. Badmaev V, Majeed M, Conte AA. Twelve-week, Double-blind, Clinical Comparison of Citrin® (C) and New Citrin® (NC) 2002. Prepared for publication 2006.



Cardiovascular and metabolic benefits of HCA derived from Citrin®

- Significant ($p < 0.05$) decrease of elevated blood levels of triglycerides (triglyceride levels before Citrin® intake was 166.5 mg/dl and after the 8 weeks was 154.8 mg/dl)
- Significant ($p < 0.01$) increase in HDL (“good cholesterol”) blood levels (increase after 8 weeks of Citrin® from value of 47.4 mg/dl to value of 50.4 mg/dl)
- The 8 week Citrin® intake lowered the risk of coronary heart disease [CHD] (as assessed from the blood lipid profile) significantly ($p < 0.01$) for the entire population studied. The risk index decreased from a mean value of 0.998 to a mean value of 0.90

Improvement in aerobic exercise; application in sports nutrition

- HCA replenishment of glycogen, and any nutritional intervention to increase stores of glycogen is particularly desired in the training
- In experiments carried out with laboratory animals at the Department of Food Sciences and Technology, Kyoto University, Faculty of Agriculture, Japan, rodents were fed with 5 mg of HCA for 3 days; animals benefited with higher content of glycogen in the muscles as compared to controls

HCA increases Fat Utilization

- Short-term ingestion of Hydroxycitric acid was found to have beneficial effects on endurance exercise performance and fat metabolism in untrained women
- Six subjects ingested 250 mg of HCA or placebo for 5 days and then participated in cycle ergometer exercise
- HCA tended to decrease the respiratory exchange ratio (RER) and carbohydrate oxidation during 1 hour of exercise
- Exercise time to exhaustion was significantly enhanced ($p < 0.05$)

Improvement in aerobic exercise; application in sports nutrition

- Anticatabolic effect
 - HCA sparing effect on proteins: hepatic glycogen level are high, the rate of deamination of amino acids is depressed, and the amino acids are thus preserved for other uses
- HCA detox effect
 - added benefit of high glycogen in the liver is an enhancement of the detox processes, e.g. acetylation and glucuronide conjugation
 - Properly functioning detox mechanisms in the liver are particularly important in handling metabolic demands during training and the heavy nutritional supplementation that is usually recommended in training

HCA in Urinary Stone Prevention

- Urinary citrate from Krebs cycle plays an important role in preventing formation of calcium-containing kidney stones by chelating calcium, preventing crystallization and precipitation of calcium and calcium oxalate complex formation
- Low urinary citrate occurs in approximately half of patients with kidney stones. One of the possible mechanisms leading to low levels of urinary citrate is due chronic metabolic acidosis and hypokalemia (low levels of potassium) associated with adaptive increases in ATP citrate lyase
- Joel Z. Melnick Northwestern University Medical School, Chicago, IL.

HCA in Urinary Stone Prevention

- ATP citrate lyase is an intracellular enzyme which cleaves citrate to oxaloacetate and acetyl CoA, thus its excess activity would lead to low levels of biologically available citrate
- Drinking water supplied Citrin®K was shown to inhibit ATP citrate lyase and improve low levels of urinary citrate (hypocitraturia) in rats
- Citrin®K increased urinary citrate excretion by 5 fold as compared to the untreated animals
- Krishna Puttaparthi, Thomas Rogers, Nabil A Eishourbagy, Moshe Levi, and Joel Z. Melnick, Renal ATP Citrate Lyase (ATP CL) Protein Localizes Throughout the Nephron and Increases Only in the Proximal Tubule with Chronic Metabolic Acidosis (CMA) Northwestern University Medical School, Chicago, IL.

Potential of HCA derived from Citrin®K as a food supplement in cancer prevention and cancer therapy

- One of the important directions of research into the mechanisms of cancer development is the link between nutrition and the cancer; in particular the association between dietary fat and the origins of human colorectal, breast, prostatic, ovarian and endometrial cancers
- Many animal studies have shown a definite positive correlation between dietary fat and the rate of tumor growth and the severity of metastases

Potential of HCA derived from Citrin®K as a food supplement in cancer prevention and cancer therapy

- It is a recognized fact that the rate of lipid synthesis in tumor cells is quite rapid. This phenomenon can be understood, because rapidly dividing cells not only need fresh copies of DNA and proteins, but they also require the security of new biomembranes composed of phospholipids and cholesterol
- The cholesterol intermediate, Farnesyl-PP, has been implicated as a factor promoting cell proliferation¹
 - A covalently attached farnesyl group is essential for the normal functioning of the Ras protein, a key regulator of cell division in normal cells

Goldstein, JL and Brown, MS. Nature. 343: 425-430, 1990).

Potential of HCA derived from Citrin®K as a food supplement in cancer prevention and cancer therapy

- Excessive activity of Ras produces uncontrolled cell growth, and activated Ras genes are the most frequently identified oncogenes in human tumors. Farnesyl-PP is an intermediate in the cholesterol synthesis pathway and must be synthesized de novo within the cell where it is to be used

Potential of HCA derived from Citrin®K as a food supplement in cancer prevention and cancer therapy

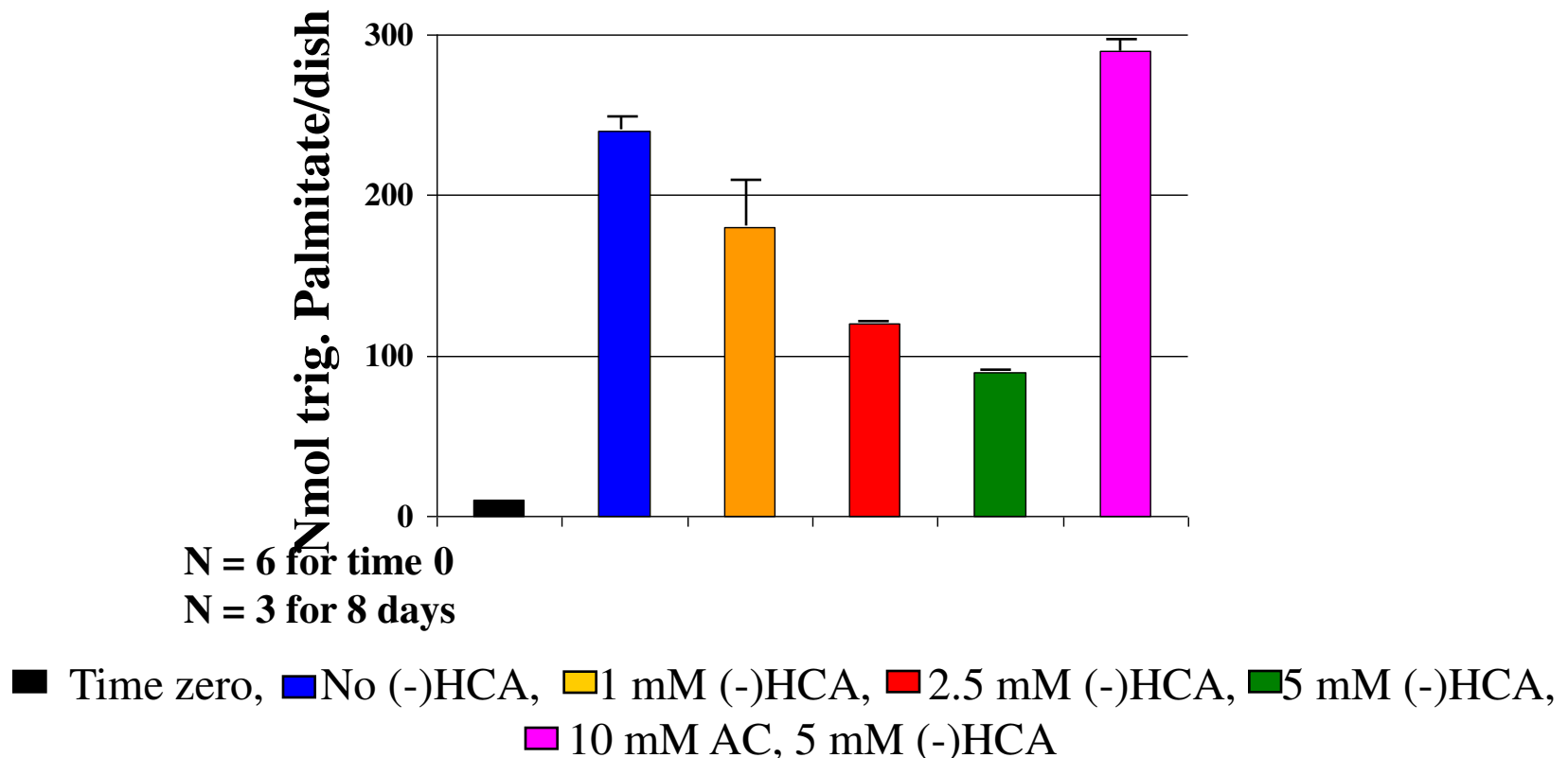
- Citrin®K incubated with cancer cell culture (hepatoma) showed dose dependent decrease in the lipid content produced by cultured cells and also inhibited the cell growth. This mechanism was dependent on inhibition of the enzyme citrate lyase

George Washington University, Department of Physiology,
Washington D.C. / Sabinsa Corporation

Effect of HCA from Citrin[®]K on synthesis of triglyceride palmitate during growth stage of HepG2 cells

The addition of 10 mM acetate with the drug represents direct carbon contribution to the intracellular pool of acetyl-CoA molecules.

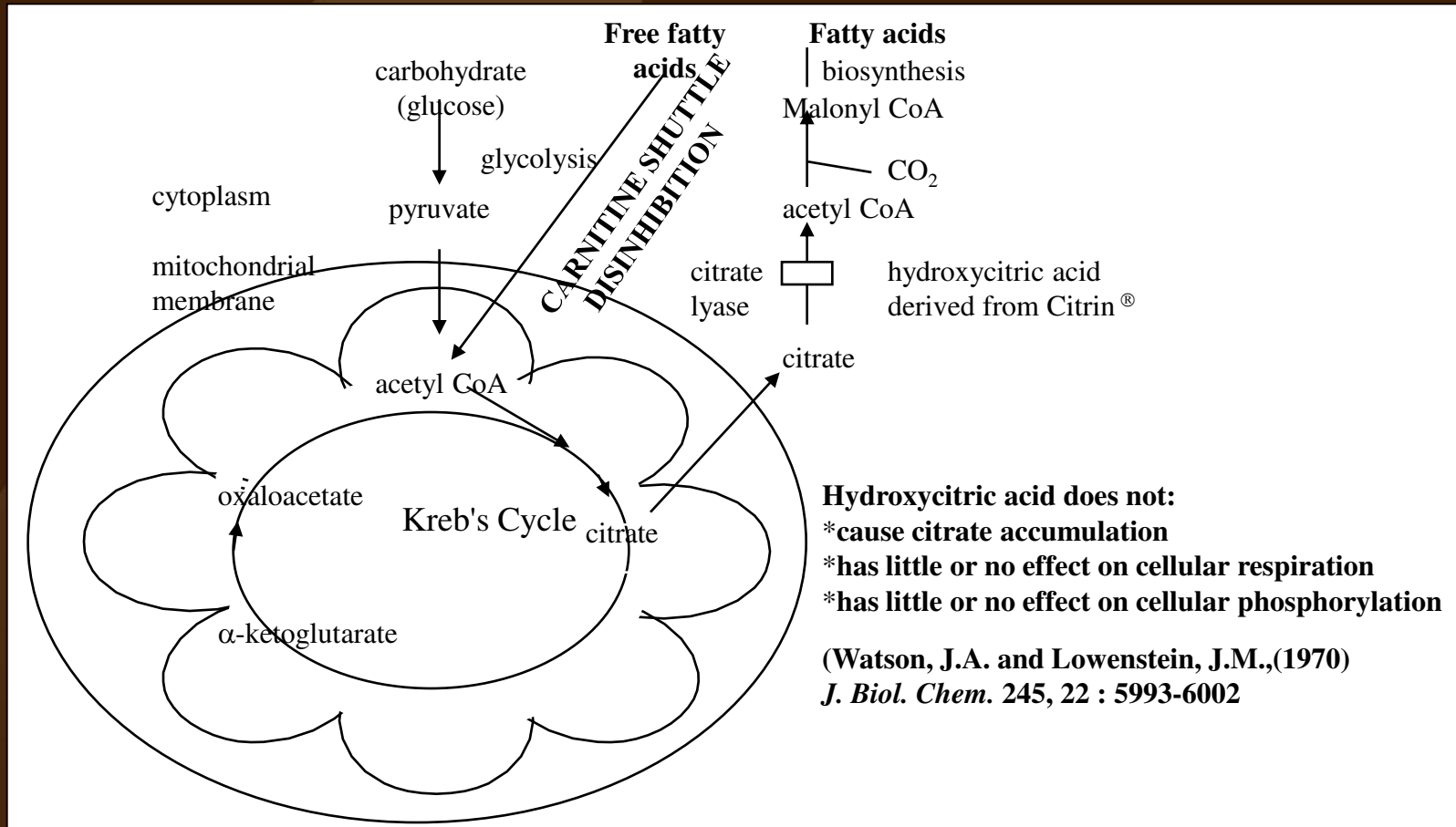
George Washington University, Department of Physiology, Washington D.C. / Sabinsa Corporation



Potential of HCA derived from Citrin®K as a food supplement in cancer prevention and cancer therapy

- Citrin®K increased catabolism of glutamine in the cancer cells making it less available for lipid synthesis. Recent experimental findings show that glutamine can contribute 20 to 40% of the acetyl CoA utilized for lipid synthesis in the cancer cells. This experiment shows that Citrin®K can block lipid synthesis independently of its other mechanism of inhibiting the enzyme citrate lyase
- It is proposed that Citrin®K blocks de novo lipogenesis of tumor cells, and can be used in preventing cancer growth in vitro

Effects of HCA on Metabolism



How to improve HCA?

Definition of Garcinol

- Garcinol is a polyisoprenylated benzophenone derived from *Garcinia* sp.
- A known anti-oxidant
 - (emulsified garcinol suppressed superoxide anion comparably to DL-alpha-tocopherol)
- Anti-carcinogen
- Has anti-microbial properties

Pre-Clinical evaluation of Garcinol

Table 1. Effect of oral administration of garcinol (GAR), hydroxycitric acid (HCA) and combination of garcinol and hydroxycitric acid on body weight, food and fluid consumption in SKH-1 mice

Group	5 weeks	7 weeks	10 weeks
	Body weight (gm; Mean±SE)		
1. Control	32.3±0.67	34.5±0.99	37.0±1.49
2. 0.05% GAR	32.8±0.37	33.9±0.14	36.4±0.55
3. 1% HCA	32.5±0.42	34.5±0.59	36.8±0.33
4. (2) + (3)	31.2±0.20	33.5±0.58	34.9±0.88
	Food consumption (gm/mouse/day; Mean±SE)		
1. Control	5.25±0.33	5.09±0.28	5.16±0.25
2. 0.05% GAR	4.98±0.17	5.09±0.46	5.26±0.17
3. 1% HCA	5.74±0.13	6.49±0.07	6.93±0.21
4. (2) + (3)	6.55±0.20	8.03±1.45	9.31±1.12
	Water consumption (gm/mouse/day; Mean±SE)		
1. Control	3.75±0.04	3.42±0.34	3.80±0.22
2. 0.05% GAR	3.66±0.07	3.63±0.05	3.73±0.17
3. 1% HCA	3.72±0.08	3.74±0.04	3.84±0.09
4. (2) + (3)	3.68±0.08	3.86±0.08	3.94±0.08

Pre-Clinical evaluation of Garcinol

Table 2. Effect of 10 week oral administration of garcinol (GAR) and hydroxycitric acid (HCA) on azoxymethane (AOM)-induced formation of aberrant colonic crypts (AC) and accumulation of fat in abdomen in CF-1 mice

Group	Body Weight (gm)	AC per colon	Parametrial fat (gm)	Retroperitoneal fat (gm)
1. Control	38.8± 1.52	11.4	1.33±0.19	0.95±0.11
2. 0.05% GAR	37.3±1.07	7.8 (31.6%)	1.21±0.18	0.85±0.01
3. 1% HCA	37.9±0.66	7.9 (30.7%)	1.24±0.06	0.79±0.04
4. (2) + (3)	36.1±0.48	8.5 (25.4%)	0.95±0.10	0.70±0.13

Rutgers / Sabinsa (2000) Preclinical Study

Twelve-week, Double-blind, Clinical Comparison of Citrin® (C)* and New Citrin (NC)** Garcitrin ®

* Bioavailable composition of Natural and Synthetic HCA. Patent (AU) 773081 (2004)

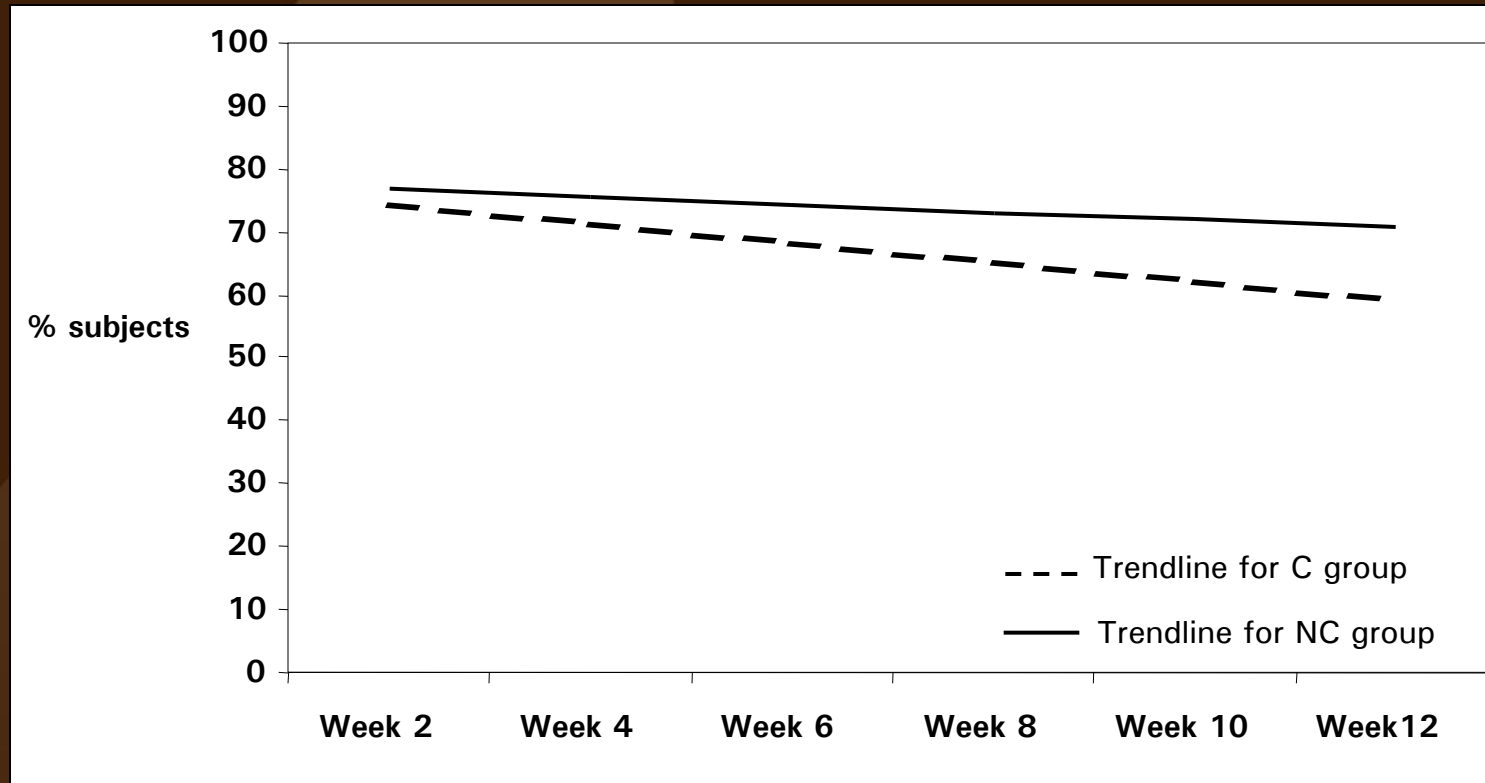
* Bioavailable composition of Natural and Synthetic HCA. Patent (NZ) Patent No. 518116 (2005)

* Bioavailable composition of Natural and Synthetic HCA. United States Patent Notice of Allowance Issued (2006)

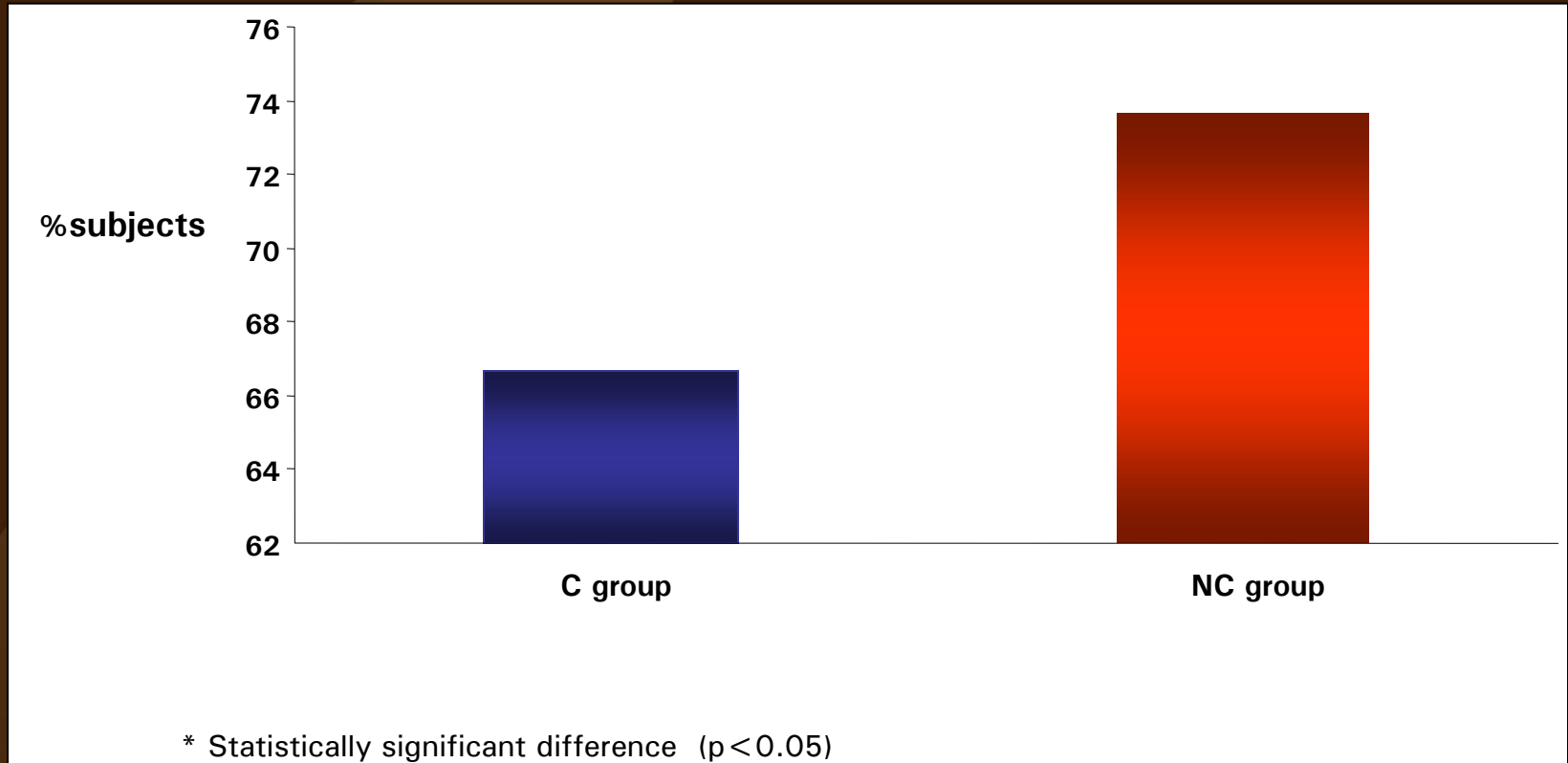
Study Design

- Patients: 46 overweight healthy women
- Dose: 500 mg (C) tid; 500 mg (NC) tid
- Duration 12 weeks
- Conditions: no change in diet and exercise
- Clinical evaluation time points: 0,2,4,6,8,10,12 weeks
- Safety parameters: physical exam, PR, BP
- Efficacy parameters: body weight, body composition, appetite and energy levels

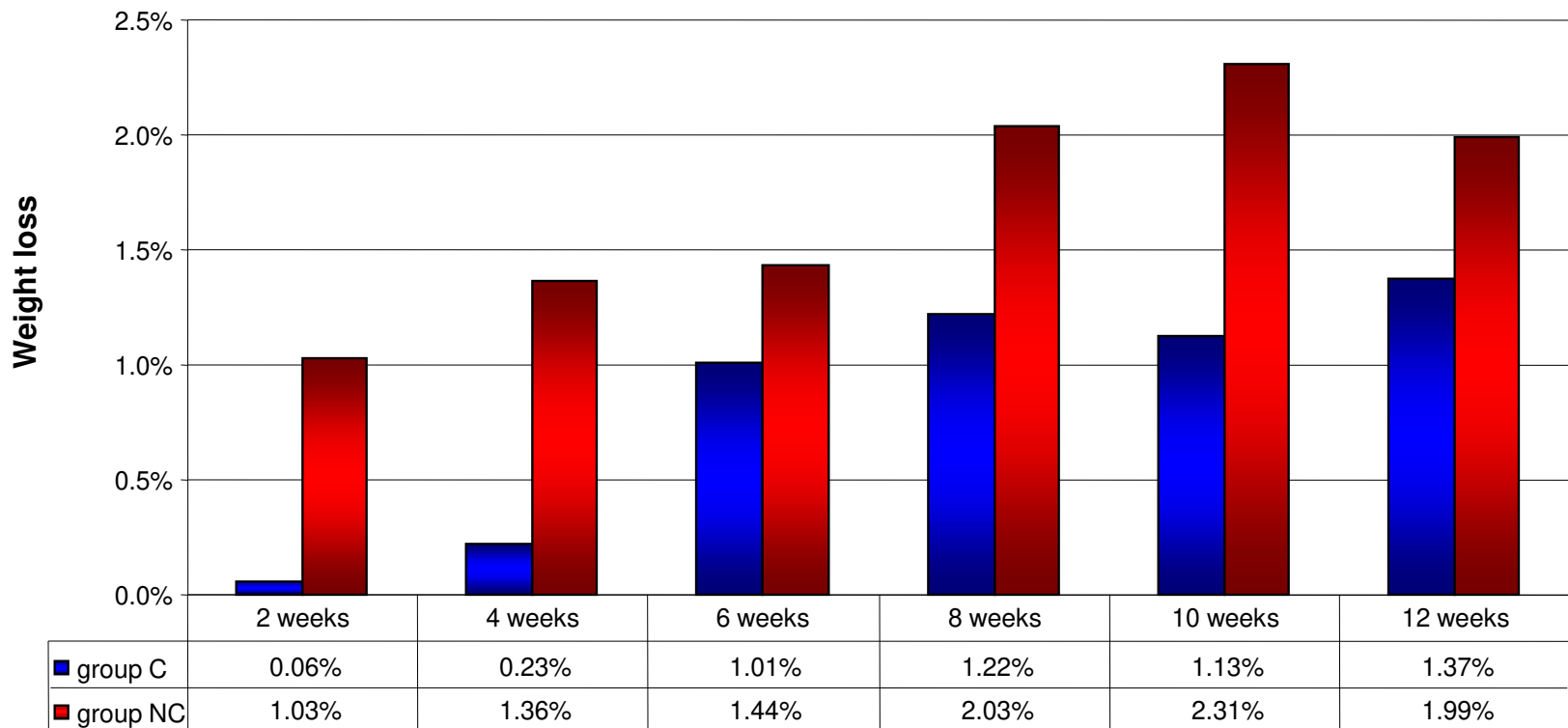
Trendlines of the percentage of subjects who experienced weight loss



Average percentage of study subjects who experienced weight loss

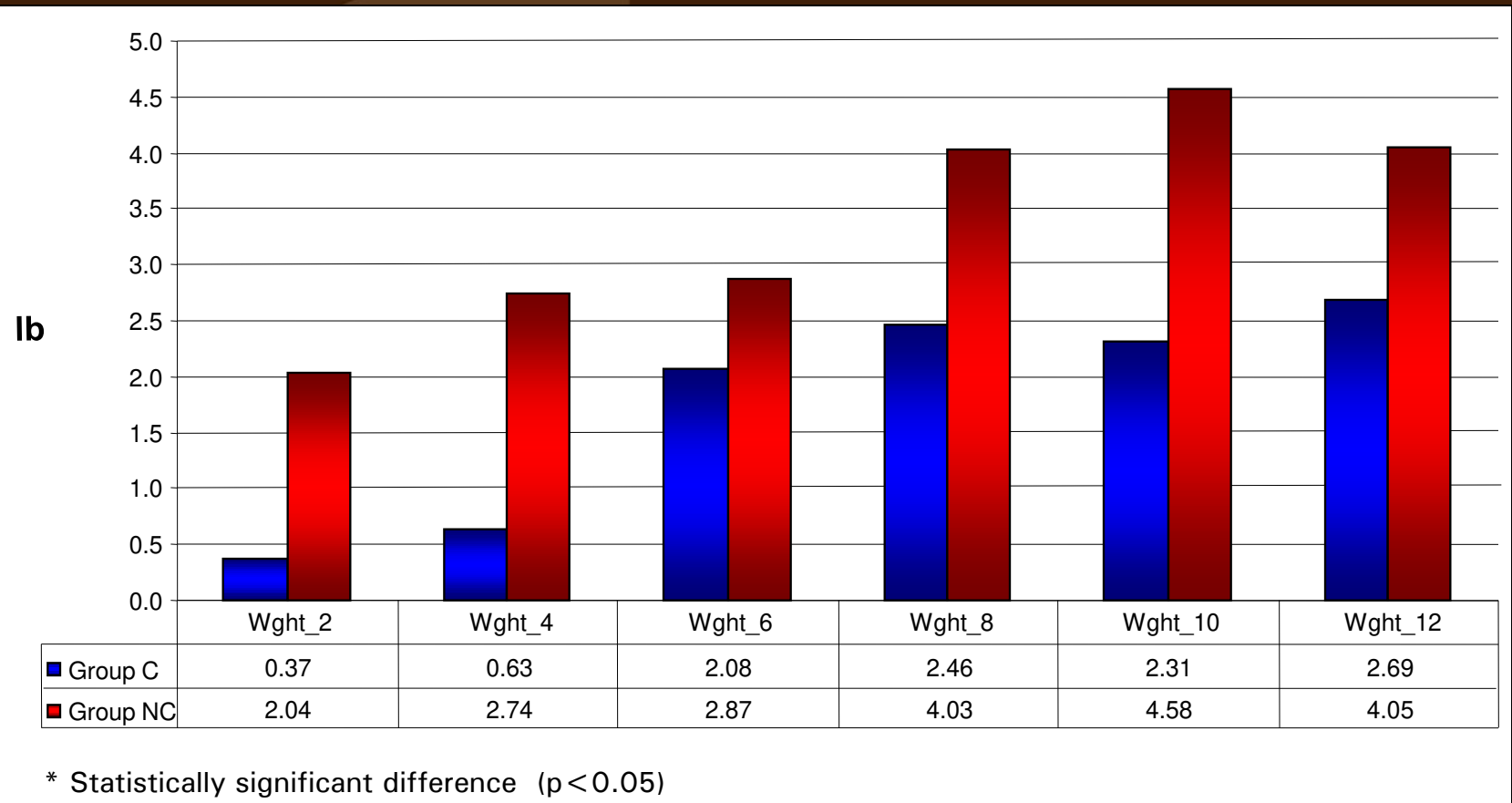


Percentage of weight loss in group C and NC at consecutive study time intervals

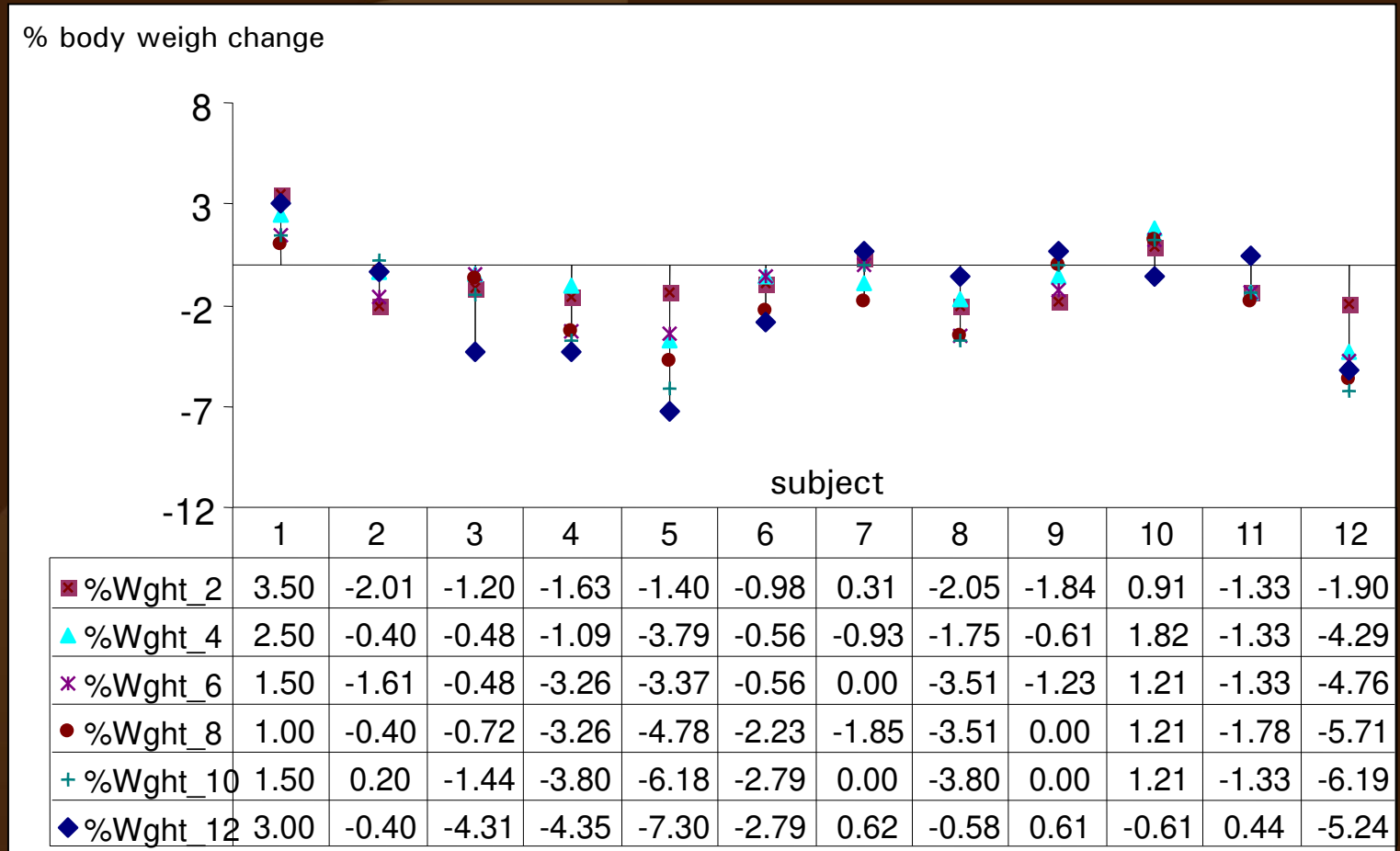


* Statistically significant difference ($p < 0.05$)

Average weight loss (lbs) in group C and NC at consecutive study intervals

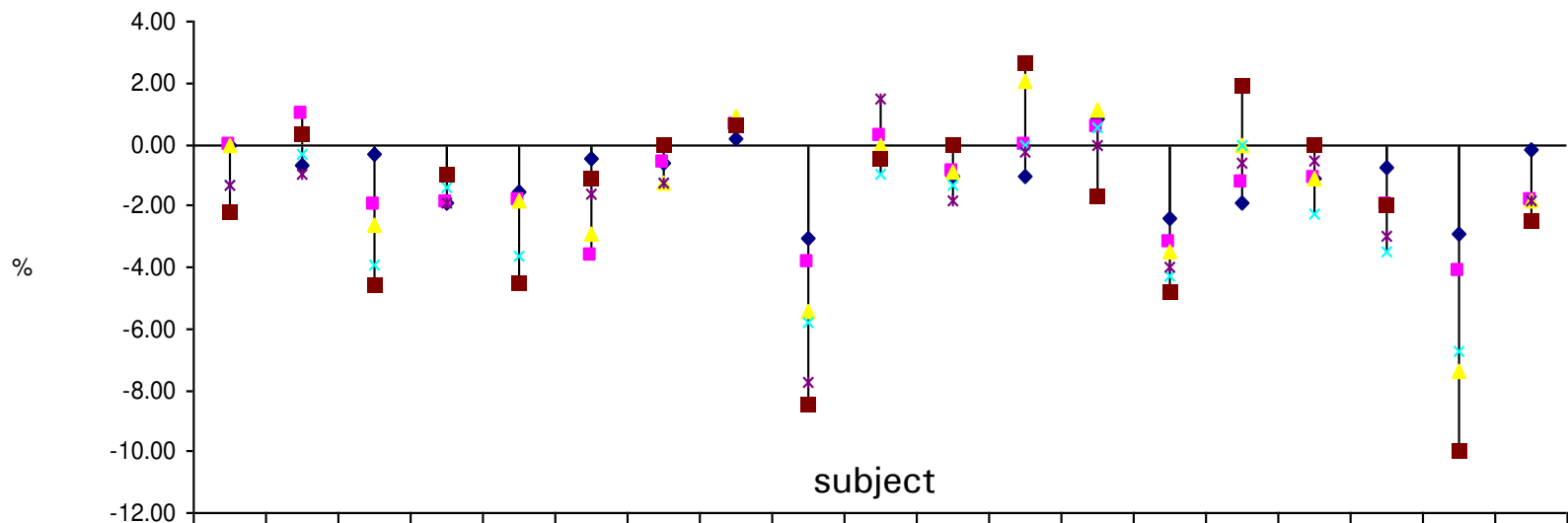


Percentage body weight change in group C subjects



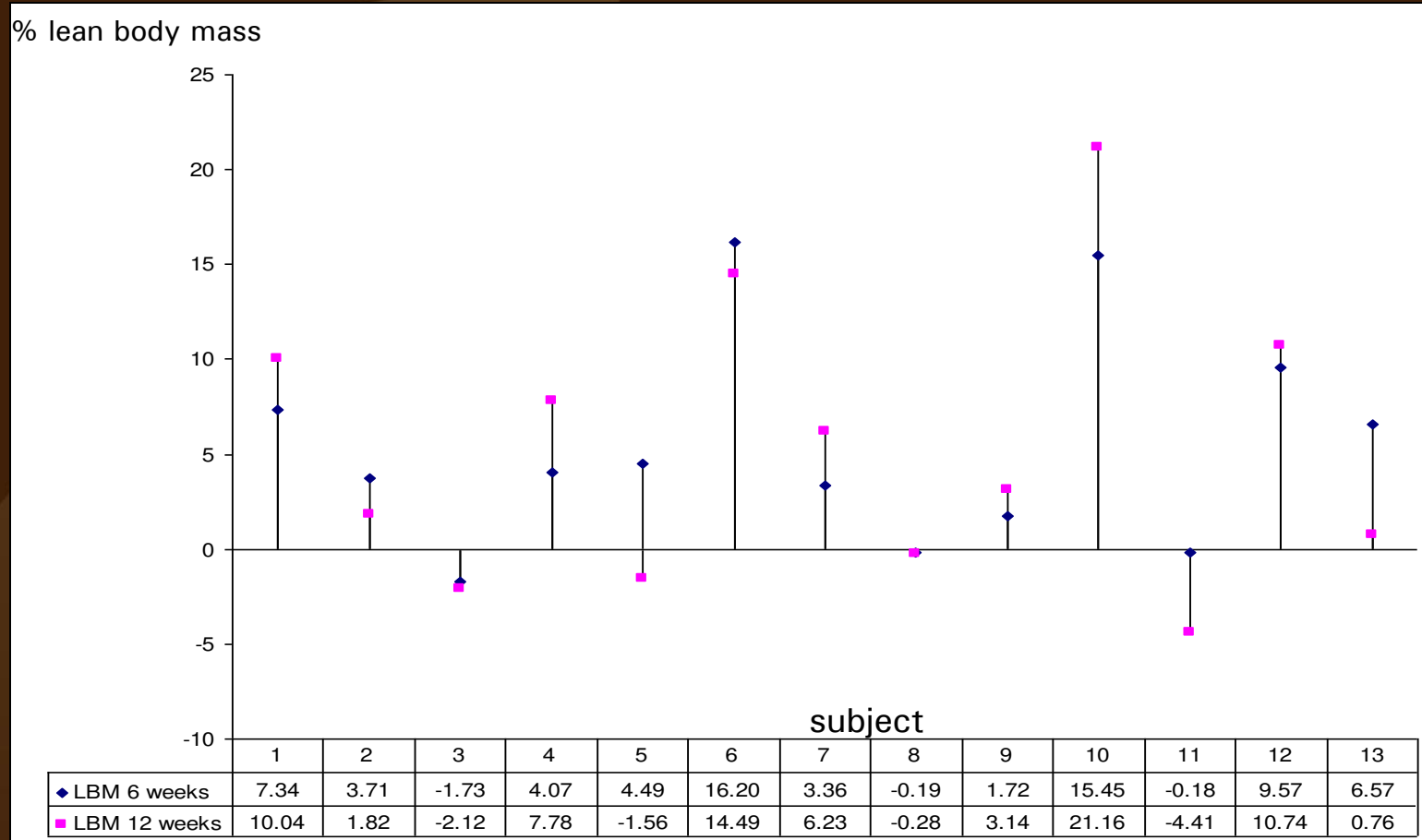
Percentage body weight change in NC group subjects

% body weigh change

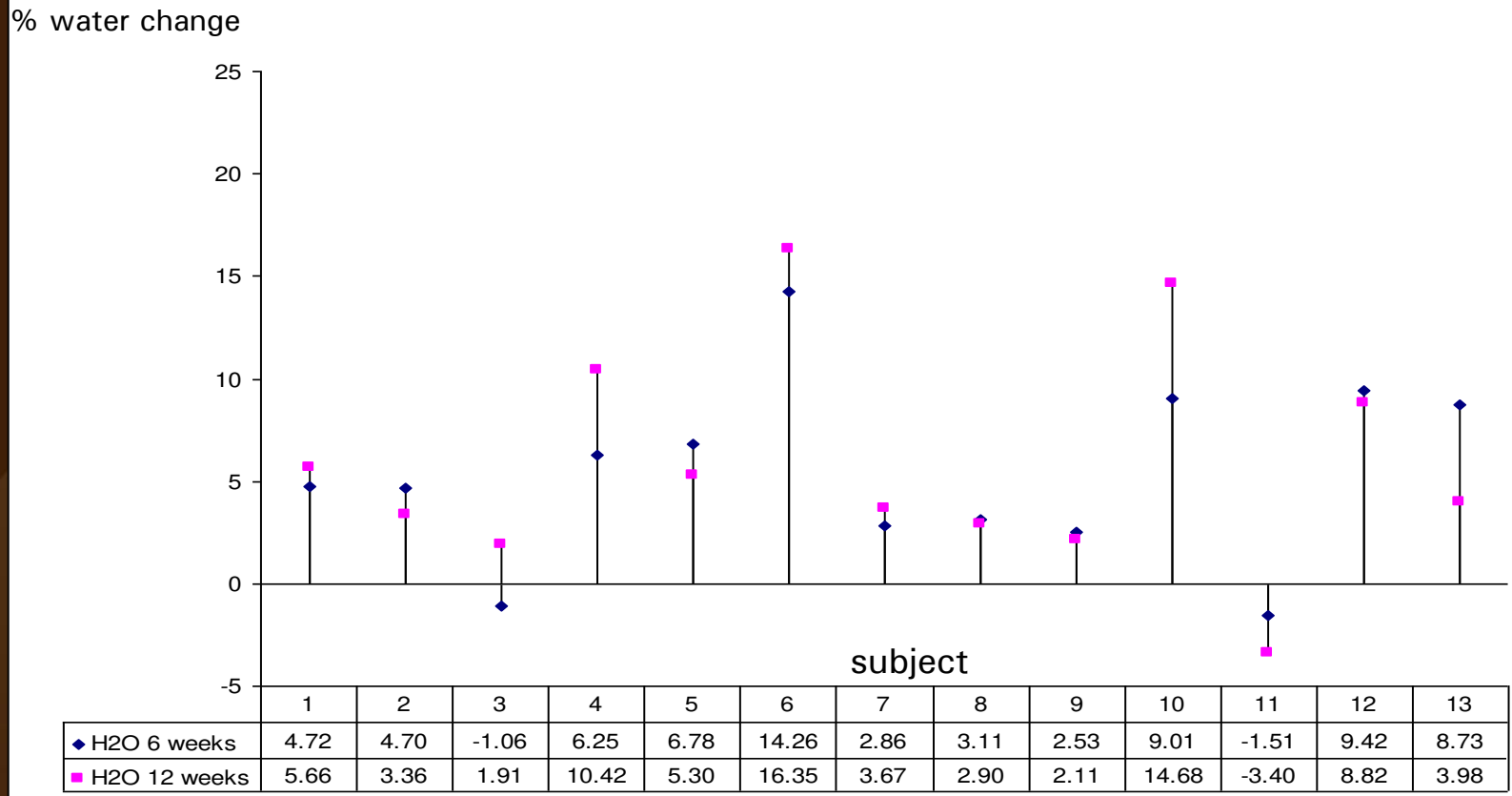


	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
◆ %Wght_2	0.00	-0.66	-0.33	-1.89	-1.58	-0.45	-0.63	0.15	-3.09	-0.49	-1.02	-1.04	0.84	-2.41	-1.92	-1.15	-0.75	-2.94	-0.15
■ %Wght_4	0.00	0.98	-1.97	-1.89	-1.80	-3.63	-0.63	0.60	-3.86	0.25	-0.91	0.00	0.56	-3.21	-1.28	-1.15	-2.00	-4.12	-1.85
▲ %Wght_6	0.00	0.33	-2.63	-0.94	-1.80	-2.95	-1.26	0.90	-5.41	0.00	-0.91	2.08	1.12	-3.48	0.00	-1.15	-2.00	-7.35	-1.85
× %Wght_8	-1.30	-0.33	-3.95	-1.42	-3.60	-1.13	-1.26	0.60	-5.79	-0.99	-1.36	0.00	0.56	-4.28	0.00	-2.30	-3.50	-6.76	-1.85
* %Wght_10	-1.30	-0.98	-4.61	-1.89	-4.50	-1.59	-1.26	0.60	-7.72	1.48	-1.82	-0.26	0.00	-4.01	-0.64	-0.57	-3.00	-10.00	-1.85
■ %Wght_12	-2.16	0.33	-4.61	-0.94	-4.50	-1.13	0.00	0.60	-8.49	-0.49	0.00	2.60	-1.69	-4.81	1.92	0.00	-2.00	-10.00	-2.47

Percentage lean body mass (LBM) change in group C subjects

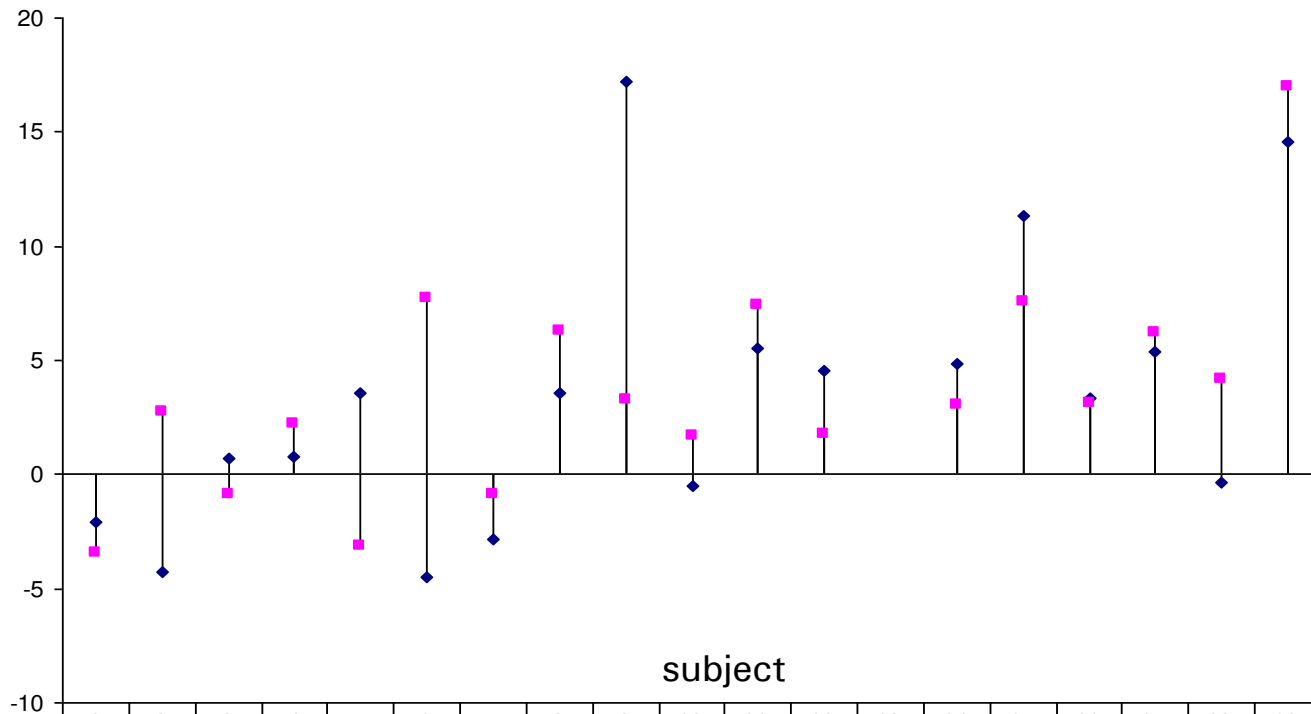


Percentage water change in group C subjects



Percentage lean body mass (LBM) change in group NC subjects

% lean body mass

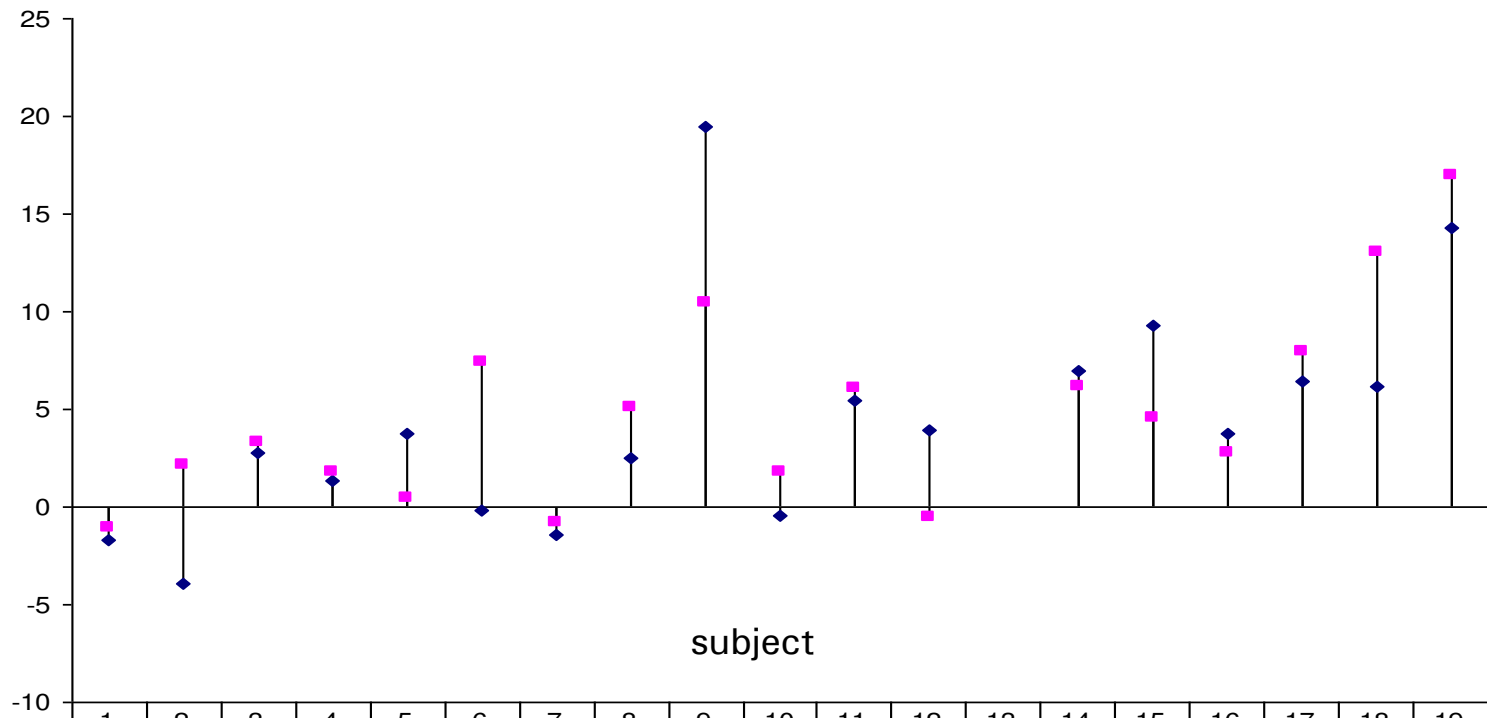


	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
◆ LBM 6 weeks	-2.08	-4.26	0.70	0.76	3.59	-4.50	-2.81	3.60	17.20	-0.50	5.56	4.58		4.82	11.32	3.31	5.40	-0.38	14.58
■ LBM 12 weeks	-3.44	2.75	-0.90	2.18	-3.12	7.70	-0.87	6.30	3.24	1.68	7.39	1.77		3.07	7.58	3.12	6.24	4.17	16.96

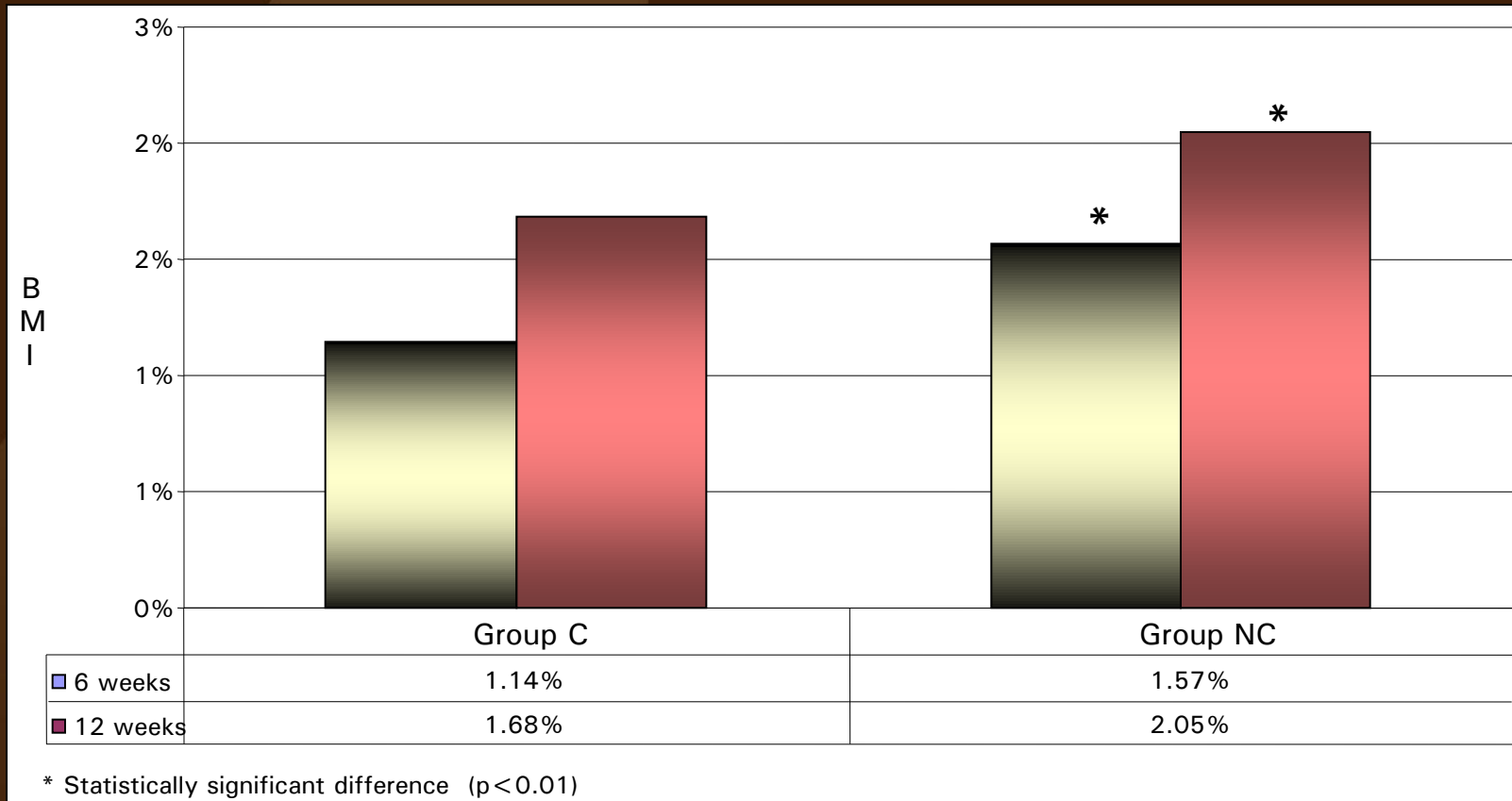


Percentage water change in group NC subjects

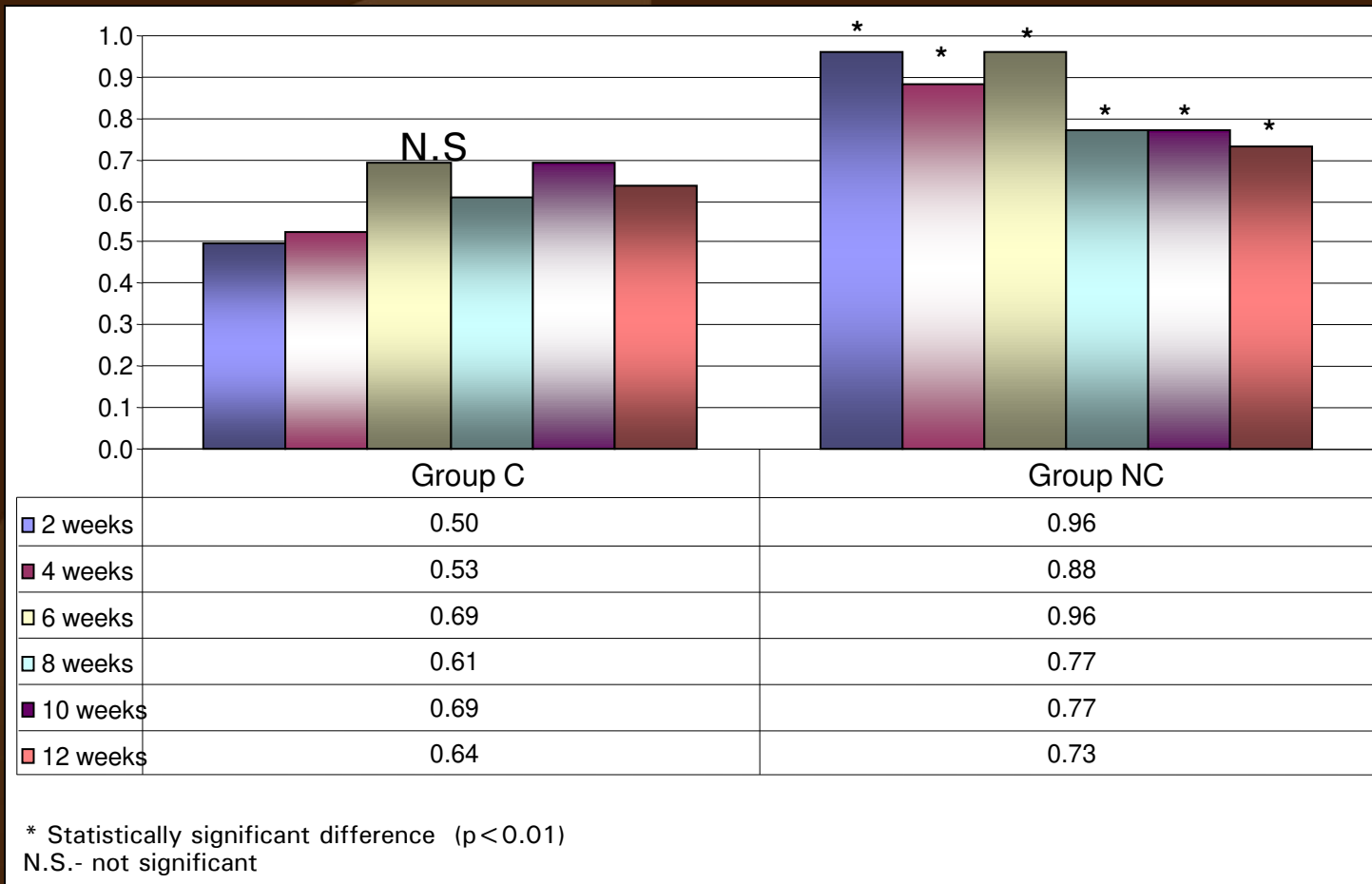
% water change



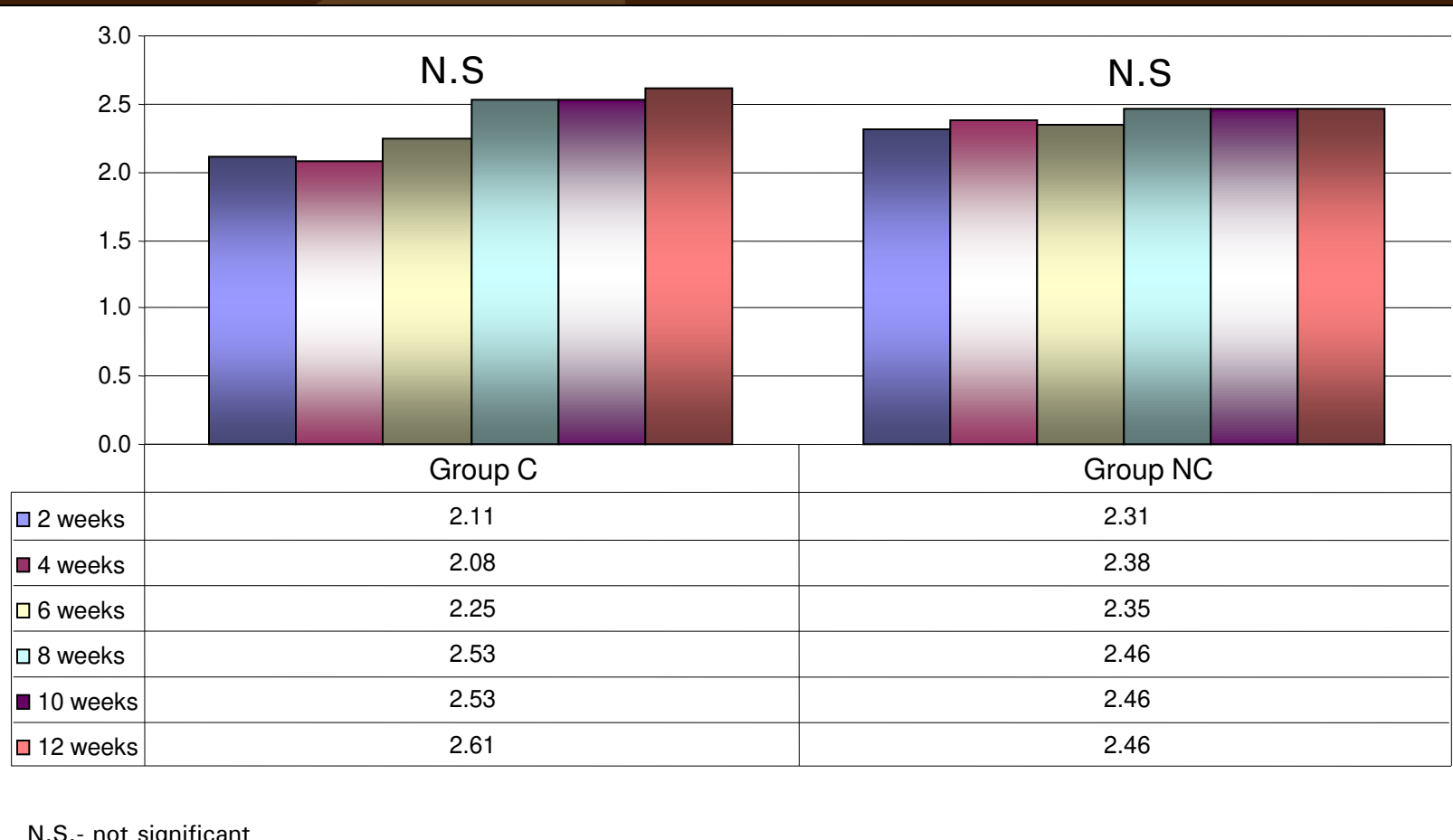
Average percentage body mass index (BMI) change in groups C and NC at two study time intervals



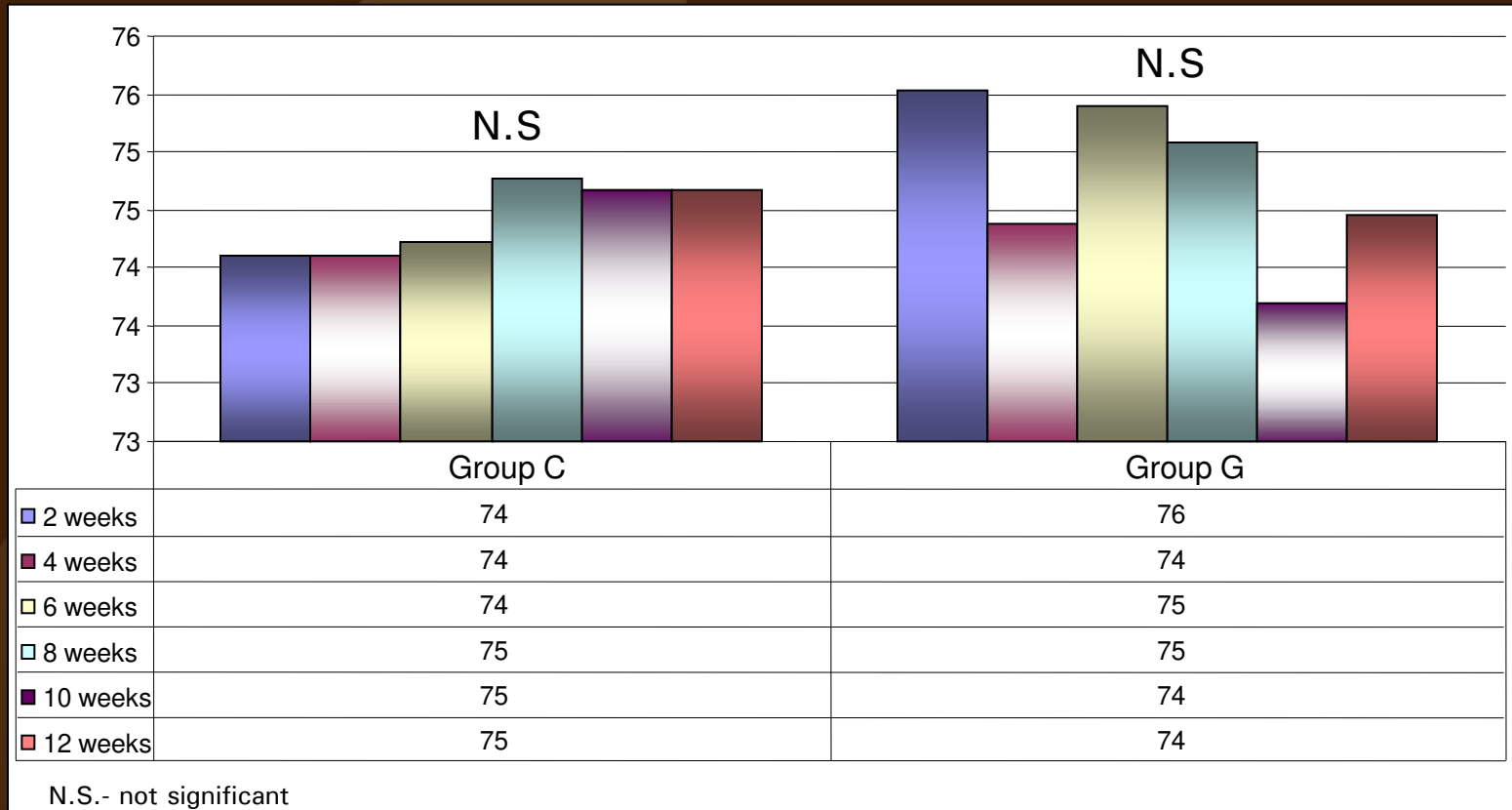
Self assessed appetite levels in group C and NC in consecutive time intervals



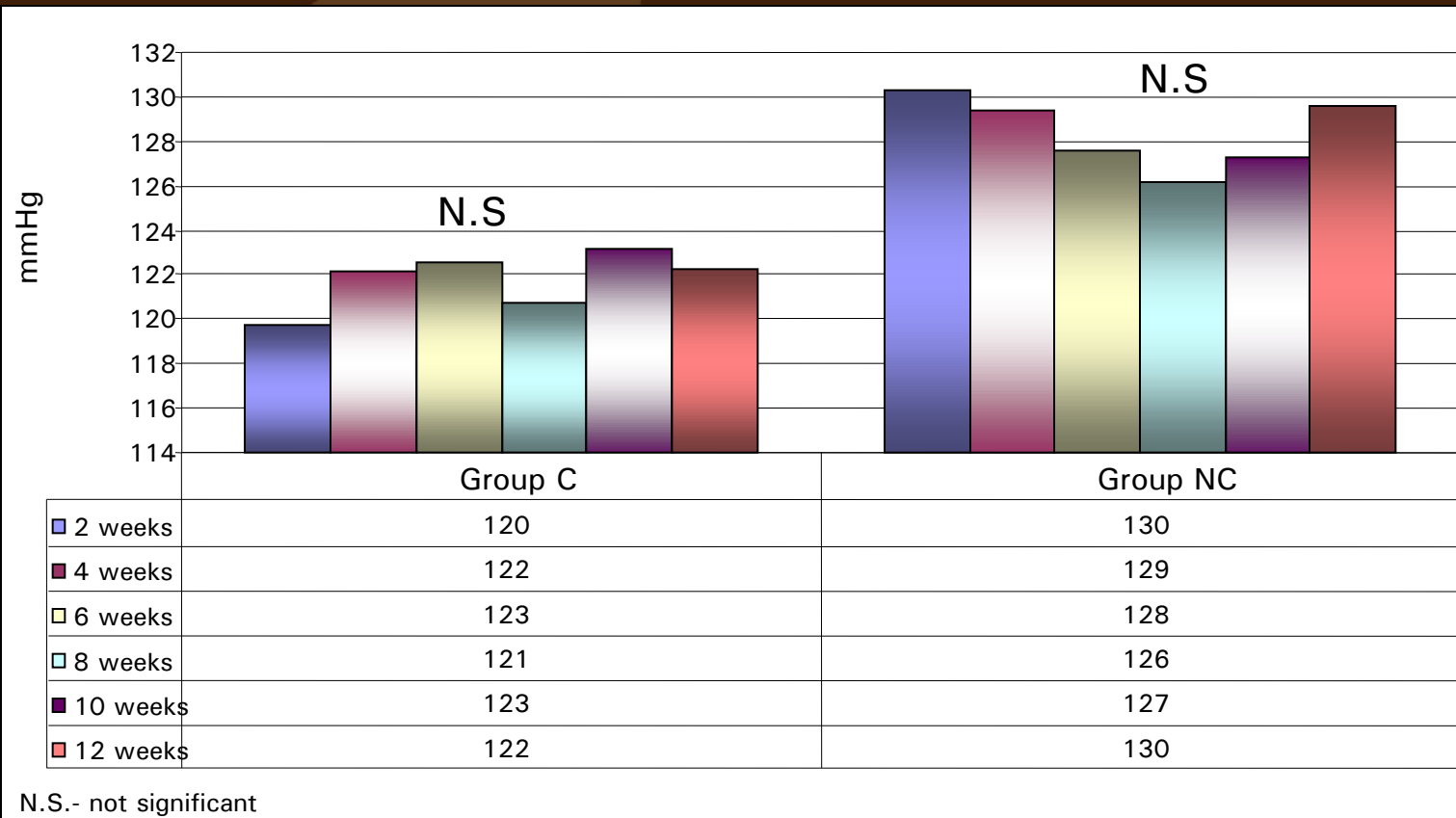
Self assessed energy levels in groups C and NC in consecutive study time intervals



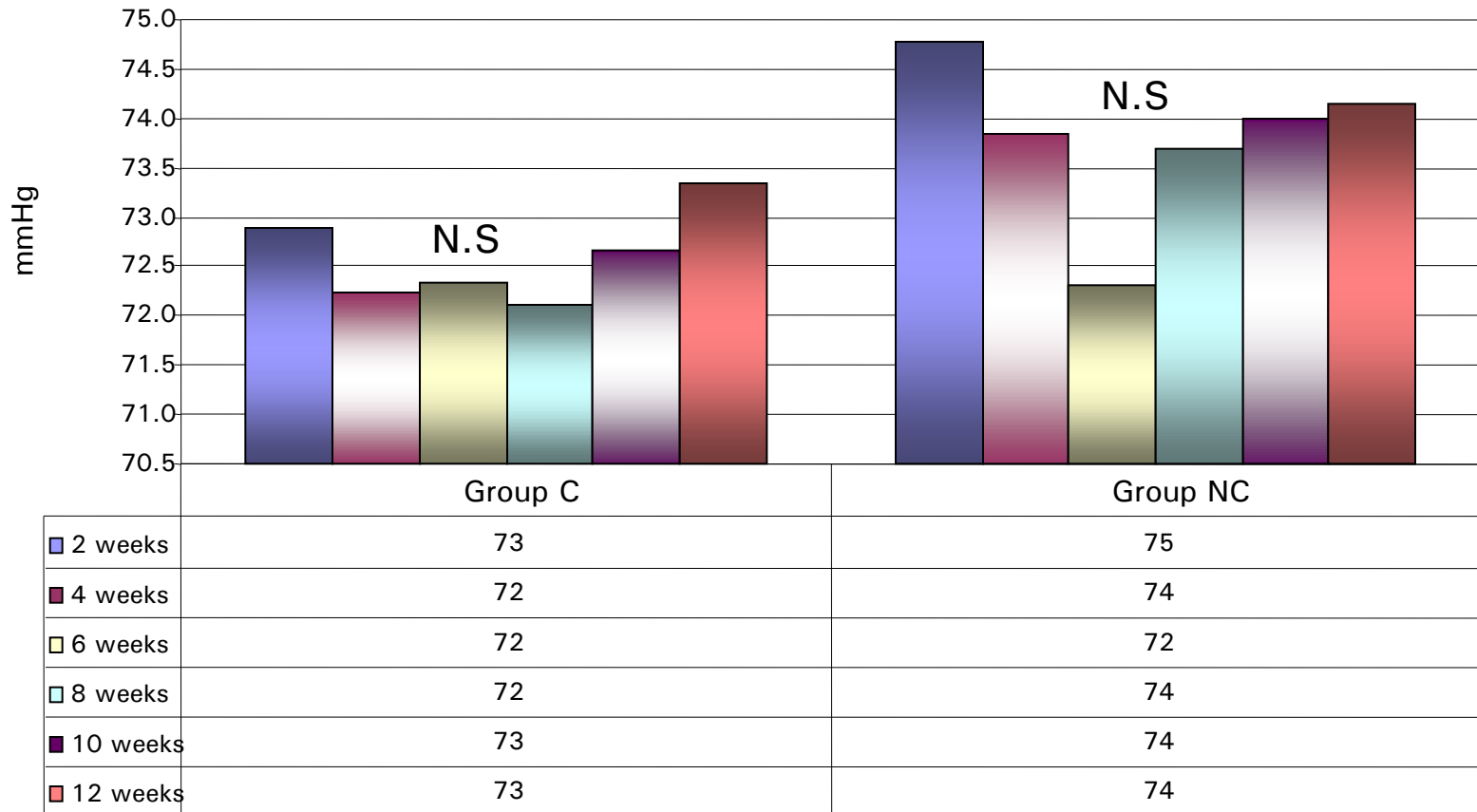
Pulse rate in groups C and NC in consecutive time intervals



Systolic blood pressure in groups C and NC in consecutive study time intervals



Diastolic blood pressure in groups C and NC in consecutive study time intervals



N.S.- not significant

Summary of clinical comparison between Citrin® and Garcitrin®

NC is statistically more effective than C in:

- reducing total body weight and body mass index
- reducing body fat
- increasing lean body mass and content of body water
- reducing levels of appetite perception

NC and C did not produce subjective or objective side effects

Citrin® - Conclusion



***WHEN SCIENCE STEPS IN
WE
SHOULD GIVE IN***