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Enhancing healing with weight loss

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Once-Weekly Semaglutide in Adults with Overweight or Obesity

John P.H. Wilding, D.M., Rachel L. Batterham, M.B., B.S., Ph.D., Salvatore Calanna, Ph.D., Melanie Davies, M.D., Luc F. Van Gaal, M.D., Ph.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Barbara M. McGowan, M.D., Ph.D., Julio Rosenstock, M.D., Marie T.D. Tran, M.D., Ph.D., Thomas A. Wadden, Ph.D., Sean Wharton, M.D., Pharm.D., Koutaro Yokote, M.D., Ph.D., Niels Zeuthen, M.Sc., and Robert F. Kushner, M.D., for the STEP 1 Study Group*

ABSTRACT

BACKGROUND

Obesity is a global health challenge with few pharmacologic options. Whether adults with obesity can achieve weight loss with once-weekly semaglutide at a dose of 2.4 mg as an adjunct to lifestyle intervention has not been confirmed.

METHODS

In this double-blind trial, we enrolled 1961 adults with a body-mass index (the weight in kilograms divided by the square of the height in meters) of 30 or greater (≥27 in persons with ≥1 weight-related coexisting condition), who did not have diabetes, and randomly assigned them, in a 2:1 ratio, to 68 weeks of treatment with once-weekly subcutaneous semaglutide (at a dose of 2.4 mg) or placebo, plus lifestyle intervention. The coprimary end points were the percentage change in body weight and weight reduction of at least 5%. The primary estimand (a precise description of the treatment effect reflecting the objective of the clinical trial) assessed effects regardless of treatment discontinuation or rescue interventions.

RESULTS

The mean change in body weight from baseline to week 68 was −14.9% in the semaglutide group as compared with −2.4% with placebo, for an estimated treatment difference of −12.4 percentage points (95% confidence interval [CI], −13.4 to −11.5; P<0.001). More participants in the semaglutide group than in the placebo group achieved weight reductions of 5% or more (1047 participants [86.4%] vs. 182 [31.5%]), 10% or more (838 [69.1%] vs. 69 [12.0%]), and 15% or more (612 [50.5%] vs. 28 [4.9%]) at week 68 (P<0.001 for all three comparisons of odds). The change in body weight from baseline to week 68 was −15.3 kg in the semaglutide group as compared with −2.6 kg in the placebo group (estimated treatment difference, −12.7 kg; 95% CI, −13.7 to −11.7). Participants who received semaglutide had a greater improvement with respect to cardiometabolic risk factors and a greater increase in participant-reported physical functioning from baseline than those who received placebo. Nausea and diarrhea were the most common adverse events with semaglutide; they were typically transient and mild-to-moderate in severity and subsided with time. More participants in the semaglutide group than in the placebo group discontinued treatment owing to gastrointestinal events (59 [4.5%] vs. 5 [0.8%]).

CONCLUSIONS

In participants with overweight or obesity, 2.4 mg of semaglutide once weekly plus lifestyle intervention was associated with sustained, clinically relevant reduction in body weight. (Funded by Novo Nordisk; STEP 1 ClinicalTrials.gov number, NCT03548935).

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Kushner at Northwestern University Feinberg School of Medicine, 645 N. Michigan Ave., Suite 530, Chicago, IL 60611, or at rkushner@northwestern.edu.

*A complete list of investigators in the STEP 1 trial is provided in the Supplementary Appendix, available at NEJM.org.

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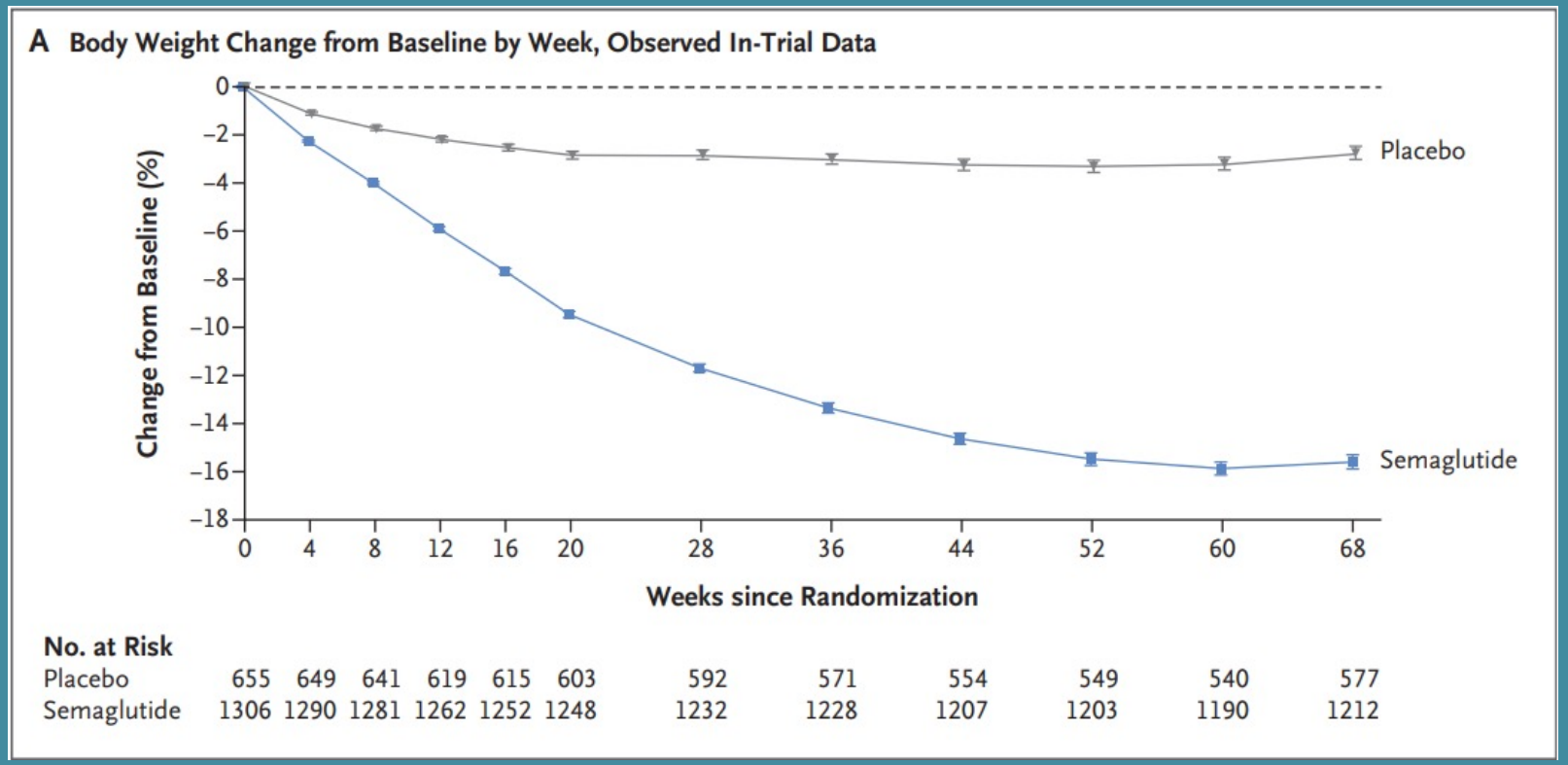

Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, McGowan BM, Rosenstock J, Tran MTD, Wadden TA, Wharton S, Yokote K, Zeuthen N, Kushner RF; STEP 1 Study Group. Once-Weekly Semaglutide in Adults with Overweight or Obesity. N Engl J Med. 2021 Mar 18;384(11):989-1002. doi: 10.1056/NEJMoa2032183. Epub 2021 Feb 10. PMID: 33567185.

	Semaglutide 2.4 mg once weekly	Placebo once weekly	Treatment comparison for semaglutide vs. placebo [95% CI]
	N=95	N=45	
Body composition change from baseline to week 68 (DEXA)			
Total fat mass			
Kg change	–8.36	–1.37	ETD: –6.99 [–9.79; –4.19]
Percentage-points change in total fat mass proportion[†]	–3.48	–0.19	ETD: –3.29 [–4.94; –1.65]
Regional visceral fat mass[‡]			
Kg change	–0.36	–0.10	ETD: –0.27 [–0.39; –0.15]
Percentage-points change in regional visceral fat mass proportion[§]	–1.99	–0.01	ETD: –1.98 [–3.69; –0.27]
Total lean body mass			
Kg change	–5.26	–1.83	ETD: –3.43 [–4.74; –2.13]
Percentage-points change in total lean body mass proportion[†]	3.04	0.09	ETD: 2.94 [1.40; 4.49]

Once-weekly semaglutide versus placebo in adults with increased fracture risk: a randomised, double-blinded, two-centre, phase 2 trial

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2024;72: 102624

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Summary

Background Previous studies have indicated that glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs) may enhance bone formation and have neutral or beneficial effects on fracture risk. We evaluated the effect of the GLP-1RA semaglutide on the bone formation marker Procollagen type I N-terminal propeptide (PINP) in adults with increased fracture risk.

Methods This randomised, placebo-controlled, double-blinded, phase 2 clinical trial was conducted at two public hospitals in Denmark. We enrolled 64 men and women with increased fracture risk based on a T-score < −1.0 at the total hip or lumbar spine and/or low-energy fracture within three years of recruitment. Participants were randomised (1:1) to receive once-weekly subcutaneous semaglutide 1.0 mg or placebo. The primary outcome was changes in plasma (P)-PINP from baseline to week 52. Primary and safety outcomes were assessed and evaluated for all participants. This trial is complete and registered with ClinicalTrials.gov, NCT04702516.

Findings Between March 24 and December 8, 2021, 55 (86%) postmenopausal women and nine men with a mean age of 63 years (SD 5.5) and BMI of 27.5 kg/m^2 (SD 4.5) were enrolled. There was no effect on changes in P-PINP from baseline to week 52 between the two groups (estimated treatment difference (ETD) semaglutide versus placebo 3.8 µg/L [95% CI −5.6 to 13.3]; p = 0.418), and no difference in P-PINP levels between groups at week 52 (semaglutide 64.3 µg/L versus placebo 62.3 µg/L [95% CI −10.8 to 15.0]; p = 0.749). The secondary outcomes showed higher plasma levels of bone resorption marker Collagen type I cross-linked C-terminal telopeptide (P-CTX) in the semaglutide group than in the placebo group (ETD 166.4 ng/L [95% CI 25.5–307.3]; p = 0.021). Compared to placebo, lumbar spine and total hip areal bone mineral densities (aBMD) were lower in the semaglutide group after 52 weeks ((ETD lumbar spine −0.018 g/cm^2 [95% CI −0.031 to −0.005]; p = 0.007); ETD total hip −0.020 g/cm^2 ([95% CI −0.032 to −0.008]; p = 0.001). Treatment differences in femoral neck aBMD were not observed ([95% CI [−0.017 to 0.006]; p = 0.328). Further, body weight was lower in the semaglutide group than in the placebo group after 52 weeks (ETD −6.8 kg [95% CI −8.8 to −4.7]; p < 0.001). Thirty-one [97%] in the semaglutide group and 18 [56%] in the placebo group experienced at least one adverse event, including four serious events (two in each group). No episodes of hypoglycaemia or deaths were reported.

Interpretation In adults with increased fracture risk, semaglutide once weekly did not increase bone formation based on the bone formation marker P-PINP. The observed increase in bone resorption in the semaglutide group may be explained by the accompanying weight loss.

Funding Region of Southern Denmark, Novo Nordisk Foundation, and Gangsted Foundation. Novo Nordisk provided the investigational drug and placebo.

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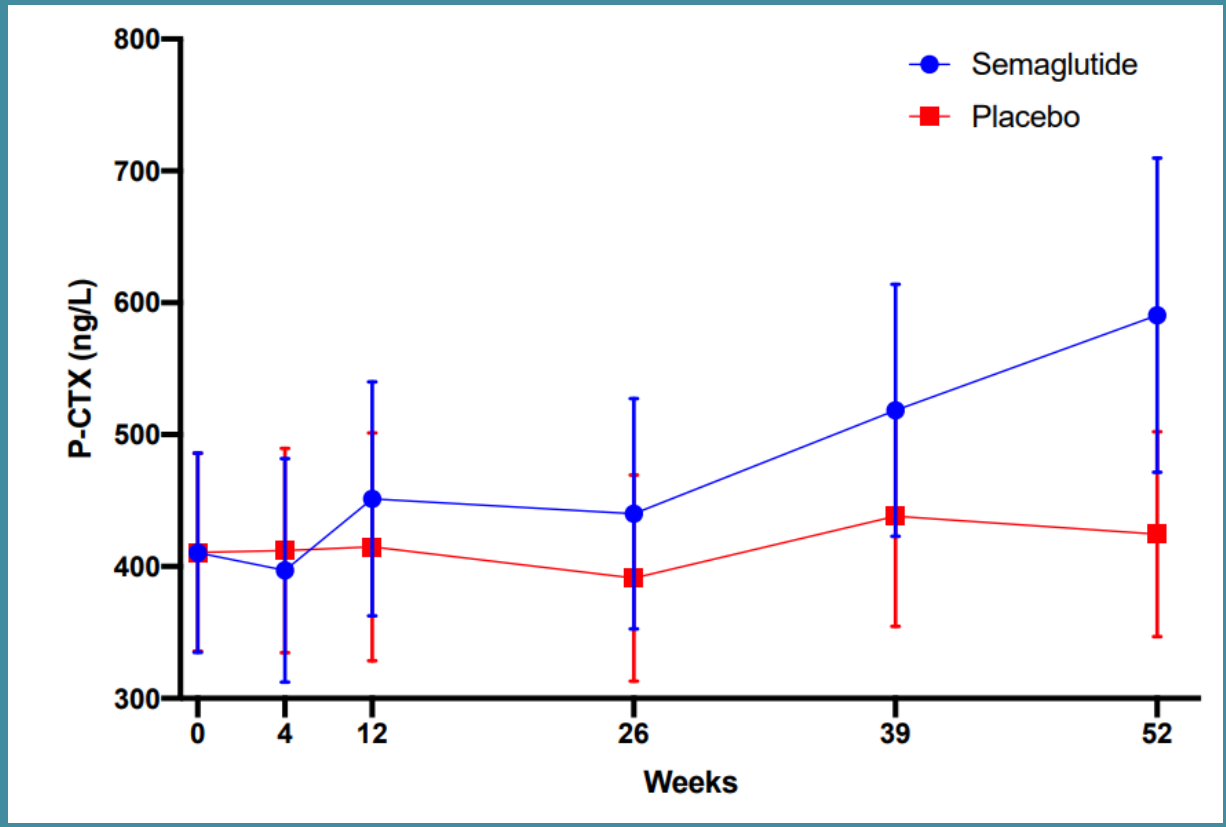
E-mail address: morten.steen.hansen@rsyd.dk (M.S. Hansen).



Hansen MS, Wölfel EM, Jeromdesella S, Møller JK, Ejersted C, Jørgensen NR, Eastell R, Hansen SG, Frost M. Once-weekly semaglutide versus placebo in adults with increased fracture risk: a randomised, double-blinded, two-centre, phase 2 trial. EClinicalMedicine. 2024 May 3;72:102624. doi: 10.1016/j.eclinm.2024.102624. PMID: 38737002; PMCID: PMC11087719.

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Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

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ABSTRACT

BACKGROUND

Semaglutide, a glucagon-like peptide-1 receptor agonist, has been shown to reduce the risk of adverse cardiovascular events in patients with diabetes. Whether semaglutide can reduce cardiovascular risk associated with overweight and obesity in the absence of diabetes is unknown.

METHODS

In a multicenter, double-blind, randomized, placebo-controlled, event-driven superiority trial, we enrolled patients 45 years of age or older who had preexisting cardiovascular disease and a body-mass index (the weight in kilograms divided by the square of the height in meters) of 27 or greater but no history of diabetes. Patients were randomly assigned in a 1:1 ratio to receive once-weekly subcutaneous semaglutide at a dose of 2.4 mg or placebo. The primary cardiovascular end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke in a time-to-first-event analysis. Safety was also assessed.

RESULTS

A total of 17,604 patients were enrolled; 8803 were assigned to receive semaglutide and 8801 to receive placebo. The mean (±SD) duration of exposure to semaglutide or placebo was 34.2±13.7 months, and the mean duration of follow-up was 39.8±9.4 months. A primary cardiovascular end-point event occurred in 569 of the 8803 patients (6.5%) in the semaglutide group and in 701 of the 8801 patients (8.0%) in the placebo group (hazard ratio, 0.80; 95% confidence interval, 0.72 to 0.90; P<0.001). Adverse events leading to permanent discontinuation of the trial product occurred in 1461 patients (16.6%) in the semaglutide group and 718 patients (8.2%) in the placebo group (P<0.001).

CONCLUSIONS

In patients with preexisting cardiovascular disease and overweight or obesity but without diabetes, weekly subcutaneous semaglutide at a dose of 2.4 mg was superior to placebo in reducing the incidence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke at a mean follow-up of 39.8 months. (Funded by Novo Nordisk; SELECT ClinicalTrials.gov number, NCT03574597.)

The authors' affiliations are listed in the Appendix. Dr. Lincoff can be contacted at lincofa@ccf.org or at the Department of Cardiovascular Medicine, Cleveland Clinic, 9500 Euclid Ave., J2–3, Cleveland, OH 44195.

*A list of the SELECT trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

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DOI: 10.1056/NEJMoa2307563

Fractures

In SELECT, the cardiovascular outcomes trial in adults, more fractures of the hip and pelvis were reported on semaglutide than on placebo in female patients: 1.0% (24/2448) vs. 0.2% (5/2424), and in patients aged 75 years and older: 2.4% (17/703) vs. 0.6% (4/663), respectively.

https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent=&id=CP-2022-PI-01930-1&d=20250501172310101

Australian Government

Department of Health and Aged Care

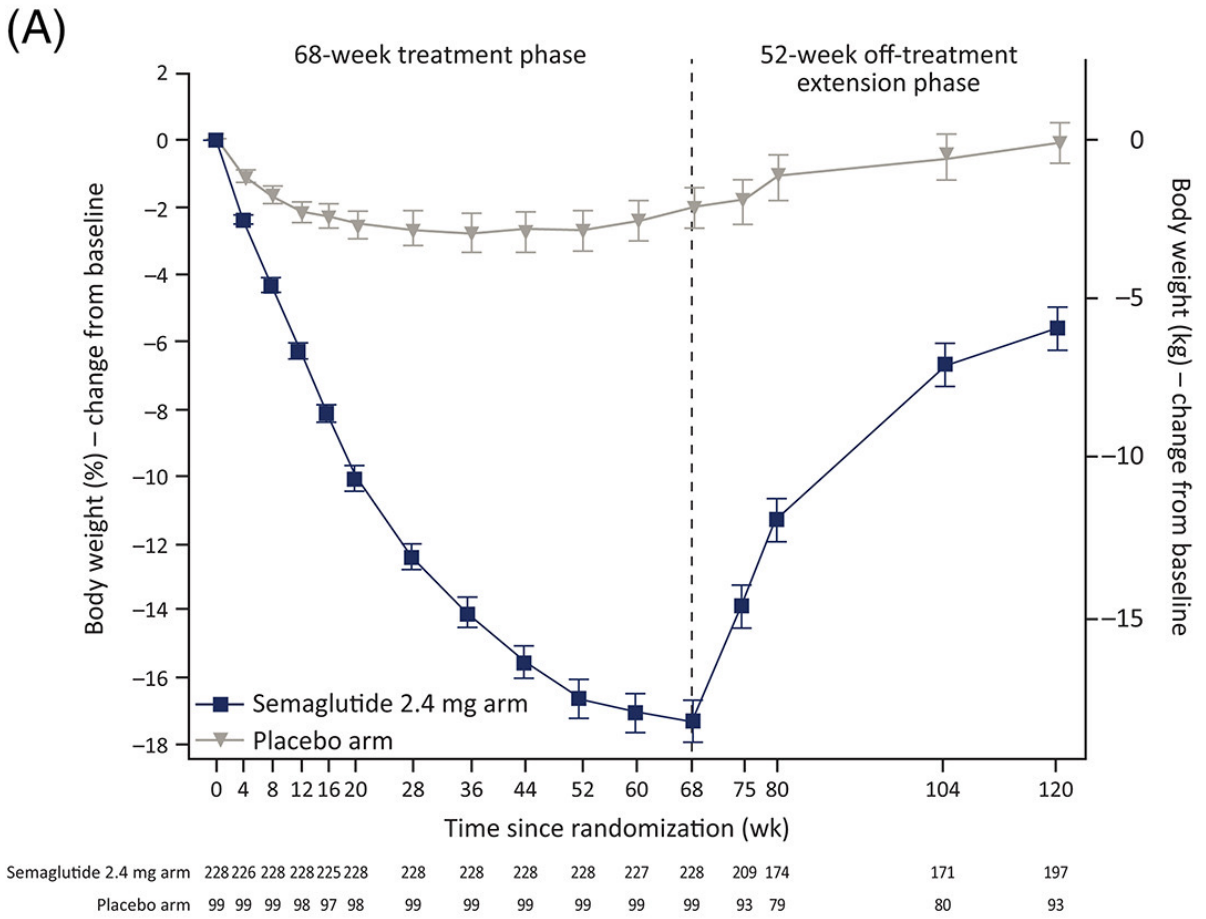
Therapeutic Goods Administration

Indication

WEGOVY is indicated as an adjunct to a reduced-energy diet and increased physical activity for chronic weight management (including weight loss and weight maintenance) in adults with an initial Body Mass Index (BMI) of:

- &ge30 kg/m2 (obesity), or
- &ge27 kg/m2 to <30 kg/m2 (overweight) in the presence of at least one weight-related comorbidity (see Section 5.1 Pharmacodynamic Properties – Clinical trials).

Weight regain after withdrawal of semaglutide: The STEP 1 trial extension



Diabetes Obesity Metabolism, Volume: 24, Issue: 8, Pages: 1553-1564, First published: 19 April 2022, DOI: (10.1111/dom.14725)

Received: 10 September 2020 | Revised: 19 November 2020 | Accepted: 30 November 2020
DOI: 10.1111/dom.14280

ORIGINAL ARTICLE

WILEY

The effect of semaglutide 2.4 mg once weekly on energy intake, appetite, control of eating, and gastric emptying in adults with obesity

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Funding information
Novo Nordisk A/S

Abstract

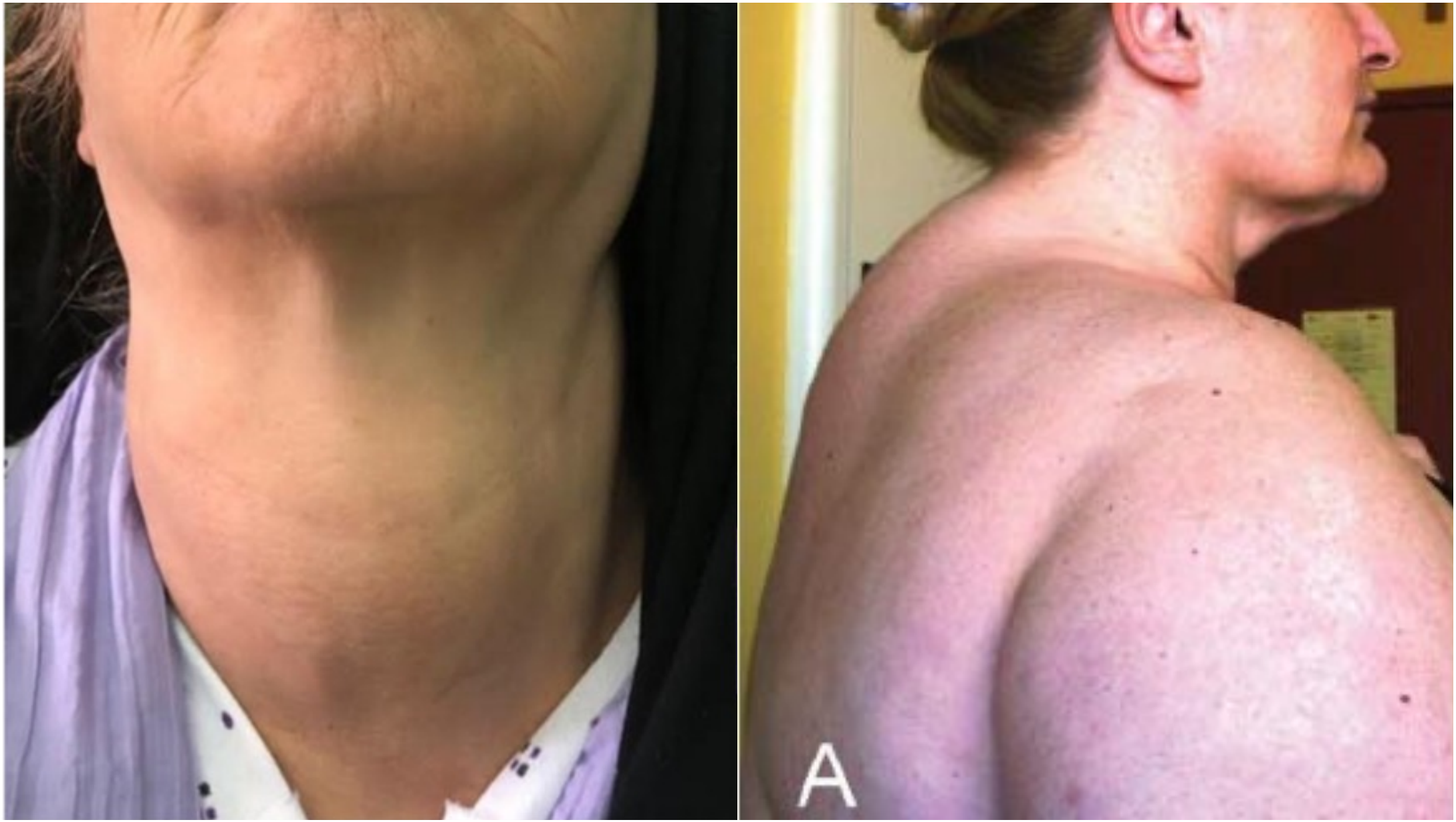
Aim: To investigate the effects of once-weekly subcutaneous (s.c.) semaglutide 2.4 mg on gastric emptying, appetite, and energy intake in adults with obesity.

Materials and Methods: A double-blind, parallel-group trial was conducted in 72 adults with obesity, randomized to once-weekly s.c. semaglutide (dose-escalated to 2.4 mg) or placebo for 20 weeks. Gastric emptying was assessed using paracetamol absorption following a standardized breakfast. Participant-reported appetite ratings and Control of Eating Questionnaire (CoEQ) responses were assessed, and energy intake was measured during ad libitum lunch.

Results: The area under the concentration–time curve (AUC) for paracetamol 0 to 5 hours after a standardized meal ($AUC_{0-5h,para}$; primary endpoint) was increased by 8% ($P = 0.005$) with semaglutide 2.4 mg versus placebo at week 20 (non-significant when corrected for week 20 body weight; $P = 0.12$). No effect was seen on $AUC_{0-1h,para}$, maximum observed paracetamol concentration, or time to maximum observed paracetamol concentration. Ad libitum energy intake was 35% lower with semaglutide versus placebo (1736 versus 2676 kJ; estimated treatment difference −940 kJ; $P < 0.0001$). Semaglutide reduced hunger and prospective food consumption, and increased fullness and satiety when compared with placebo (all $P < 0.02$). The CoEQ indicated better control of eating and fewer/weaker food cravings with semaglutide versus placebo ($P < 0.05$). Body weight was reduced by 9.9% with semaglutide and 0.4% with placebo. Safety was consistent with the known profile of semaglutide.

Conclusions: In adults with obesity, once-weekly s.c. semaglutide 2.4 mg suppressed appetite, improved control of eating, and reduced food cravings, ad libitum energy intake and body weight versus placebo. There was no evidence of delayed gastric emptying at week 20, assessed indirectly via paracetamol absorption.

KEYWORDS
appetite, control of eating, energy intake, food craving, gastric emptying, GLP-1 analogue, glucagon-like peptide-1, obesity, randomized trial, semaglutide


A

Weight Gain Associated With Intensive Therapy in the Diabetes Control and Complications Trial

The DCCT Research Group

Identifiable risks such as increased frequency of hypoglycemia accompany the treatment of insulin-dependent diabetes mellitus (IDDM) with intensive insulin therapy. During yr 1 of the Diabetes Control and Complications Trial (DCCT), weight gain was identified as a sequela of intensive insulin therapy. The DCCT is a multicenter controlled clinical trial designed to determine the long-term effects of two different diabetes treatment regimens on the early vascular and neurologic complications of IDDM. Subjects randomized to the intensive treatment regimen gained significantly more weight (5.1 ± 4.6 kg) than the standard treatment subjects (2.4 ± 3.7 kg, $P < .0001$) during the 1st yr of therapy. Higher baseline HbA_{1c} levels and greater decrements in HbA_{1c} during intensive therapy were both associated with greater weight gain. In addition, intensively treated subjects with one or more severe hypoglycemic episodes gained more weight than the intensively treated subjects with no severe episodes. There was no relationship between reported caloric intake or exercise level and the weight changes. These data suggest that improved utilization of calories through a decrease in glycosuria and perhaps other mechanisms led to the weight gain in the intensively treated subjects. The results from the 1st yr of experience in the DCCT indicate that weight gain accompanies efforts to lower blood glucose levels with intensive insulin therapy. Because of the potential adverse consequences of undesirable weight gain, including diminished long-term compliance with therapy and an adverse effect on blood pressure and lipid status, efforts to prevent undesirable weight gain in the intensively treated group of the DCCT are being pursued. *Diabetes Care* 11:567–73, 1988

Prepared for the DCCT by Rena R. Wing and Patricia A. Cleary. A complete listing of the DCCT Research Group appeared in *Diabetes Care* 10:1–19, 1987.
Address correspondence and reprint requests to The DCCT Research Group, Box NDIC/DCCT, Bethesda, MD 20892.

Intensive insulin therapy with insulin-delivery devices or multiple daily injections (MDI) is being used increasingly to treat insulin-dependent diabetes mellitus (IDDM). The putative benefit of lowering blood glucose levels with intensive therapy, especially with regard to the development and progression of microvascular complications, is being investigated (1–4). Although the definitive answer to whether such therapy is beneficial must await the completion of long-term controlled clinical trials, the risks of such therapy have begun to be defined. Increased frequency of hypoglycemia has been noted to occur with intensive insulin regimens (4), and diabetic ketoacidosis may be more frequent in insulin-pump–treated patients (5–6). This study from the Diabetes Control and Complications Trial (DCCT) suggests that weight gain may be another consequence of intensive therapy.

The DCCT is a multicenter randomized clinical trial to study the effect of two different diabetes treatment regimens on the development or progression of early vascular complications in people with IDDM. DCCT subjects are randomly assigned either to a standard treatment group or to an experimental treatment group; the goal of the latter is to achieve blood glucose levels as close to the nondiabetic range as possible while minimizing hypoglycemia. Results from the 1st yr of the study reveal that weight gain is associated with experimental therapy. We describe the magnitude of the weight gain and the variables associated with weight gain during intensive insulin therapy.

SUBJECTS AND METHODS

Subjects. DCCT eligibility criteria have been described in detail (7). The eligibility criteria presented here will be limited to those most pertinent to this study. In brief,

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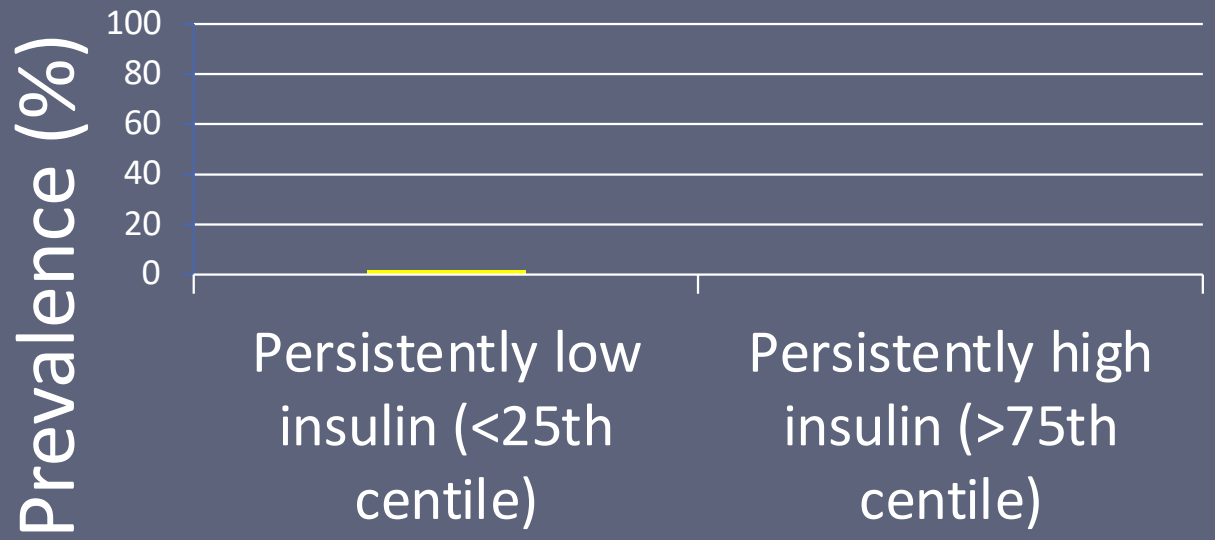
Risk of obesity in young adults (over 8 year period)



Circulation. 1996 Jan 1;93(1):54-9. Persistent elevation of plasma insulin levels is associated with increased cardiovascular risk in children and young adults. The Bogalusa Heart Study. Bao W et al.

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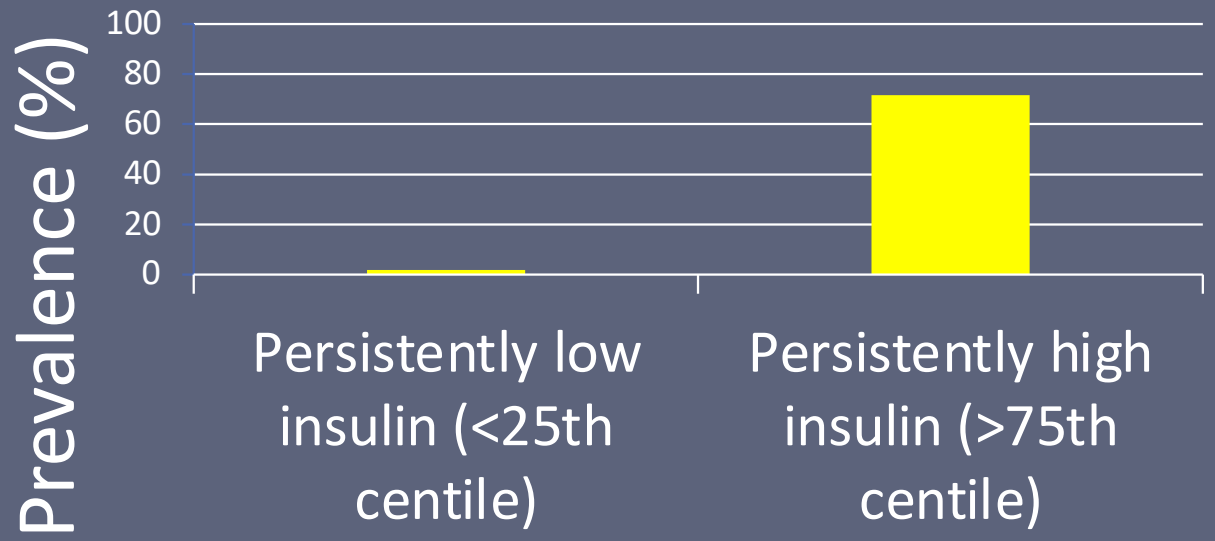

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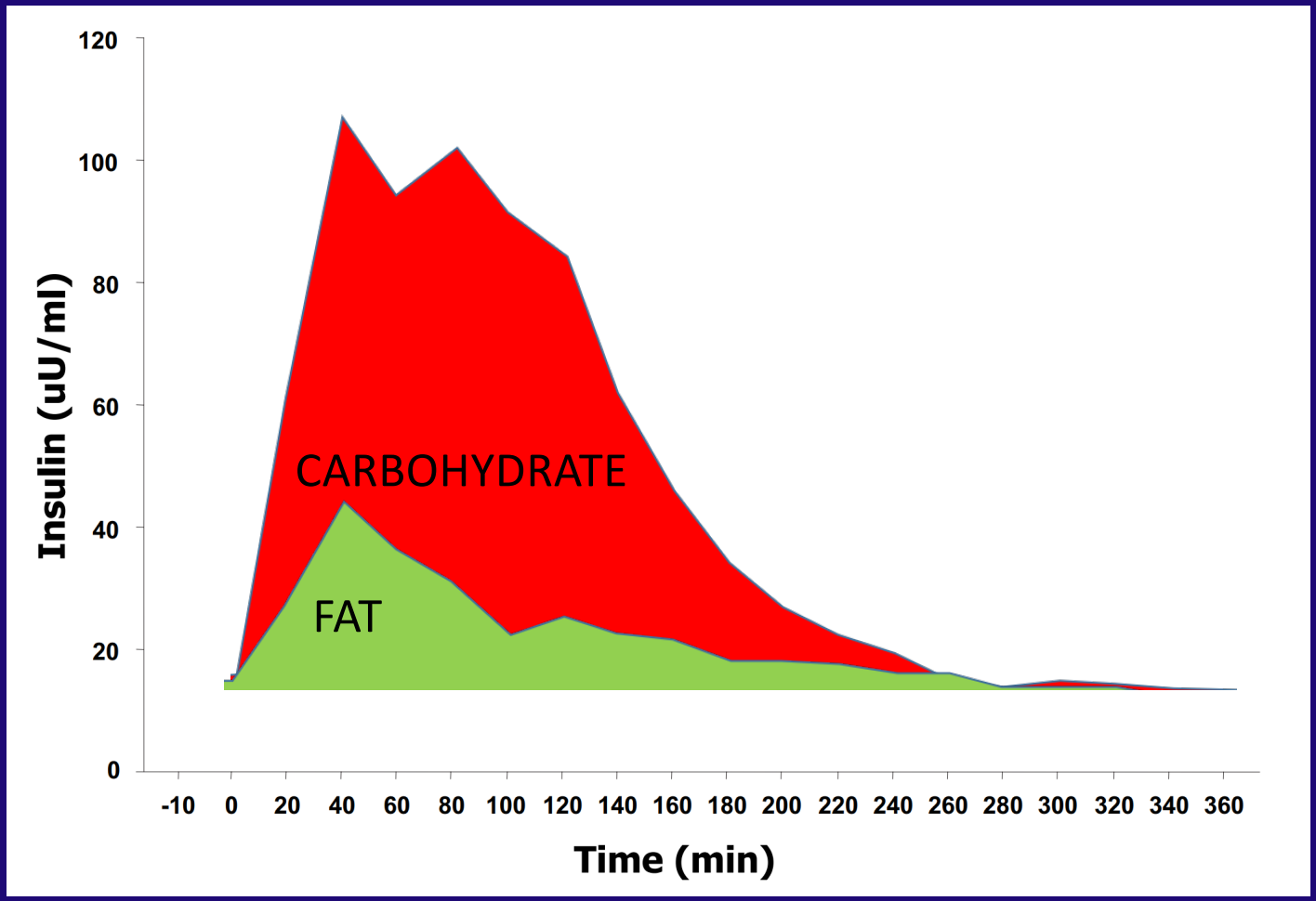
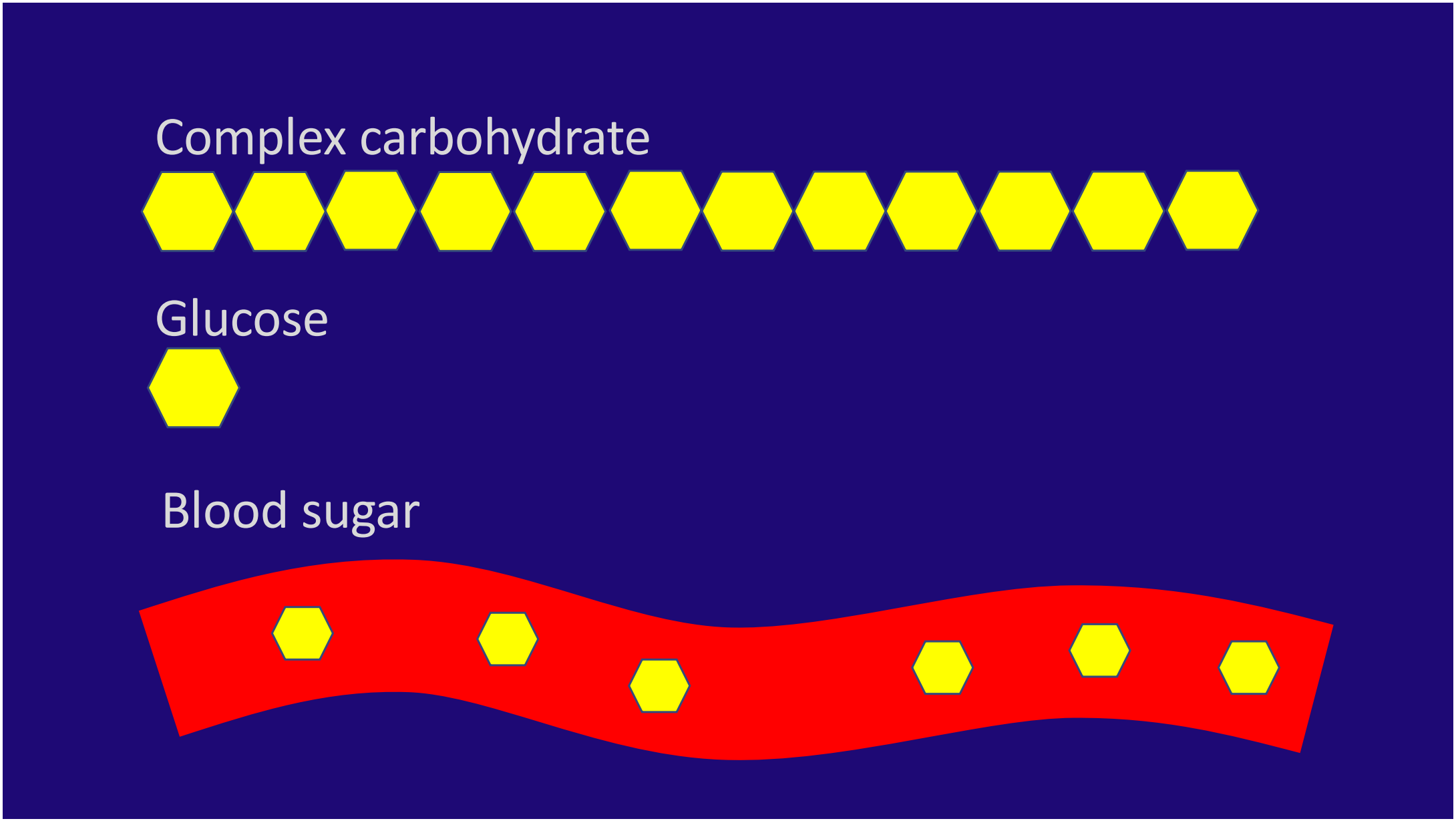


J Clin Endocrinol Metab. 2008 May;93(5):1971-9. doi: 10.1210/jc.2007-2289. Epub 2008 Jan 15. Acyl and total ghrelin are suppressed strongly by ingested proteins, weakly by lipids, and biphasically by carbohydrates.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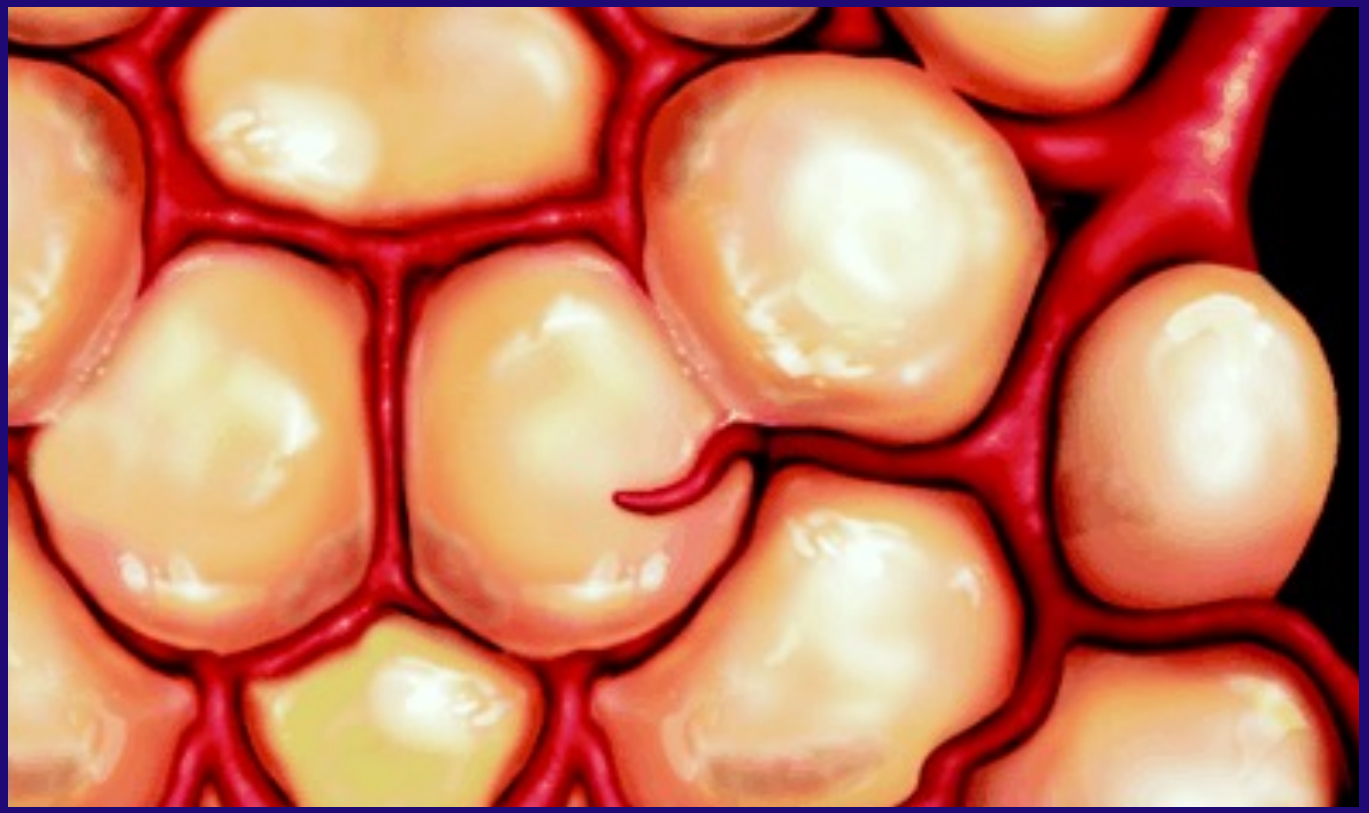
Glucose
Blood sugar



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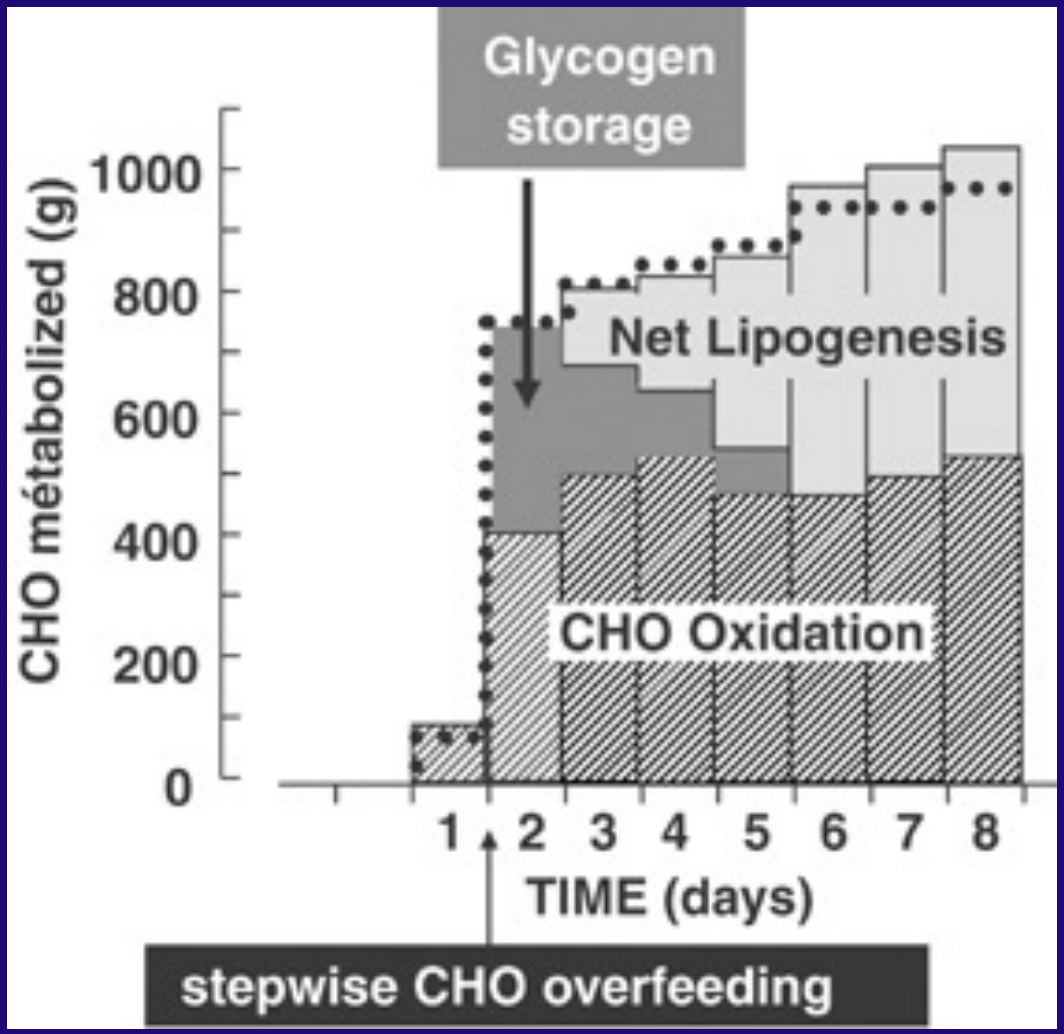
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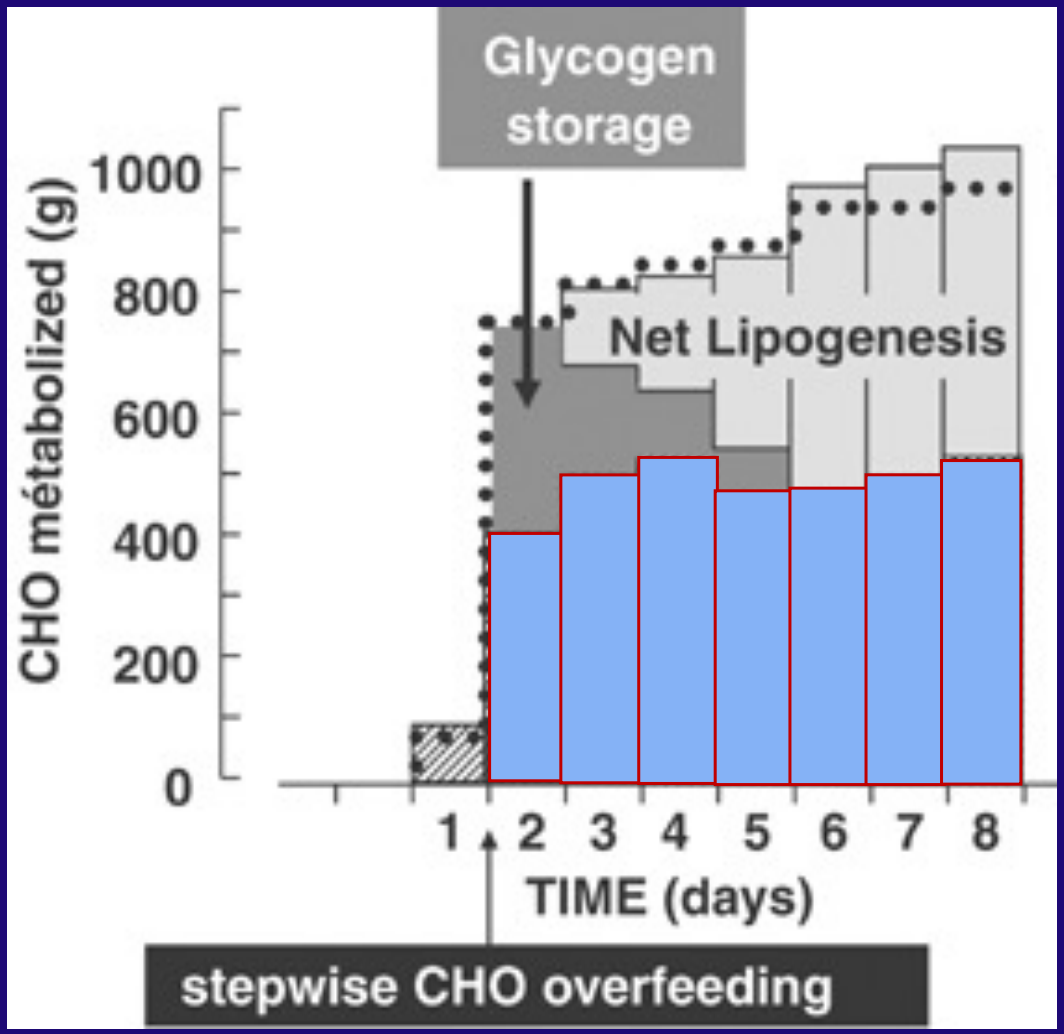
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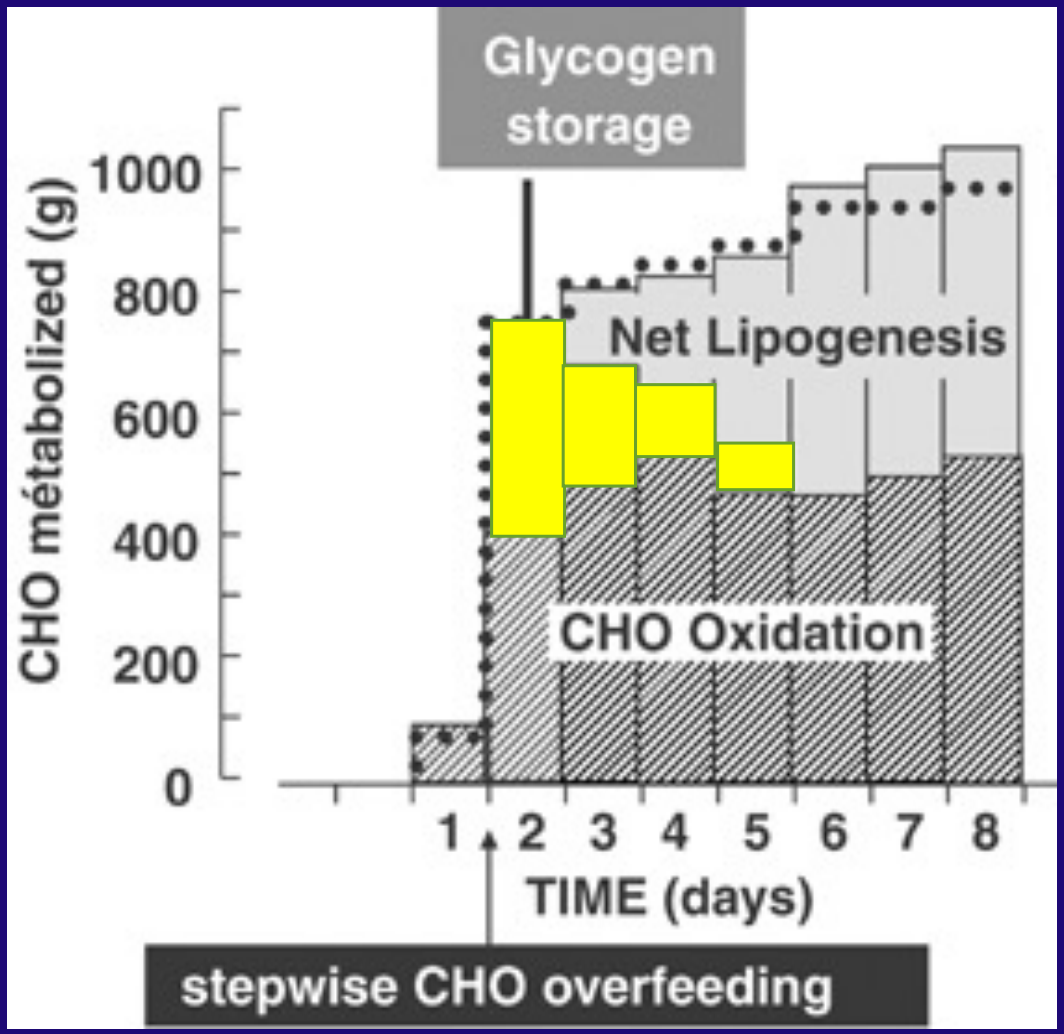
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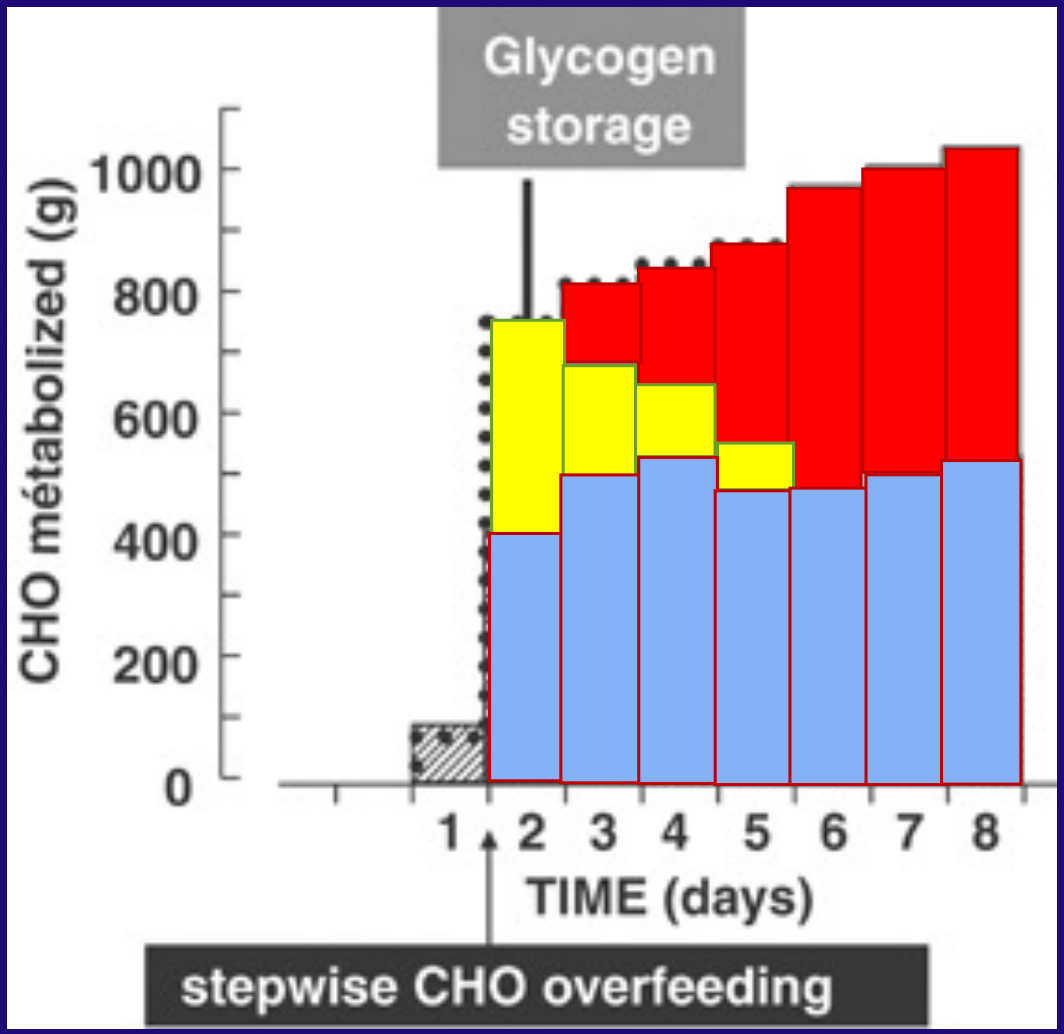
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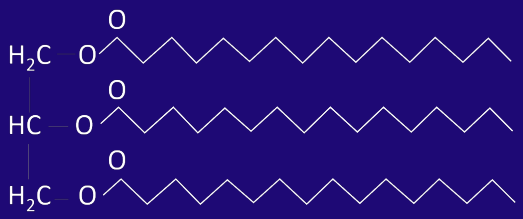
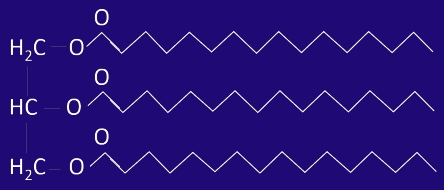
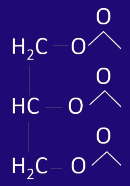

O
H2C
O
O
HC
O
O
H2C
O



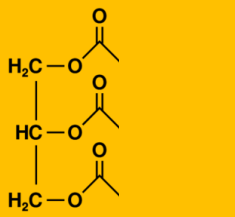
lipoprotein lipase

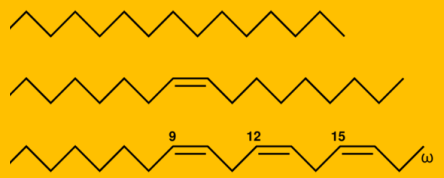
+

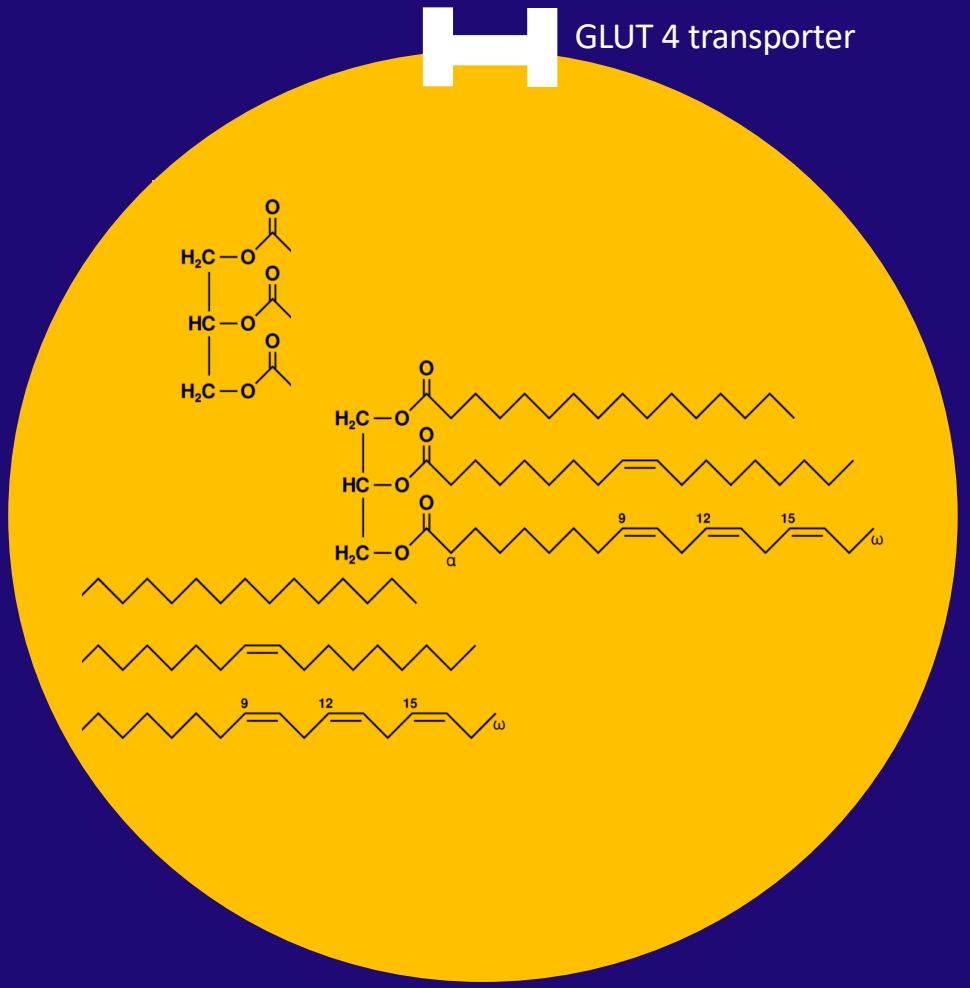

O
H2C
O
O
HC
O
O
H2C
O

glucose

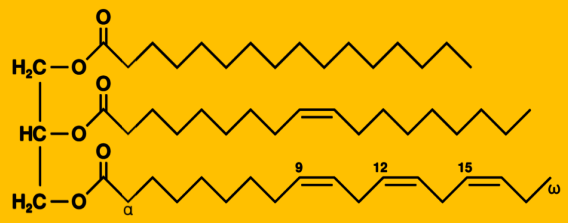
GLUT 4 transporter



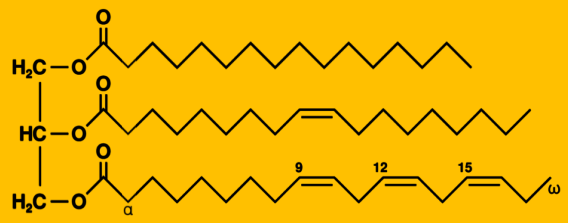



GLUT 4 transporter
O
H2C — O
HC — O
H2C — O
9
12
15
ω
α

GLUT 4 transporter

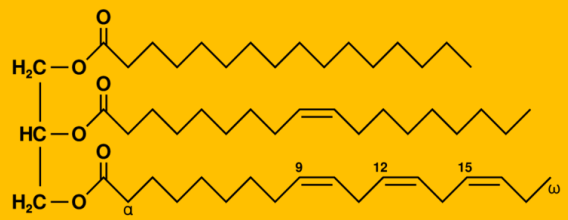


GLUT 4 transporter

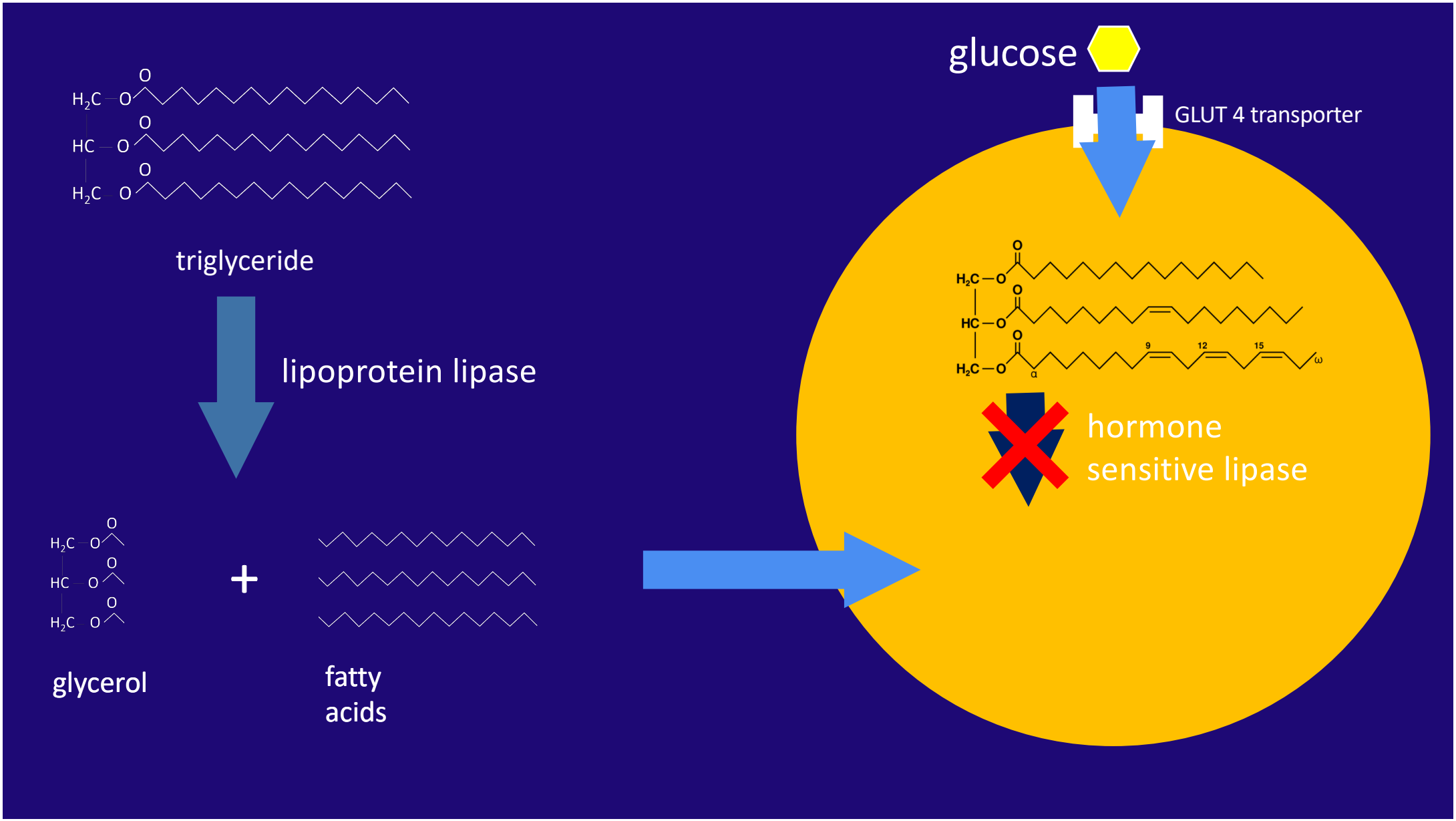


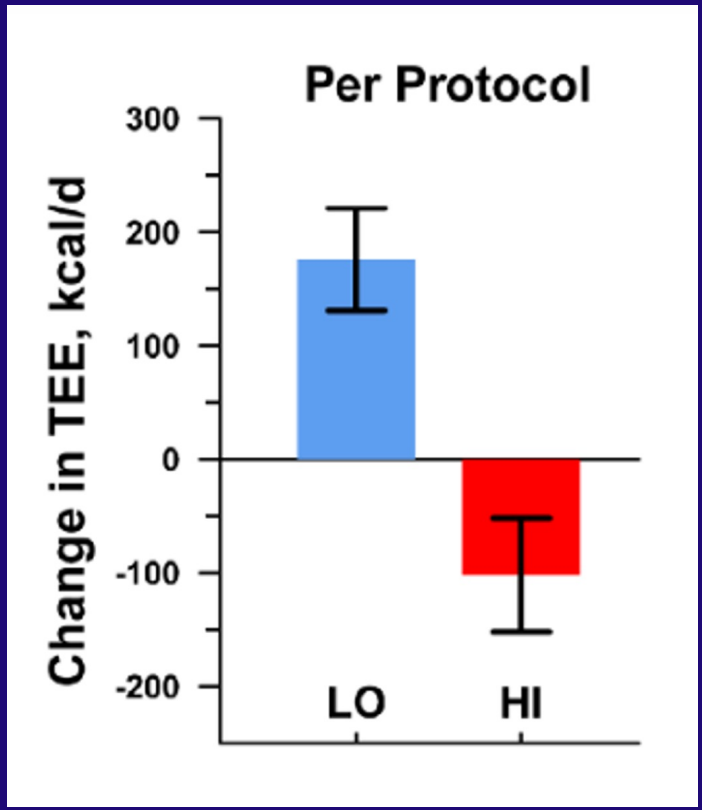
hormone sensitive lipase

GLUT 4 transporter



hormone sensitive lipase


glucose
GLUT 4 transporter
triglyceride
lipoprotein lipase
hormone
sensitive lipase
glycerol
fatty
acids



https://elemental.medium.com/major-study-supports-carbohydrate-insulin-model-of-obesity-cb7d47a571d9

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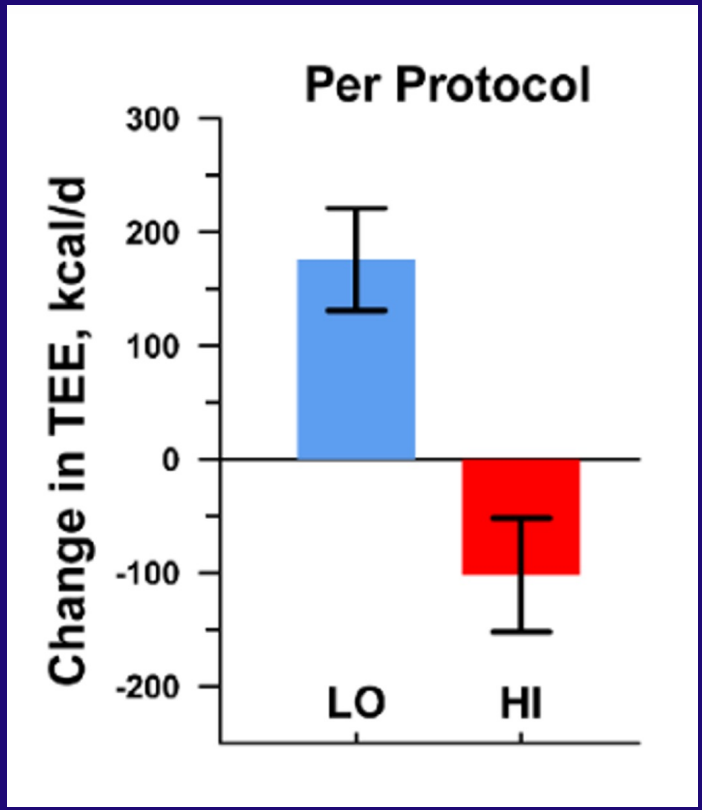

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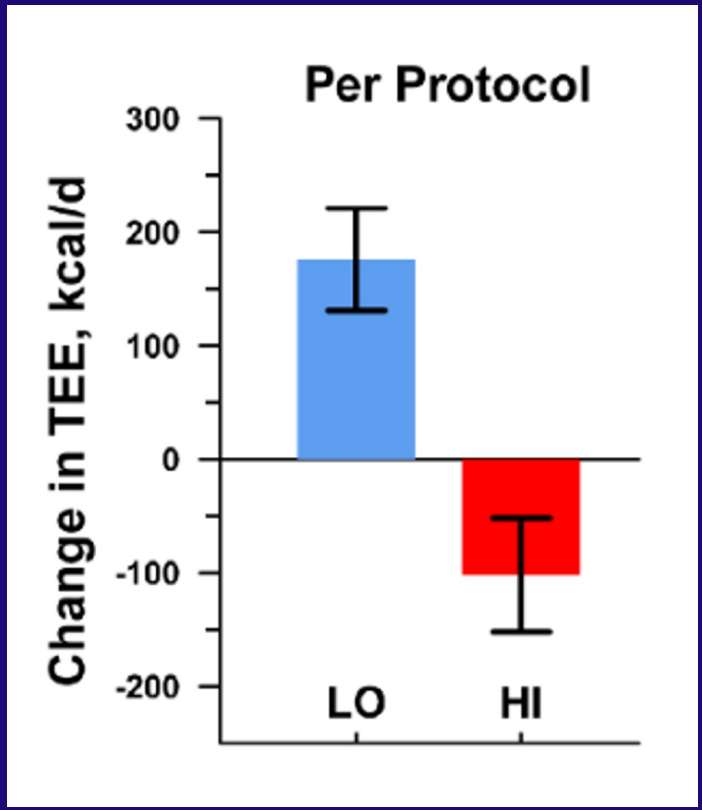

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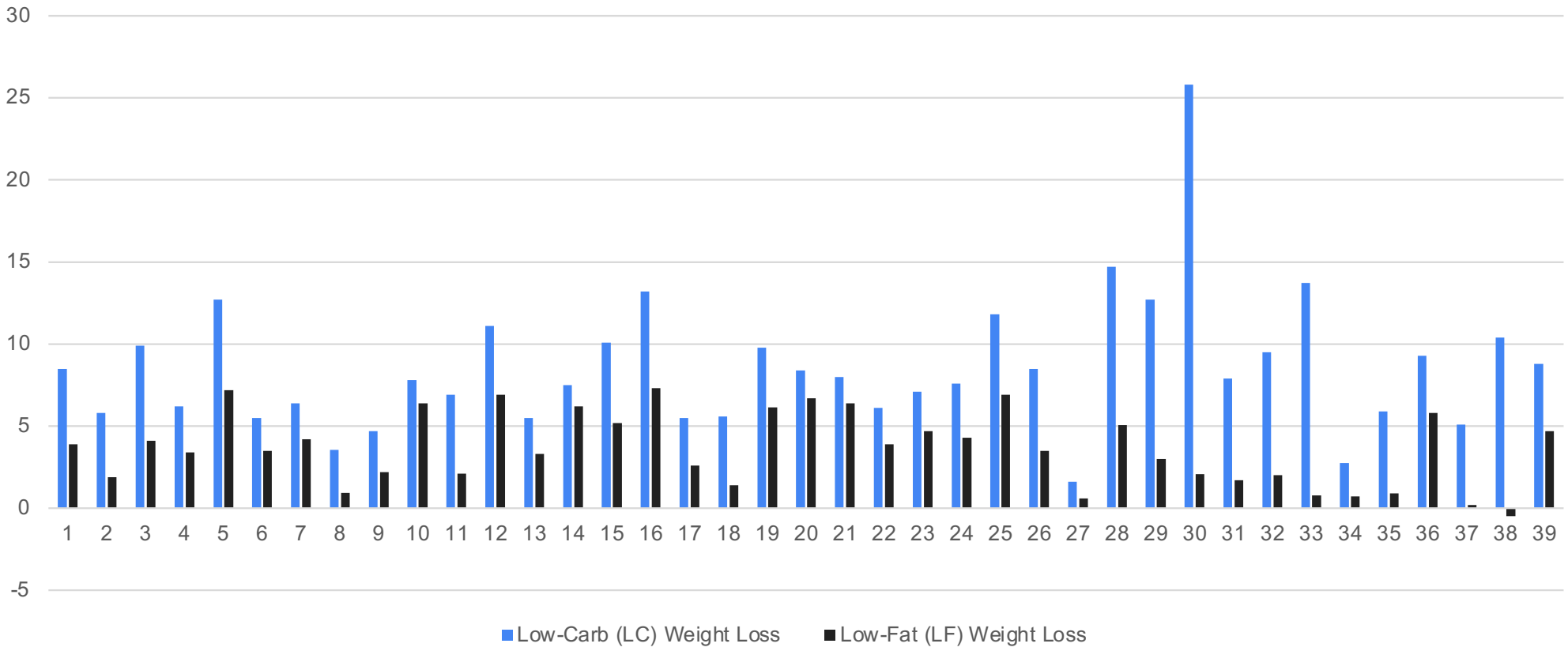
RCT's (with statistically significant findings) comparing weight loss on Low Carb vs Low Fat diets between 2003-2023



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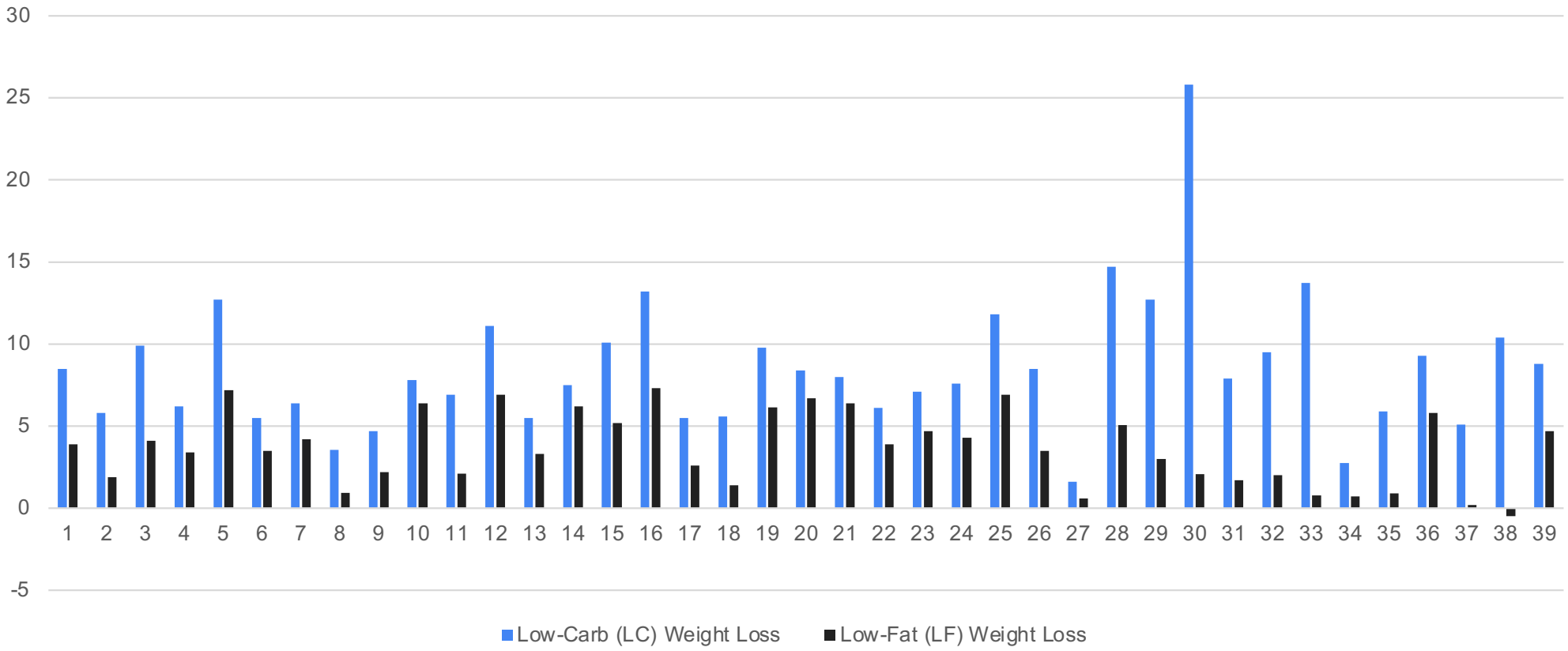
RCT's (with statistically significant findings) comparing weight loss on Low Carb vs Low Fat diets between 2003-2023



https://phcuk.org/evidence/rcts/

DIETARY REFERENCE INTAKES

FOR

Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids

Panel on Macronutrients, Panel on the Definition of Dietary Fiber, Subcommittee on Upper Reference Levels of Nutrients, Subcommittee on Interpretation and Uses of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes

Food and Nutrition Board

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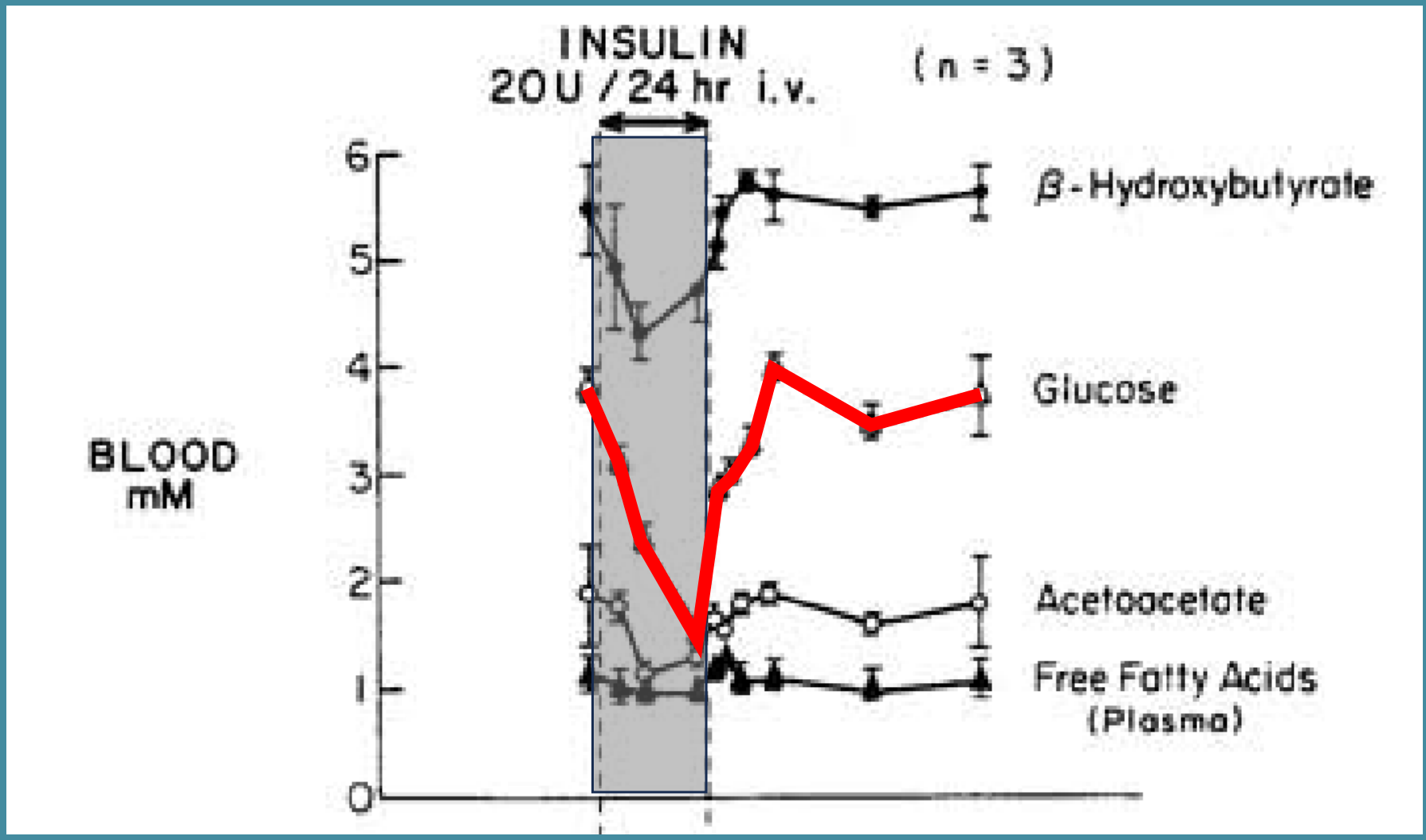
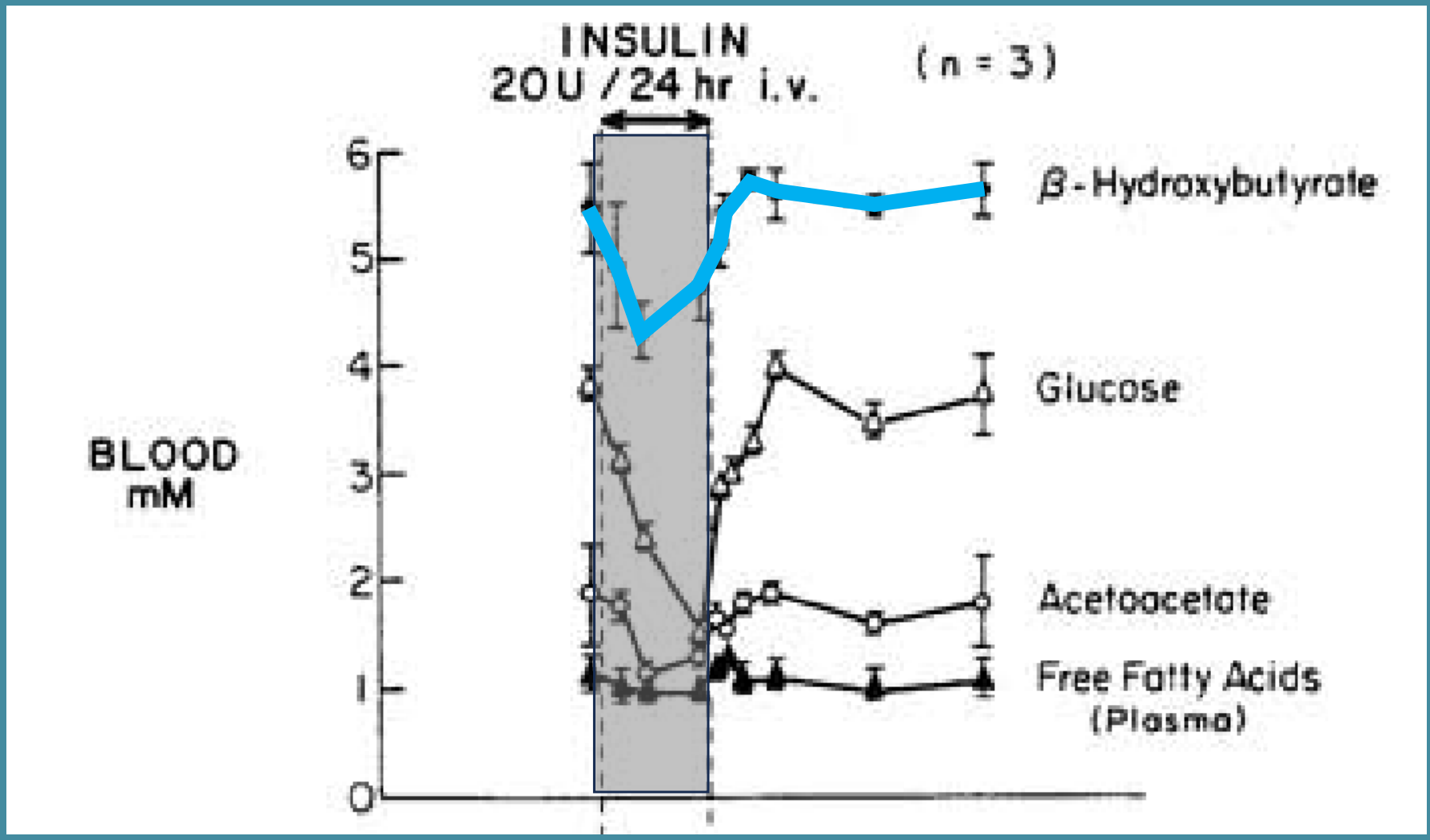


Alternate Fuel Utilization by Brain. GF Cahill, TT Aoki Cerebral Metabolism and Neural Function 1980, Ch.26



Alternate Fuel Utilization by Brain. GF Cahill, TT Aoki Cerebral Metabolism and Neural Function 1980, Ch.26

3.1 Limit intake of foods high in saturated fat

3.1.1 Setting the scene

Continuing research into diet and cardiovascular disease emphasises reducing saturated fat in the diet, which means limiting intake of foods with high saturated fat content. Fat is a nutrient in food but the term 'fats' has also been applied to whole foods (e.g. butter, margarine and oils). Foods known as fats can also be ingredients in other foods (e.g. cakes and biscuits) or added as a culinary adjunct (e.g. oil in cooking or dressings). As a nutrient, fat has high energy value (fat delivers about 37 kJ/g, compared to around 17 kJ/g for carbohydrate and protein).

The evidence indicates that replacing dietary saturated fat with monounsaturated and polyunsaturated fats is associated with improved blood lipid profiles and reduced risk of cardiovascular disease. Replacing the type of fatty acids in fats requires a total diet approach and is not always possible with all foods. Both the amount and type of fat need to be carefully considered as all types of fat provide kilojoules and the proportion of total fat in a diet influences energy intake, which may have an impact on weight management (see Chapter 1).

As people choose to eat foods, rather than food components or nutrients, the focus of this guideline recommendation is on foods containing fats, not fatty acids *per se*. Information on particular types of fatty acids is included in the NRV Document.[8]

Most fats in foods are in the form of triglycerides, which are made up of a unit of glycerol combined with three fatty acids that may be the same or different. The differences between one triglyceride and another are largely due to the fatty acids attached to the glycerol unit. Other dietary fats include phospholipids, phytosterols and cholesterol.[8]

Over time, the understanding of physiological effects and pathways have been gradually refined – for example, with the discovery of low-density and high-density cholesterol and more recently, the discovery of sub-fractions of these.[664] Additional physiological characteristics are being studied as possible markers of cardiovascular risk (e.g. vascular reactivity and carotid intima medial thickness). It is also apparent that not all fatty acids within each group have the same effects – for example, stearic acid might not have the same effects as some other saturated fatty acids (SFAs).[664] However, as a general message to the public, limiting total dietary saturated fat remains the best guide.

Corn Oil in Treatment of Ischaemic Heart Disease

G. A. ROSE,* D.M., M.R.C.P. ; W. B. THOMSON,† M.D., M.R.C.P. ; R. T. WILLIAMS,‡ M.B., M.R.C.P.

Brit. med. J., 1965, **1**, 1531–1533

It has been shown that ischaemic heart disease tends to be associated with elevated levels of serum cholesterol, both in populations (Keys *et al.*, 1958) and in individuals (Kannel *et al.*, 1961). There is also evidence that population levels of serum cholesterol are sometimes correlated with (among other characteristics) a high intake of animal fats and a relatively low intake of unsaturated vegetable oils (Bronte-Stewart *et al.*, 1955). Attempts to demonstrate such a correlation in individuals between customary diet and serum-cholesterol level have been unsuccessful (Morris *et al.*, 1963) ; but the level may be altered by changes in fat intake (Ahrens *et al.*, 1955 ; Gordon and Brock, 1958 ; and Pilkington *et al.*, 1960).

From this it has seemed worth investigating the effects on ischaemic heart disease of reducing the level of serum cholesterol. Adequately controlled therapeutic trials have been reported for cholesterol-lowering hormones (Stamler *et al.*, 1960; Oliver and Boyd, 1961), with negative results. Nevertheless it is desirable to test the dietary hypothesis more directly. The results of prophylactic trials of this kind are unlikely to be available for some time. In the meantime it is of clinical interest to know whether patients with established ischaemic heart disease can be benefited by dietary manipulation. A simple reduction of fat intake has failed to show any benefit (Ball *et al.*, 1964) ; but no adequately controlled " double-blind " trial of an unsaturated oil has yet been reported.

Aims

Our purpose was to study the effects of prescribing a vegetable oil and a restricted fat diet to patients with ischaemic heart disease. The primary interest was in an unsaturated oil with a cholesterol-lowering effect. But large doses of any oil may have secondary effects on diet and nutrition, so that differences between an unsaturated-oil group and a control group might be due to these secondary effects rather than to unsaturated fatty acids as such. It could, for example, be relevant that mortality from heart disease is low in Italy and Greece, whose inhabitants consume much olive oil ; this oil has no major effect on serum-cholesterol level, its main fatty acid (oleic acid) being only mono-unsaturated. The trial was therefore designed to study the effects not only of a more highly unsaturated oil (corn oil) but also of olive oil. It seemed likely that if any differences emerged between the olive-oil and corn-oil groups these would reflect the specific effects of polyunsaturated fatty acids.

Methods

Patients were accepted for the trial who met the following criteria. (1) *Either* electrocardiographic evidence of infarction (abnormal Q/QS waves, or typical serial ST/T changes) *or* clear history of angina of effort, meeting World Health Organization precise criteria (Rose, 1962) with or without changes in the resting electrocardiogram, but without valvular disease, anaemia, or syphilis. (2) Age under 70 years. (3) Absence of heart failure, and also of any non-cardiac disease likely to threaten life within two years. (4) Absence of personal or geographical factors likely to interfere with clinic attendance or the taking of oil.

When a new patient was accepted for the trial a sealed envelope was opened containing the allocation instructions. In the case of patients allocated to an oil group the instructions referred only to a code number. Thus the physicians in charge knew which patients were receiving oil, but they did not know until the end of the trial the kind of oil that they were receiving.

All patients received conventional treatments, at the discretion of the physicians. At the time when the trial started long-term anticoagulant therapy was seldom used. Later it became more popular, especially for patients suffering reinfarction. To avoid confusion by possible interactions between treatments a few patients already receiving this treatment were excluded from entry to the trial ; and in addition the occurrence of infarction after entry was taken as an end-point, the patient being then withdrawn from the trial.

Patients in both oil groups were instructed to avoid fried foods, fatty meat, sausages, pastry, ice-cream, cheese, cakes (except plain sponge), etc. Milk, eggs, and butter were restricted. An oil supplement of 80 g./day was prescribed, to be taken in three equal doses at meal-times. The general nature and purpose of treatment were explained, together with the fact that different patients were receiving different kinds of oil. No advice on dietary fat was give to control patients.

All patients attended a special follow-up clinic, initially at monthly intervals, and later every two months. Assessment was by standardized history, physical examination, and electrocardiography. The electrocardiograms were assessed without knowledge of the patient's treatment group. The trial was planned to cover three years' observation of each patient ; but by the end of two years only one-half of the patients remained in the trial, the rest being dead, removed for reinfarction, or lost to follow-up. Consequently the results for only the first two years will be reported here.

Fears have recently been expressed, both within the profession and outside it, that clinical trials may sometimes operate against the best interests of the patients. We would like to

TABLE I.—*Characteristics of Patients at Entry to Trial in the Three Treatment Groups*

	Treatment Group		
	Control	Olive Oil	Corn Oil
Total No. of patients	26	26	28
Mean age at entry (years)	58·8	55·0	52·6
„ body weight (kg.)	71·8	71·4	75·9
„ serum cholesterol (mg./100 ml.)	253	262	263
History of angina only	5	4	4
Resting E.C.G. normal	0	3	2
„ „ abnormal	5	1	2
History of infarction	21	22	24
1 infarct only	17	17	20
2 or more infarcts	4	5	4
Resting E.C.G. normal	1	4	3
„ „ abnormal	20	18	21
Diastolic B.P. ≤ 90 mm.	9	14	13
„ „ > 90 mm.	12	8	11
No exertional dyspnoea	9	7	15
Exertional dyspnoea	12	15	9
No heart failure	14	15	19
Heart failure*	7	7	5

* Jugular venous congestion *or* oedema *or* basal fine rales.

* Senior Lecturer to the Medical Unit, St. Mary's Hospital, London.
† Consultant Physician, High Wycombe Group Hospitals ; formerly Senior Registrar, St. Mary's Hospital, London.
‡ Consultant Physician, Crumpshall Hospital, Manchester ; formerly Registrar, St. Mary's Hospital, London.

RESEARCH

Use of dietary linoleic acid for secondary prevention of coronary heart disease and death: evaluation of recovered data from the Sydney Diet Heart Study and updated meta-analysis

Christopher E Ramsden *clinical investigator*[1 2], Daisy Zamora *epidemiologist*[2], Boonseng Leelarthaepin *retired, original study investigator*[3], Sharon F Majchrzak-Hong *research chemist*[1], Keturah R Faurot *epidemiology doctoral candidate*[2], Chirayath M Suchindran *senior biostatistician*[4], Amit Ringel *guest researcher*[1], John M Davis *professor*[5], Joseph R Hibbeln *senior clinical investigator*[1]

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Abstract

Objective To evaluate the effectiveness of replacing dietary saturated fat with omega 6 linoleic acid, for the secondary prevention of coronary heart disease and death.

Design Evaluation of recovered data from the Sydney Diet Heart Study, a single blinded, parallel group, randomized controlled trial conducted in 1966-73; and an updated meta-analysis including these previously missing data.

Setting Ambulatory, coronary care clinic in Sydney, Australia.

Participants 458 men aged 30-59 years with a recent coronary event.

Interventions Replacement of dietary saturated fats (from animal fats, common margarines, and shortenings) with omega 6 linoleic acid (from safflower oil and safflower oil polyunsaturated margarine). Controls received no specific dietary instruction or study foods. All non-dietary aspects were designed to be equivalent in both groups.

Outcome measures All cause mortality (primary outcome), cardiovascular mortality, and mortality from coronary heart disease (secondary outcomes). We used an intention to treat, survival analysis approach to compare mortality outcomes by group.

Results The intervention group (n=221) had higher rates of death than controls (n=237) (all cause 17.6% *v* 11.8%, hazard ratio 1.62 (95% confidence interval 1.00 to 2.64), P=0.05; cardiovascular disease 17.2% *v* 11.0%, 1.70 (1.03 to 2.80), P=0.04; coronary heart disease 16.3% *v* 10.1%, 1.74 (1.04 to 2.92), P=0.04). Inclusion of these recovered data in an updated meta-analysis of linoleic acid intervention trials showed non-significant trends toward increased risks of death from coronary heart disease (hazard ratio 1.33 (0.99 to 1.79); P=0.06) and cardiovascular disease (1.27 (0.98 to 1.65); P=0.07).

Conclusions Advice to substitute polyunsaturated fats for saturated fats is a key component of worldwide dietary guidelines for coronary heart disease risk reduction. However, clinical benefits of the most abundant polyunsaturated fatty acid, omega 6 linoleic acid, have not been established. In this cohort, substituting dietary linoleic acid in place of saturated fats increased the rates of death from all causes, coronary heart disease, and cardiovascular disease. An updated meta-analysis of linoleic acid intervention trials showed no evidence of cardiovascular benefit. These findings could have important implications for worldwide dietary advice to substitute omega 6 linoleic acid, or polyunsaturated fats in general, for saturated fats.

Trial registration Clinical trials NCT01621087.

Introduction

Advice to substitute vegetable oils rich in polyunsaturated fatty acids (PUFAs) for animal fats rich in saturated fatty acids (SFAs) has been a cornerstone of worldwide dietary guidelines

Test of Effect of Lipid Lowering by Diet on Cardiovascular Risk

The Minnesota Coronary Survey

Ivan D. Frantz Jr., Emily A. Dawson, Patricia L. Ashman, Laël C. Gatewood, Glenn E. Bartsch, Kanta Kuba, and Elizabeth R. Brewer

The Minnesota Coronary Survey was a 4.5-year, open enrollment, single end-time, double-blind, randomized clinical trial that was conducted in six Minnesota state mental hospitals and one nursing home. It involved 4393 institutionalized men and 4664 institutionalized women. The trial compared the effects of a 39% fat control diet (18% saturated fat, 5% polyunsaturated fat, 16% monounsaturated fat, 446 mg dietary cholesterol per day) with a 38% fat treatment diet (9% saturated fat, 15% polyunsaturated fat, 14% monounsaturated fat, 166 mg dietary cholesterol per day) on serum cholesterol levels and the incidence of myocardial infarctions, sudden deaths, and all-cause mortality. The mean duration of time on the diets was 384 days, with 1568 subjects consuming the diet for over 2 years. The mean serum cholesterol level in the pre-admission period was 207 mg/dl, falling to 175 mg/dl in the treatment group and 203 mg/dl in the control group. For the entire study population, no differences between the treatment and control groups were observed for cardiovascular events, cardiovascular deaths, or total mortality. A favorable trend for all these end-points occurred in some younger age groups.
(Arteriosclerosis 9:129–135, January/February 1989)

The institutions chosen for the trial were the Minnesota state mental hospitals at Anoka, Fergus Falls, Hastings, Moose Lake, St. Peter, and Willmar and the nursing home at Oak Terrace. Before initiation of the experimental phase, the populations were observed for a 3-year period, during which their suitability for a long-term dietary trial was studied. The feeding program began in the Willmar State Hospital in November, 1968. The program was phased in to the other institutions in succession over the following 15 months. The trial was an outgrowth of the National Diet-Heart Feasibility Study.[1]

Methods

Ethical Considerations

The project was approved by the Clinical Research Committee of the University and, after extensive discussion with the relevant institutional committees, by each of the collaborating hospitals. No consent forms were required on the grounds that the two diets were both acceptable as house diets and the tests all contributed to better patient care. Before initiation of the study in each hospital, all the residents and staff were invited to a meeting at which the investigators explained the project. Samples of the foods were served at these meetings. There was a question and answer period, and the residents were invited to make appointments for one-to-one further explanations if they wished. They were allowed to decline to participate or to discontinue their participation at any time. Nonparticipants were served the control diet, which was similar to the pre-study institutional diets. Blood was not drawn from nonparticipants, and electrocardiograms were not recorded. Participation was nearly 100% with fewer than a dozen refusals throughout the trial.

Experimental Plan

The original population was initially stratified into 512 cells on the basis of eight variables. These were: age, sex, length of stay in the hospital, weight, blood pressure, diabetes, cigarette smoking, and evidence by electrocardiogram of a previous myocardial infarction. When new subjects were admitted later, they were divided among four cells, based on only age and sex.

Two diets were served. The control diet involved little departure from the institutional diet served before the trial. The treatment diet represented a compromise between the B and C diets of the National Diet-Heart Study, with target values of 45% of calories from fat, a polyunsaturated/saturated fat (P/S) ratio of 2.5, and less than 150 mg of cholesterol daily.

Both diets were served in a single line. As a participant entered the line, he or she was handed a label bearing his or her name and a code number that was incomprehensible to the uninitiated but easily interpreted by the food servers to determine which diet was to be served. A new set of 21 labels was prepared by computer each week for each participant based on changes in the population during that week. The label served multiple purposes.

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This work was supported by Grant No. HE 09686 from the National Heart, Lung, and Blood Institute.

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Re-evaluation of the traditional diet-heart hypothesis: analysis of recovered data from Minnesota Coronary Experiment (1968-73)

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ABSTRACT

OBJECTIVE

To examine the traditional diet-heart hypothesis through recovery and analysis of previously unpublished data from the Minnesota Coronary Experiment (MCE) and to put findings in the context of existing diet-heart randomized controlled trials through a systematic review and meta-analysis.

DESIGN

The MCE (1968-73) is a double blind randomized controlled trial designed to test whether replacement of saturated fat with vegetable oil rich in linoleic acid reduces coronary heart disease and death by lowering serum cholesterol. Recovered MCE unpublished documents and raw data were analyzed according to hypotheses prespecified by original investigators. Further, a systematic review and meta-analyses of randomized controlled trials that lowered serum cholesterol by providing vegetable oil rich in linoleic acid in place of saturated fat without confounding by concomitant interventions was conducted.

SETTING

One nursing home and six state mental hospitals in Minnesota, United States.

PARTICIPANTS

Unpublished documents with completed analyses for the randomized cohort of 9423 women and men aged 20-97; longitudinal data on serum cholesterol for the 2355 participants exposed to the study diets for a year or more; 149 completed autopsy files.

INTERVENTIONS

Serum cholesterol lowering diet that replaced saturated fat with linoleic acid (from corn oil and corn oil polyunsaturated margarine). Control diet was high in saturated fat from animal fats, common margarines, and shortenings.

MAIN OUTCOME MEASURES

Death from all causes; association between changes in serum cholesterol and death; and coronary atherosclerosis and myocardial infarcts detected at autopsy.

RESULTS

The intervention group had significant reduction in serum cholesterol compared with controls (mean change from baseline −13.8% *v* −1.0%; P<0.001). Kaplan Meier graphs showed no mortality benefit for the intervention group in the full randomized cohort or for any prespecified subgroup. There was a 22% higher risk of death for each 30 mg/dL (0.78 mmol/L) reduction in serum cholesterol in covariate adjusted Cox regression models (hazard ratio 1.22, 95% confidence interval 1.14 to 1.32; P<0.001). There was no evidence of benefit in the intervention group for coronary atherosclerosis or myocardial infarcts. Systematic review identified five randomized controlled trials for inclusion (n=10 808). In meta-analyses, these cholesterol lowering interventions showed no evidence of benefit on mortality from coronary heart disease (1.13, 0.83 to 1.54) or all cause mortality (1.07, 0.90 to 1.27).

CONCLUSIONS

Available evidence from randomized controlled trials shows that replacement of saturated fat in the diet with linoleic acid effectively lowers serum cholesterol but does not support the hypothesis that this translates to a lower risk of death from coronary heart disease or all causes. Findings from the Minnesota Coronary Experiment add to growing evidence that incomplete publication has contributed to overestimation of the benefits of replacing saturated fat with vegetable oils rich in linoleic acid.

WHAT IS ALREADY KNOWN ON THIS TOPIC

The traditional diet-heart hypothesis predicts that replacing saturated fat with vegetable oils rich in linoleic acid will reduce cardiovascular deaths by lowering serum cholesterol

This paradigm has never been causally demonstrated in a randomized controlled trial and thus has remained uncertain for over 50 years

Key findings from landmark randomized controlled trials including the Sydney Diet Heart Study and the Minnesota Coronary Experiment (MCE) were not fully published

WHAT THIS STUDY ADDS

Though the MCE intervention lowered serum cholesterol, this did not translate to improved survival

Paradoxically, MCE participants who had greater reductions in serum cholesterol had a higher, rather than lower, risk of death

Results of a systematic review and meta-analysis of randomized controlled trials do not provide support for the traditional diet heart hypothesis

Introduction

The traditional diet-heart hypothesis[1 2] predicts that the serum cholesterol lowering effects of replacing saturated fat with vegetable oil rich in linoleic acid will diminish deposition of cholesterol in the arterial wall,[3 4] slow progression of atherosclerosis,[5] reduce coronary heart disease events, and improve survival.[6 7] This diet-heart paradigm is supported by evidence from randomized controlled trials showing that replacement of saturated fat with linoleic acid lowers serum total cholesterol and low density lipoprotein[8-12] and by observational evidence linking serum cholesterol to coronary heart disease events and deaths (fig 1).[13] Despite these

Low-Fat Dietary Pattern and Risk of Cardiovascular Disease

The Women's Health Initiative Randomized Controlled Dietary Modification Trial

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Context Multiple epidemiologic studies and some trials have linked diet with cardiovascular disease (CVD) prevention, but long-term intervention data are needed.

Objective To test the hypothesis that a dietary intervention, intended to be low in fat and high in vegetables, fruits, and grains to reduce cancer, would reduce CVD risk.

Design, Setting, and Participants Randomized controlled trial of 48 835 postmenopausal women aged 50 to 79 years, of diverse backgrounds and ethnicities, who participated in the Women's Health Initiative Dietary Modification Trial. Women were randomly assigned to an intervention (19 541 [40%]) or comparison group (29 294 [60%]) in a free-living setting. Study enrollment occurred between 1993 and 1998 in 40 US clinical centers; mean follow-up in this analysis was 8.1 years.

Intervention Intensive behavior modification in group and individual sessions designed to reduce total fat intake to 20% of calories and increase intakes of vegetables/fruits to 5 servings/d and grains to at least 6 servings/d. The comparison group received diet-related education materials.

Main Outcome Measures Fatal and nonfatal coronary heart disease (CHD), fatal and nonfatal stroke, and CVD (composite of CHD and stroke).

Results By year 6, mean fat intake decreased by 8.2% of energy intake in the intervention vs the comparison group, with small decreases in saturated (2.9%), monounsaturated (3.3%), and polyunsaturated (1.5%) fat; increases occurred in intakes of vegetables/fruits (1.1 servings/d) and grains (0.5 serving/d). Low-density lipoprotein cholesterol levels, diastolic blood pressure, and factor VIIc levels were significantly reduced by 3.55 mg/dL, 0.31 mm Hg, and 4.29%, respectively; levels of high-density lipoprotein cholesterol, triglycerides, glucose, and insulin did not significantly differ in the intervention vs comparison groups. The numbers who developed CHD, stroke, and CVD (annualized incidence rates) were 1000 (0.63%), 434 (0.28%), and 1357 (0.86%) in the intervention and 1549 (0.65%), 642 (0.27%), and 2088 (0.88%) in the comparison group. The diet had no significant effects on incidence of CHD (hazard ratio [HR], 0.97; 95% confidence interval [CI], 0.90-1.06), stroke (HR, 1.02; 95% CI, 0.90-1.15), or CVD (HR, 0.98; 95% CI, 0.92-1.05). Excluding participants with baseline CVD (3.4%), the HRs (95% CIs) for CHD and stroke were 0.94 (0.86-1.02) and 1.02 (0.90-1.17), respectively. Trends toward greater reductions in CHD risk were observed in those with lower intakes of saturated fat or *trans* fat or higher intakes of vegetables/fruits.

Conclusions Over a mean of 8.1 years, a dietary intervention that reduced total fat intake and increased intakes of vegetables, fruits, and grains did not significantly reduce the risk of CHD, stroke, or CVD in postmenopausal women and achieved only modest effects on CVD risk factors, suggesting that more focused diet and lifestyle interventions may be needed to improve risk factors and reduce CVD risk.

Clinical Trials Registration ClinicalTrials.gov Identifier NCT00000611

JAMA. 2006;295:655-666 www.jama.com

CLINICAL TRIALS AND OBSERVATIONAL studies have identified strong associations between low-density lipoprotein cholesterol (LDL-C) level and other cardiovascular disease (CVD) risk factors and dietary intake of fats, particularly

See also pp 629, 643, and 693.

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RESEARCH

Use of dietary linoleic acid for secondary prevention of coronary heart disease and death: evaluation of recovered data from the Sydney Diet Heart Study and updated meta-analysis

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Abstract

Objective To evaluate the effectiveness of replacing dietary saturated fat with omega 6 linoleic acid, for the secondary prevention of coronary heart disease and death.

Design Evaluation of recovered data from the Sydney Diet Heart Study, a single blinded, parallel group, randomized controlled trial conducted in 1966-73; and an updated meta-analysis including these previously missing data.

Setting Ambulatory, coronary care clinic in Sydney, Australia.

Participants 458 men aged 30-59 years with a recent coronary event.

Interventions Replacement of dietary saturated fats (from animal fats, common margarines, and shortenings) with omega 6 linoleic acid (from safflower oil and safflower oil polyunsaturated margarine). Controls received no specific dietary instruction or study foods. All non-dietary aspects were designed to be equivalent in both groups.

Outcome measures All cause mortality (primary outcome), cardiovascular mortality, and mortality from coronary heart disease (secondary outcomes). We used an intention to treat, survival analysis approach to compare mortality outcomes by group.

Results The intervention group (n=221) had higher rates of death than controls (n=237) (all cause 17.6% *v* 11.8%, hazard ratio 1.62 (95% confidence interval 1.00 to 2.64), P=0.05; cardiovascular disease 17.2% *v* 11.0%, 1.70 (1.03 to 2.80), P=0.04; coronary heart disease 16.3% *v* 10.1%, 1.74 (1.04 to 2.92), P=0.04). Inclusion of these recovered data in an updated meta-analysis of linoleic acid intervention trials showed non-significant trends toward increased risks of death from coronary heart disease (hazard ratio 1.33 (0.99 to 1.79); P=0.06) and cardiovascular disease (1.27 (0.98 to 1.65); P=0.07).

Conclusions Advice to substitute polyunsaturated fats for saturated fats is a key component of worldwide dietary guidelines for coronary heart disease risk reduction. However, clinical benefits of the most abundant polyunsaturated fatty acid, omega 6 linoleic acid, have not been established. In this cohort, substituting dietary linoleic acid in place of saturated fats increased the rates of death from all causes, coronary heart disease, and cardiovascular disease. An updated meta-analysis of linoleic acid intervention trials showed no evidence of cardiovascular benefit. These findings could have important implications for worldwide dietary advice to substitute omega 6 linoleic acid, or polyunsaturated fats in general, for saturated fats.

Trial registration Clinical trials NCT01621087.

Introduction

Advice to substitute vegetable oils rich in polyunsaturated fatty acids (PUFAs) for animal fats rich in saturated fatty acids (SFAs) has been a cornerstone of worldwide dietary guidelines

Test of Effect of Lipid Lowering by Diet on Cardiovascular Risk

The Minnesota Coronary Survey

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The Minnesota Coronary Survey was a 4.5-year, open enrollment, single end-time, double-blind, randomized clinical trial that was conducted in six Minnesota state mental hospitals and one nursing home. It involved 4393 institutionalized men and 4664 institutionalized women. The trial compared the effects of a 39% fat control diet (18% saturated fat, 5% polyunsaturated fat, 16% monounsaturated fat, 446 mg dietary cholesterol per day) with a 38% fat treatment diet (9% saturated fat, 15% polyunsaturated fat, 14% monounsaturated fat, 166 mg dietary cholesterol per day) on serum cholesterol levels and the incidence of myocardial infarctions, sudden deaths, and all-cause mortality. The mean duration of time on the diets was 384 days, with 1568 subjects consuming the diet for over 2 years. The mean serum cholesterol level in the pre-admission period was 207 mg/dl, falling to 175 mg/dl in the treatment group and 203 mg/dl in the control group. For the entire study population, no differences between the treatment and control groups were observed for cardiovascular events, cardiovascular deaths, or total mortality. A favorable trend for all these end-points occurred in some younger age groups.
(Arteriosclerosis 9:129–135, January/February 1989)

The institutions chosen for the trial were the Minnesota state mental hospitals at Anoka, Fergus Falls, Hastings, Moose Lake, St. Peter, and Willmar and the nursing home at Oak Terrace. Before initiation of the experimental phase, the populations were observed for a 3-year period, during which their suitability for a long-term dietary trial was studied. The feeding program began in the Willmar State Hospital in November, 1968. The program was phased in to the other institutions in succession over the following 15 months. The trial was an outgrowth of the National Diet-Heart Feasibility Study.[1]

Methods

Ethical Considerations

The project was approved by the Clinical Research Committee of the University and, after extensive discussion with the relevant institutional committees, by each of the collaborating hospitals. No consent forms were required on the grounds that the two diets were both acceptable as house diets and the tests all contributed to better patient care. Before initiation of the study in each hospital, all the residents and staff were invited to a meeting at which the investigators explained the project. Samples of the foods were served at these meetings. There was a question and answer period, and the residents were invited to make appointments for one-to-one further explanations if they wished. They were allowed to decline to participate or to discontinue their participation at any time. Nonparticipants were served the control diet, which was similar to the pre-study institutional diets. Blood was not drawn from nonparticipants, and electrocardiograms were not recorded. Participation was nearly 100% with fewer than a dozen refusals throughout the trial.

Experimental Plan

The original population was initially stratified into 512 cells on the basis of eight variables. These were: age, sex, length of stay in the hospital, weight, blood pressure, diabetes, cigarette smoking, and evidence by electrocardiogram of a previous myocardial infarction. When new subjects were admitted later, they were divided among four cells, based on only age and sex.

Two diets were served. The control diet involved little departure from the institutional diet served before the trial. The treatment diet represented a compromise between the B and C diets of the National Diet-Heart Study, with target values of 45% of calories from fat, a polyunsaturated/saturated fat (P/S) ratio of 2.5, and less than 150 mg of cholesterol daily.

Both diets were served in a single line. As a participant entered the line, he or she was handed a label bearing his or her name and a code number that was incomprehensible to the uninitiated but easily interpreted by the food servers to determine which diet was to be served. A new set of 21 labels was prepared by computer each week for each participant based on changes in the population during that week. The label served multiple purposes.

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was 0.86 to 1.12. After women with history of CVD at baseline were removed (n=1656 [3.4%]), HRs (95% CIs) for major CHD, composite CHD, stroke, and total CVD were 0.93 (0.83-1.05), 0.94 (0.86-1.02), 1.02 (0.90-1.17), and 0.96 (0.89-1.03), respectively. The HR for the 3.4% of women with CVD at baseline was 1.26 (95% CI, 1.03-1.54). We considered the potential confounding effects of changing medication use during the trial by examining use of statins, aspirin, and angiotensin-converting enzyme inhibitors at year 6. All differences in medication use between groups were less than 1%.

In examining trends over time (FIGURE 2), there was no apparent influence of the dietary intervention on stroke at any point up to 9 years of follow-up. There appeared to be a slight, nonsignificant trend toward de-

intake revealed no significant interactions between the intervention group and any of these variables (FIGURE 3), either in the group as a whole or if women with baseline CVD were excluded. A significant interaction was observed between the intervention effect and baseline disease ($P=.006$).

Additional Analyses

When the effect of the intervention was assessed using adherence criteria based on participation in intervention activities,[28] the HRs did not change. Trends for changes in specific components of the diet were examined by evaluating CHD risk in individuals stratified by quartiles of achieved levels of key nutrients at year 1, using the rate in the comparison group as the reference. Analyses were adjusted for age, baseline CHD, and HT randomiza-

served toward reduction of CHD risk among those in the intervention group who reached the lowest levels of saturated fat (HR, 0.81; 95% CI, 0.69-0.96 in the group that consumed <6.1% energy; $P<.001$ [adjusted HR, 0.82; 95% CI, 0.67-0.99; $P=.05$]) and *trans* fat (HR, 0.81; 95% CI, 0.69-0.95 in group consuming <1.1% energy intake; $P<.001$ [adjusted HR, 0.84; 95% CI, 0.69-1.02; $P=.10$]) or the highest intakes of vegetables and fruits (HR, 0.88; 95% CI, 0.76-1.03 in the group that consumed ≥6.5 servings/d; $P<.001$ [adjusted HR, 0.89; 95% CI, 0.74-1.06; $P=.11$]). While these additional analyses are subject to residual confounding because of reporting bias or the lack of a comparable comparison group, some confidence in their validity is supported by parallel patterns of LDL-C reductions in participants strati-

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Effect of reducing saturated fat intake on cardiovascular disease in adults: an umbrella review

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Introduction: Our objective was to explore the effect of the reduction of saturated fat (SAF) intake on cardiovascular disease, mortality and other health-related outcomes in adults.

Methods: We conducted an umbrella review, searching Medline, Scopus, EMBASE, Cochrane Library, and LILACS databases for systematic reviews from December 1, 2012, to December 1, 2022. We have included meta-analyses of randomized controlled trials (RCTs) and cohort studies. We extracted effect sizes (95%CI), heterogeneity (I^2), and evidence quality rating based on the population, intervention, comparator, and outcomes.

Results: 21 meta-analyses were included (three were from RCTs, and 18 were from cohort studies). Among meta-analyses of RCTs, 15 of the 45 associations were significant. The effect of reduction in SAF intake on combined cardiovascular events (RR 0.79, 95%CI 0.66–0.93) was graded as having moderate certainty of evidence. We found no effect on all-cause mortality, cardiovascular mortality, cancer deaths, and other cardiovascular events. Among meta-analyses of cohort studies, five of the 19 associations were significant. There was an increase in coronary heart disease mortality (HR 1.10, 95% CI 1.01–1.21) and breast cancer mortality (HR 1.51, 95% CI 1.09–2.09) in participants with higher SFA intake compared to reduced SFA. We found no effect on all-cause mortality, cardiovascular mortality, and other cardiovascular events.

Conclusion: This umbrella review found the reduction in SAF intake probably reduces cardiovascular events and other health outcomes. However, it has little or no effect on cardiovascular mortality and mortality from other causes. More high-quality clinical trials with long-term follow-up are needed.

Systematic review registration: CRD42022380859.

KEYWORDS

adult, cardiovascular diseases, fatty acids, dietary fats, mortality

Elemental Balances during Intravenous Hyperalimentation of Underweight Adult Subjects

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ABSTRACT Intravenous hyperalimentation was done in 11 underweight adults whose body weight (body wt) was less than 85% of ideal. For the first 6 days, "complete formula" was infused furnishing per kilogram ideal body wt per day: 15 g glucose, 0.40 g N, 0.018 g P, 2.4 meq K, 3.0 meq Na, 2.3 meq Cl, 0.5 meq Mg, 0.45 meq Ca, and 50 ml H_2O. Patients gained weight at an average rate of 9.0 g/kg ideal body wt/day and showed average balances/kilogram ideal body wt/day as follows: + 0.14 g N; + 0.012 g P; + 0.43 meq K; + 0.49 meq Na; + 0.37 meq Cl; and + 0.085 meq Ca. Application of standard equations to the elemental balances indicated weight gain consisted of 35–50% protoplasm, 35–50% extracellular fluid, 5–25% adipose tissue, and < 1% bone.

Withdrawal of N, P, Na, or K impaired or abolished retention of other elements. Removal of N halted retention of P, K, Na, and Cl; withdrawal of K stopped retention of N and P; and removal of Na or P interrupted retention of all other elements. Weight gain continued at a rate of 1.4–3.1 g/kg ideal body wt/day despite zero or negative elemental balances of N, K, P, and sometimes Na and Cl. Calculations showed that weight gain during infusion of fluids lacking N, P, K, or Na consisted largely of adipose tissue, with little or no contribution by protoplasm or extracellular fluid.

Data show that repletion of protoplasm and extracellular fluid of wasted adults by intravenous hyperalimentation is retarded or abolished if N, P, Na, or K is lacking. Repletion of bone mineral does not occur in absence of Na or P but proceeds in absence of N or K. Repletion of adipose tissue proceeds in absence of N, P, K, or Na. Thus, quality of weight gained by underfed adult patients during hyperalimentation depends on elemental composition of the infusate.

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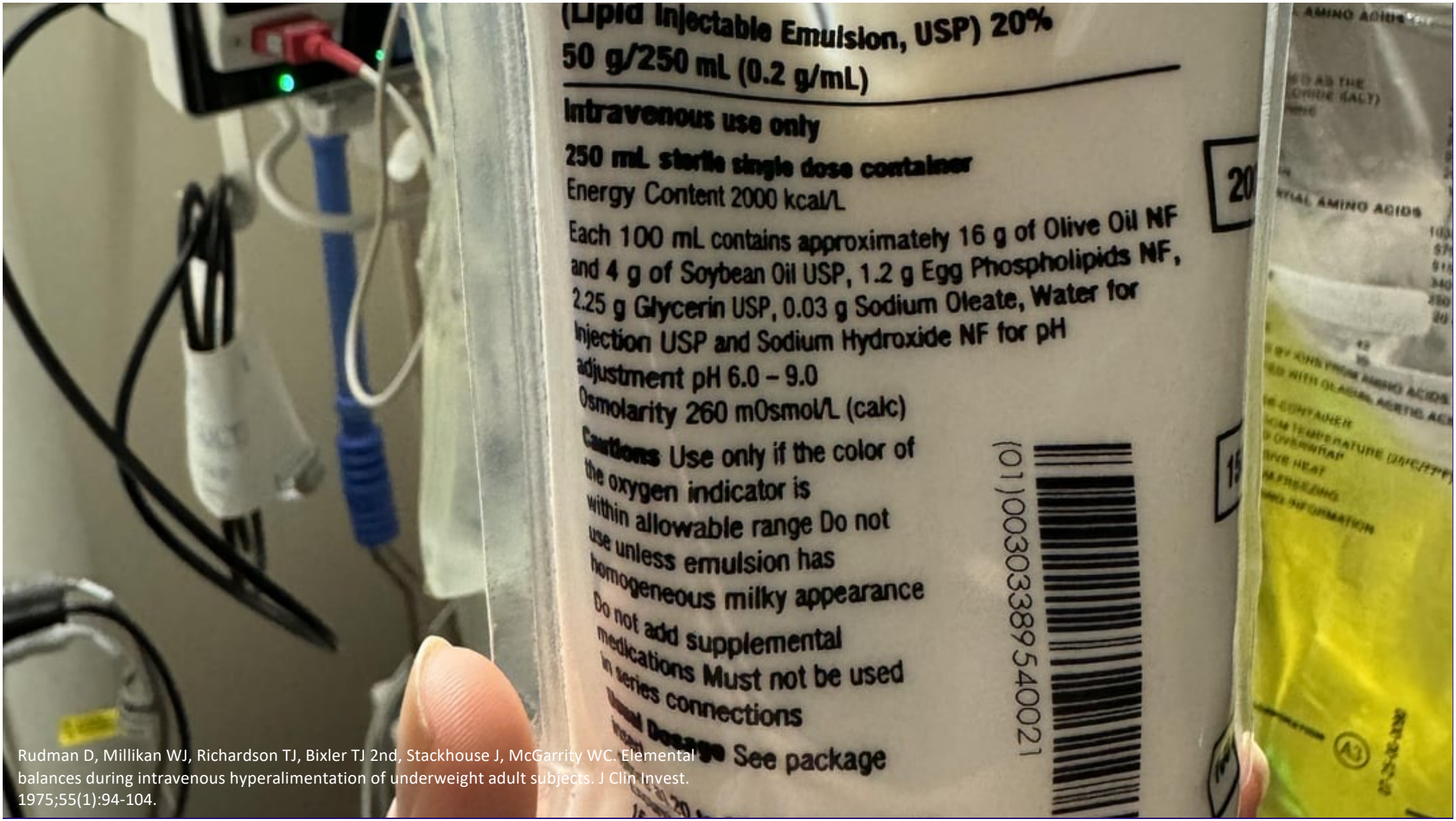
INTRODUCTION

For emaciated patients who cannot satisfy their nutritional requirements by eating, the intravenous hyperalimentation technique of Dudrick, Long, Steiger, and Rhoads (1) provides a means of achieving rapid gain in body weight (body wt).

Increase in body wt is caused by enlargement of one or more of four body compartments: protoplasm, extracellular fluid, adipose tissue, and bone. Each compartment has a characteristic content of N, P, Na, K, Cl, and Ca (2). N and K are largely intracellular, Cl is almost exclusively extracellular, Na is two-thirds extracellular and one-third skeletal, and Ca is located almost entirely in bone. Therefore, retention of N and K indicate net formation of protoplasm, retention of Cl reflects net expansion of extracellular fluid, and retention of Ca shows net deposition of mineral in bone. Provided that elemental composition of body tissues remains normal during a period of weight gain, the change in mass of each compartment during the period can be estimated from amounts of N, P, Na, K, Ca, and Cl retained (3).

Hyperalimentation fluid provides glucose, amino acids (furnishing N), P, Na, K, Cl, Ca, and Mg. Concentrations of these elements in the fluid have varied from one clinic to another (1, 4–9). Do these differing elemental contents influence the quality of weight gained by emaciated patients during intravenous hyperalimentation? Are the ratios of increments in the four compartments influenced by the ratios of elements in the hyperalimentation fluid? Can repletion of a particular body compartment be selectively suppressed by omitting an element specific for that compartment?



Rudman D, Millikan WJ, Richardson TJ, Bixler TJ 2nd, Stackhouse J, McGarrity WC. Elemental balances during intravenous hyperalimentation of underweight adult subjects. J Clin Invest. 1975;55(1):94-104.

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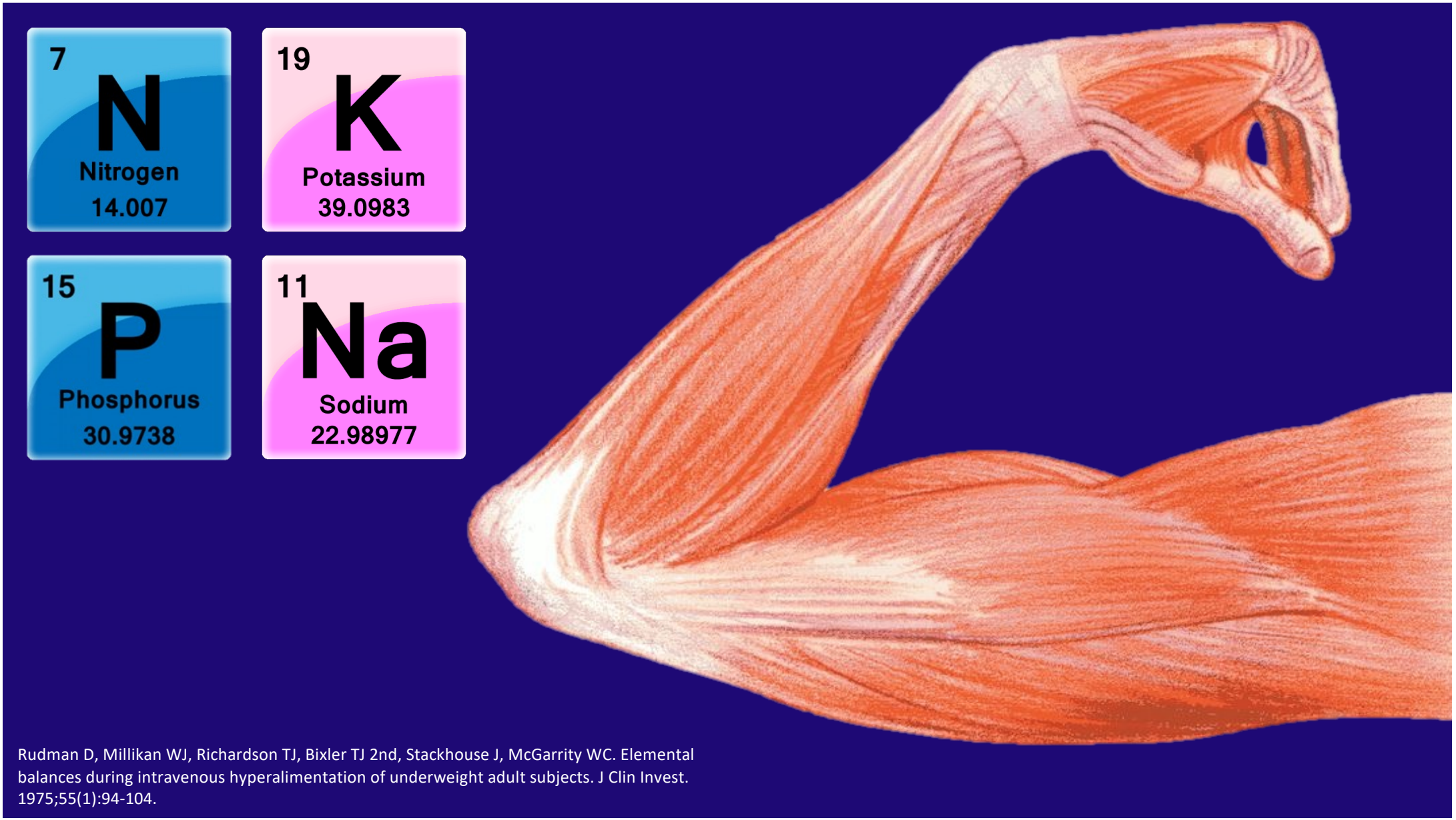

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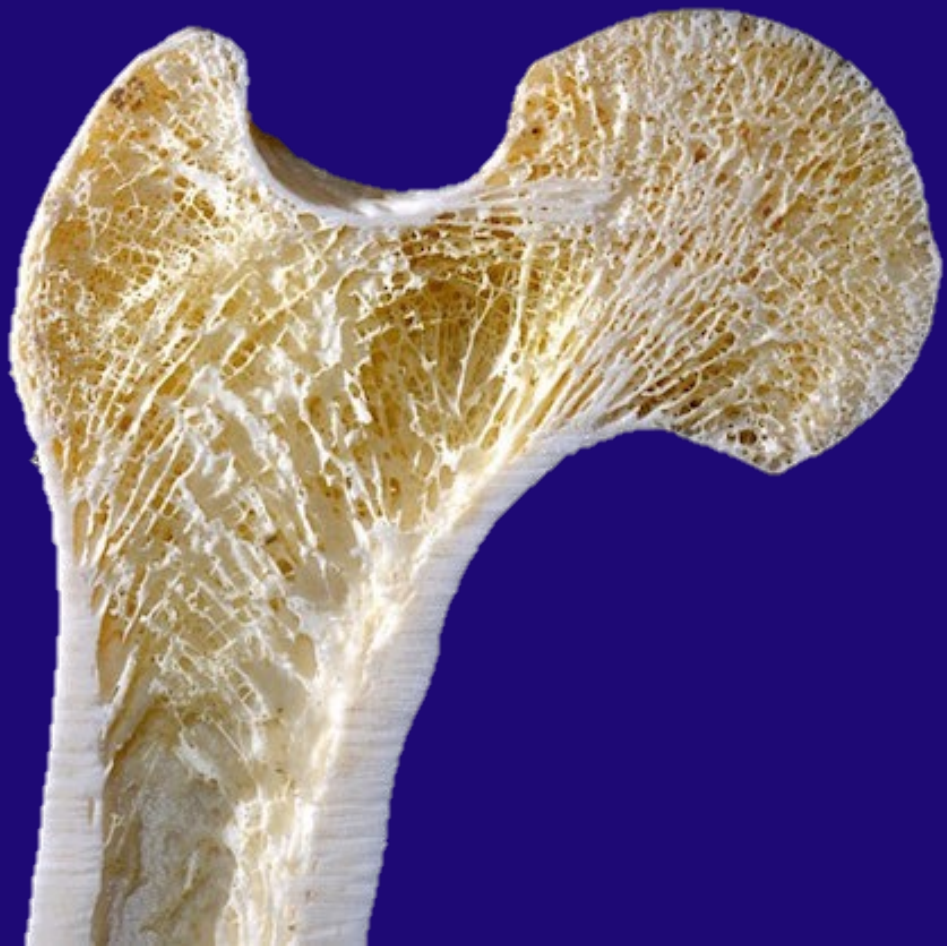

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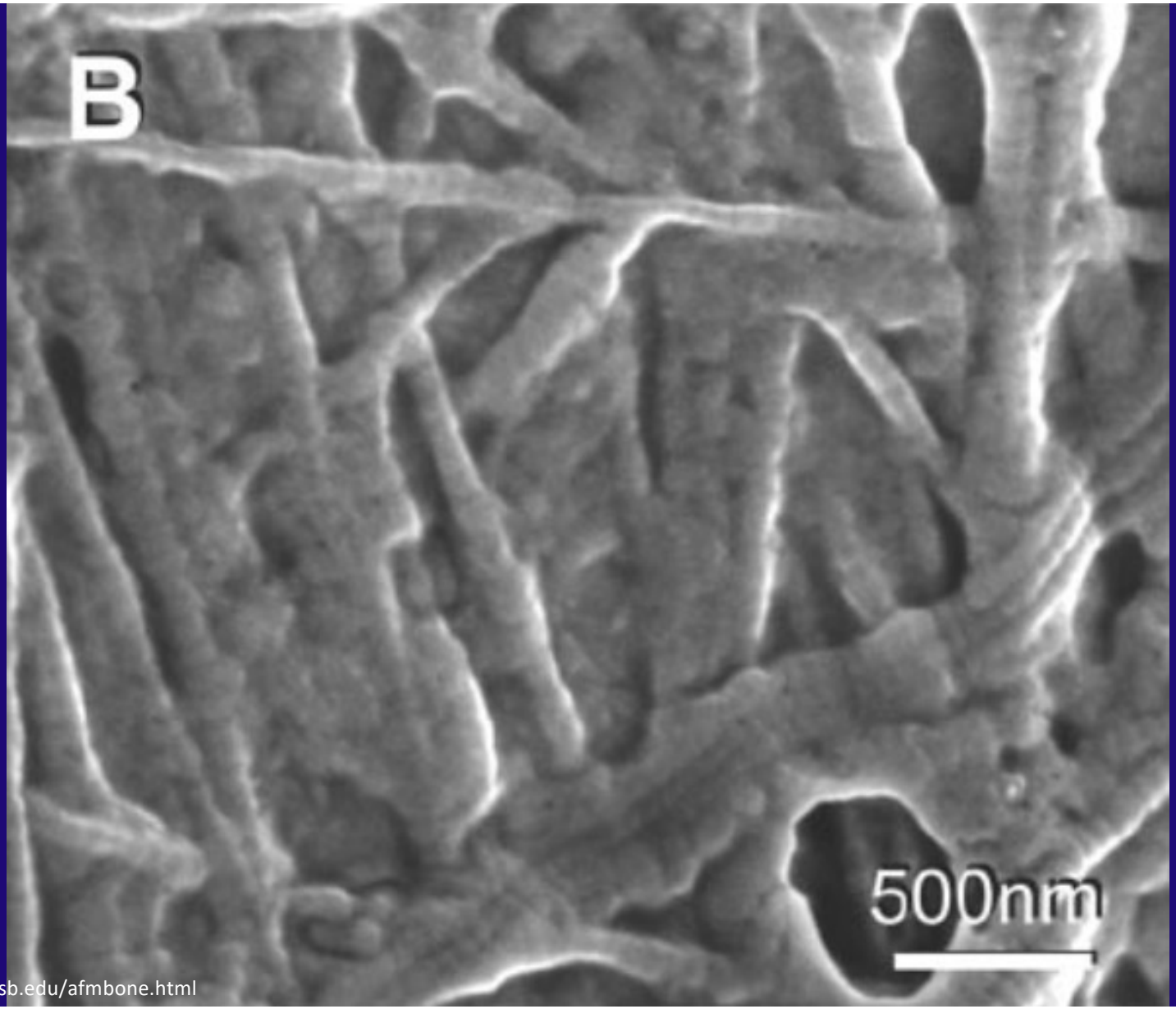

https://hansmalab.physics.ucsb.edu/afmbone.html

Calcium intake influences the association of protein intake with rates of bone loss in elderly men and women[1–4]

Bess Dawson-Hughes and Susan S Harris

ABSTRACT

Background: There is currently no consensus on the effect of dietary protein intake on the skeleton, but there is some indication that low calcium intakes adversely influence the effect of dietary protein on fracture risk.

Objective: The objective of the present study was to determine whether supplemental calcium citrate malate and vitamin D influence any associations between protein intake and change in bone mineral density (BMD).

Design: Associations between protein intake and change in BMD were examined in 342 healthy men and women (aged ≥65 y) who had completed a 3-y, randomized, placebo-controlled trial of calcium and vitamin D supplementation. Protein intake was assessed at the midpoint of the study with the use of a food-frequency questionnaire and BMD was assessed every 6 mo by dual-energy X-ray absorptiometry.

Results: The mean (±SD) protein intake of all subjects was 79.1 ± 25.6 g/d and the mean total calcium intakes of the supplemented and placebo groups were 1346 ± 358 and 871 ± 413 mg/d, respectively. Higher protein intake was significantly associated with a favorable 3-y change in total-body BMD in the supplemented group (in a model containing terms for age, sex, weight, total energy intake, and dietary calcium intake) but not in the placebo group. The pattern of change in femoral neck BMD with increasing protein intake in the supplemented group was similar to that for the total body.

Conclusion: Increasing protein intake may have a favorable effect on change in BMD in elderly subjects supplemented with calcium citrate malate and vitamin D. *Am J Clin Nutr* 2002; 75:773–9.

KEY WORDS Calcium intake, protein intake, bone loss, bone mineral density, potential alkali, calcium absorption, vitamin D, elderly

See corresponding editorial on page 609.

INTRODUCTION

Several studies have identified associations between dietary protein intake and bone mineral density (BMD) (1), rates of bone loss (2, 3), and fracture incidence (3–5). In the original Framingham cohort, subjects with lower total and animal protein intakes had greater rates of bone loss from the femoral neck and spine than did subjects consuming more protein (2). Munger et al (6) reported that higher total (and animal) protein intake was associated with a reduced incidence of hip fracture in postmenopausal women. In contrast, a high intake ratio of animal to plant protein was associated with greater bone loss from the femoral neck and a greater risk of hip fracture in women aged ≥65 y (3). Higher total and animal protein intakes were also associated with an increased risk of forearm fracture in younger postmenopausal women (4). Meyer et al (5) noted no association between protein intake and risk of hip fracture in most women, but among those with very low calcium intakes (400 mg/d), a higher protein intake was associated with an increased risk of hip fracture. In a controlled, 1-y intervention study, 20 g supplemental dietary protein/d improved hip BMD in elderly patients with a recent hip fracture (7). All the patients in that study received supplemental calcium and vitamin D.

Dietary protein has several opposing effects on calcium balance. First, it influences urinary calcium excretion over at least the ensuing several months (8–10). Women placed on high-protein diets have increased urinary calcium excretion and rises in *N*-telopeptide, suggesting that some of the increase in urinary calcium results from increased bone resorption (11). In contrast, Shapses et al (12) found that increased protein intake has no effect on bone resorption markers in subjects with calcium intakes in the high-normal range. Dietary protein may affect intestinal calcium absorption, but the evidence for this is mixed. Rats consuming high-protein diets appear to compensate for increased urinary calcium losses by increasing net calcium absorption (13). Balance studies in humans found little to no effect of dietary protein on calcium absorption (8, 14, 15).

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[2] Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the authors and do not necessarily reflect the views of the US Department of Agriculture.

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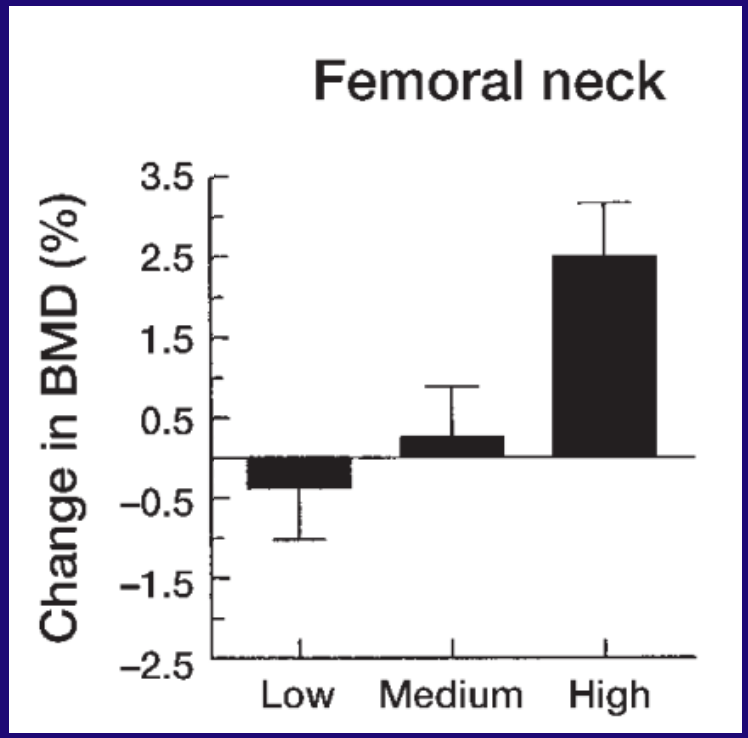

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ORIGINAL ARTICLE

Effect of phosphorus supplementation on weight gain and waist circumference of overweight/obese adults: a randomized clinical trial

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BACKGROUND: Phosphorus status is inversely correlated with body weight; however, the effect of phosphorus supplementation on body weight in a controlled design has not been studied.

METHODS: This is a double-blind, randomized, placebo-controlled trial of 63 adults aged 18–45 years with a body mass index (BMI) of $\geqslant 25\ kg\ m^{-2}$ and normal kidney function at the American University of Beirut. Participants were randomly assigned to the placebo or phosphorus group where daily placebo or phosphorus supplements were ingested with three main meals (breakfast, lunch and dinner) for a period of 12 weeks. Primary outcomes were changes in anthropometric measures, blood metabolites (including lipid profile, glucose and insulin) and subjective appetite scores. The trial is registered with Clinical Trial.gov, NCT02329990.

RESULTS: Body weight was significantly lower in the phosphorus group when compared with the placebo group (−0.65 kg (95% confidence interval (CI) −1.69 to 0.40) vs 1.13 kg (95% CI 0.19 to 2.06), $P=0.01$). Similarly, BMI and waist circumference were significantly lower in the phosphorus group when compared with the placebo group ($-0.24\ kg\ m^{-2}$ (95% CI −0.59 to 0.12) vs $0.42\ kg\ m^{-2}$ (95% CI 0.05 to 0.78), $P=0.01$; −3.62 cm (95% CI −4.90 to −2.33) vs 0.38 cm (95% CI −0.44 to 1.20), $P<0.001$; respectively). Several parameters of subjective appetite scores were decreased in the phosphorus-supplemented group.

CONCLUSIONS: Phosphorus supplementation for 12 weeks significantly decreases body weight, BMI, waist circumference and subjective appetite scores. These findings support a promising role of the mineral phosphorus in the prevention and management of obesity, especially abdominal adiposity. The exact mechanisms of action and longer-term effects still need to be elucidated.

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INTRODUCTION

Obesity is increasing at alarming rates in many high-, medium- and low-income countries.[1] This is contributing to the development of many metabolic diseases, including diabetes and cardiovascular disease.[2]

Modernization, including food industrialization and globalization of food markets, has been correlated with the increased consumption of products containing negligible amounts of phosphorus such as refined cereals (whereby refinement reduces phosphorus content by ~70%), oils, sugars and sweeteners that are currently contributing to >50% of the food supply (kcal per capita per day) in most countries.[3] This has caused a decrease in daily phosphorus ingestion to $\sim 1–1.5\ g\ day^{-1}$,[4,5] as compared with our ancestors' estimated intake of $2.5\ g\ day^{-1}$ (based on primarily raw, unprocessed foods with a $2500\ kcal\ day^{-1}$ diet and ~1 mg phosphorus per kcal).[3]

Low phosphorus status has been positively associated with increased body weight.[3,6,7] This may be attributed to the impact of hepatic adenosine triphosphate (ATP), which depends on adequate dietary supply of phosphorus, on suppressing food intake.[3,8,9] This mechanism is supported by an inverse relation between body weight and hepatic ATP status.[10–12] In line with that, we have previously found that phosphorus addition to carbohydrate preloads significantly reduces *ad libitum* energy intake at subsequent meal.[13]

Given the increased prevalence of obesity among individuals consuming abundant quantities of food containing low levels of phosphorus, it is reasonable to postulate that decreased phosphorus intake may be involved in the development of obesity and its metabolic abnormalities. Hence, we conducted a randomized, placebo-controlled trial to examine the effects of 12-week phosphorus supplementation on body weight, body mass index (BMI), waist circumference and subjective appetite scores in overweight and obese adults.

MATERIALS AND METHODS

Participants

After approval of the study by the institutional review board at the American University of Beirut (Beirut, Lebanon), 63 adults aged 18 to 45 years with a BMI $\geqslant 25\ kg\ m^{-2}$, who provided signed informed consent, were recruited from the general public using poster advertisements or direct approach. Details about recruitment, randomization and follow-up are presented in Figure 1. Exclusion criteria included glomerular filtration rate $<60\ ml\ min^{-1}$ per $1.73\ m^2$, presence of any significant medical

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