

Highlights From the Institute for Functional Medicine's 2014 Annual Conference: Functional Perspectives on Food and Nutrition: The Ultimate Upstream Medicine

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No one disagrees: Diet significantly affects health. And emerging research is clearly revealing that food is far more than calories delivered in the form of carbohydrates, proteins, and fats. Food is information with epigenetic effects that impact—for better or worse—the phenotype of not only the individual currently consuming it, but that of future generations of offspring.

Although all agree that a high-quality diet is essential for health, disagreement abounds regarding what type of diet is best. Proponents of each of the leading dietary approaches—the Mediterranean diet, Paleo diet, and vegetarian/vegan diet—can all cite abundant (and carefully selected) research support of their chosen diet's health benefits. But as epigenetics firmly ushers us into the era of personalized medicine, it is becoming increasingly obvious that no single dietary approach is optimal for all.

The issue of how to personalize dietary recommendations arises where the proverbial tire meets the road: The patient who has come to your office for medical care. How can you determine the optimal nutritional recommendations for the person sitting in front of you, who is likely to be an overweight (or normal weight but overfat/VAT [visceral adipose tissue]) individual with metabolic syndrome, cardiovascular disease (CVD), and/or type 2 diabetes? What lab tests and what biomarkers can be used to pinpoint your recommendations and then evaluate their efficacy? How can you support your patients' real-world compliance with your dietary recommendations? How can you *efficiently* integrate personalized dietary and nutritional therapies into your practice? All these questions were addressed during 3 days packed with science-cum-practical information the Institute for Functional Medicine's (IFM's) Annual International Conference: "Functional Perspectives on Food and Nutrition: The Ultimate Upstream Medicine," held in San Francisco from May 29 through May 31, 2014.

Following are a few highlights regarding how to choose the "right" diet for the individual patient, assess the efficacy of your dietary recommendations with lab tests/biomarkers, and support patient compliance. Another resource for creating personalized dietary and nutritional therapy is IFM's Clinical Practice Toolkit, which includes a variety of

customizable food plans along with recipes and a 1-day, 3-day, and 7-day Diet, Nutrition and Lifestyle Journal and patient information handouts on key food-related issues and topics, such as glycemic index and load; anti-inflammatory and elimination-diet food plans; acid/alkaline body balance; and food sources of fiber, antioxidants, vitamins, minerals, and phytonutrients.

If you were fortunate enough to have been present, let me apologize upfront if a favorite clinical takeaway is not mentioned below. Only 2 of the many deserving presentations are summarized here because of space limitations. If you were not there—or want to hear one or all of the presentations again—the full audio and video conference proceedings are available on the IFM Web site.¹

Choosing the "Right" Diet for the Individual Patient

"Nutrition Controversies, What's the Right Diet?" was one the most clinically useful presentations. After Christopher Gardener, PhD, provided an overview of key issues involved, proponents of the Mediterranean diet (Erminia Guarneri, MD), the Paleo diet (Loren Cordain, PhD), and the plant-based diet (Joel Fuhrman, MD) presented the research in support of each of these dietary approaches. A panel discussion followed, moderated by Dr Gardener, in which a surprising amount of consensus was reached.

Christopher Gardener, PhD, Director of Nutrition Studies at the Stanford Prevention Research Center, Associate Professor of Medicine, Stanford University

Weight loss efficacy of 3 popular weight loss diets (Atkins, Zone, and Ornish) was compared using data from 181 free-living overweight/obese women (aged 43 ± 5 [mean \pm SD]; body mass index [BMI] = 31 ± 4 kg/m²) participating in a 1-year randomized clinical trial (the "A TO Z" study).¹

What researchers learned: If you follow any of these 3 diets, you will lose weight; if you don't, you won't. Subjects'

i. Visit <https://www.functionalmedicine.org/conference.aspx?id=2825&cid=116§ion=home> for more information.

insulin resistance and insulin sensitivity explained differences in their adherence to diets. One diet does not fit all; for some, insulin sensitivity is better on a low-fat diet; for others, a low-carb diet more effectively improves insulin sensitivity.

The Mediterranean Diet: Erminia Guarneri, MD, FACC, President of ABIHM/ABIM, Senior Advisor of Integrative Medicine at the Atlantic Health System, Founder of Scripps Center for Integrative Medicine

The Mediterranean diet is a collection of dietary habits followed by countries bordering the Mediterranean Sea. No single Mediterranean diet exists, but all versions share commonalities: high olive oil, vegetable, legume, whole grain, fruit, and nut consumption; moderate consumption of fish and poultry; low consumption of red meat, dairy, and saturated fatty acids; and low-moderate alcohol consumption.

“From Hippocrates, we say, ‘Let your food be your medicine,’ but in functional medicine, we also say, ‘Food is information’—it is not just random. It is turning genes on and off, setting up the release of certain transcription factors and signaling cascades.”

Prospective and Interventional Studies Confirm Benefits of the Mediterranean Diet on Type 2 Diabetes and CVD

Mediterranean Diet Reduces Risk of Type 2 Diabetes. Prospective design studies on the Mediterranean diet and type 2 diabetes show a 12% to 83% reduced risk of type 2 diabetes with highest adherence to a Mediterranean diet:

- (1) Gissi Prevenzione Trial: 35% decreased risk.
- (2) SUN Study: 85% decreased risk.
- (3) Health Professionals Follow-up Study: 9% to 13% decreased risk.
- (4) EPIC: 12% decreased risk (20% reduction in risk if on low glycemic load Mediterranean diet).
- (5) Nurses’ Health Study II: 40% reduction in risk of gestational diabetes, even if prior history.

In patients with newly diagnosed type 2 diabetes, dietary intervention using the Mediterranean diet resulted in greater reduction of HbA_{1c} levels, higher rate of diabetes mellitus remission, and delayed need for diabetes medication compared with a low-fat diet.²

Low-Carbohydrate Mediterranean Diet Most Effective in Treatment of Type 2 Diabetes. The Mediterranean diet and low-carbohydrate Mediterranean diet were compared with the American Dietetic Association (ADA) diet in overweight persons with type 2 diabetes in a 12-month dietary intervention trial: “Only the low carbohydrate Mediterranean diet improved HDL levels and was superior to both the American Dietetic Association and traditional Mediterranean diet in improving glycemic control.”³

Mediterranean Diet Provides Effective Prevention of CVD and Cancer.

- (1) PREDIMED: In participants at high cardiovascular risk, a Mediterranean diet supplemented with mixed nuts or extra-virgin olive oil reduced incidence of cardiovascular events by 28% and 30%, respectively.⁴
- (2) Lyon Heart Study: Patients with CVD were randomized to a Mediterranean diet high in a-linoleic acid or the prudent standard American diet (SAD). Total fat intake was the same in both groups. The study was stopped early after 27 months because of the 70% reduction in cardiovascular events and in the development of new cancers was seen in the Mediterranean diet group. Additional follow-up at 47 months showed persistent benefits and continued adherence to the Mediterranean diet.⁵
- (3) Health Professionals Follow-up Study and the Nurses’ Health Study: Adherence to the Mediterranean diet was associated with lower relative risk of all-cause mortality (19%), CVD mortality (15%), and cancer mortality (15%) in individuals with CVD.⁶

Mediterranean Diet More Effective Than Low-protein Diet for Individuals With Chronic Kidney Disease and Methylenetetrahydrofolate Reductase C677T Polymorphism. An Italian Mediterranean diet (both conventional and organic) was compared with a low-protein diet in chronic kidney disease patients, according to their carrier status for the methylenetetrahydrofolate reductase C677T (*MTHFR C677T*) polymorphism. (Carriers of this single-nucleotide polymorphism [SNP] are at risk for elevated plasma homocysteine levels, particularly if the diet is not rich in folate.) At baseline, *MTHFR C677T* carriers’ homocysteine levels were an average of 8.24 mol/L higher than those who were not carriers of this SNP. After 14 days, homocysteine levels were significantly lower in *MTHFR C677T* carriers on a Mediterranean diet compared with those on a low-protein diet.⁷

Clinical application: Within 14 days, plasma homocysteine levels can be used to verify beneficial effects of Mediterranean diet on *MTHFR C677T* carriers.

Mediterranean Diet Reduces Rheumatoid Arthritis Activity and Pain. Within 12 weeks of following a Mediterranean diet, patients with well-controlled, although active rheumatoid arthritis of at least a 2-years duration, who were receiving stable pharmacological treatment, experienced reduction in inflammatory activity, increase in physical function, and improved vitality.⁸

Mediterranean Diet Safeguards Cognitive Function. “What’s good for the heart is good for the brain.” Mediterranean diet slows decline in cognitive function and lowers risk of developing Alzheimer’s disease.⁹

Mediterranean Diet Promotes Healthy Aging and Prolongs Life. “Greater adherence to a Mediterranean diet is associated with a significant improvement in health status, as seen by a significant reduction in overall mortality (9%), mortality from CVD (9%), incidence of or mortality from cancer (6%), and incidence of Parkinson’s disease and Alzheimer’s disease (13%).”¹⁰ A 10-year study, HALE looked at the effects of diet and lifestyle in people 70 to 90 years old. Adherence to Mediterranean diet and healthy lifestyle was associated with a greater than 50% lower rate of all-causes and cause-specific mortality, a 64% reduction in CVD events, and a 60% reduction in cancer.¹¹

Why Is the Mediterranean Diet Effective?

Mediterranean Diet Lowers Markers of Vascular Inflammation in Individuals With Metabolic Syndrome. Compared with patients consuming the control diet, patients consuming the intervention diet (Mediterranean diet) had significantly reduced serum concentrations of high-sensitivity C-reactive protein (hs-CRP), interleukin (IL) 6, IL-7, and IL-18, as well as decreased insulin resistance.¹²

Clinical application: Use lab tests to check the Mediterranean diet’s effects on your patients’ hs-CRP, IL-6, IL-7, IL-18, and insulin resistance.ⁱⁱ

Mediterranean Diet Activates Sirtuins. Resveratrol, a polyphenol present in grapes, nuts, and berries, activates sirtuins, which are now thought to be key intracellular mediators of the beneficial effects of the Mediterranean diet. SIRT1 and the regulatory proteins it encodes act as a cellular redox/energy sensor, responding to the current state of the cell by deacetylating a wide array of pivotal metabolic transcription factors that modulate insulin secretion, gluconeogenesis, mitochondrial biogenesis and fatty acid oxidation, endothelial function, lipid metabolism, cell cycling, apoptosis, and autophagy.^{iii,13}

Mediterranean Diet Increases Serum Levels of Vitamin A. “We know inflammation is driving the train for heart disease, cerebral disease, rheumatoid arthritis; it’s one of those final common pathways for disease.” Key components of the Mediterranean diet are rich in provitamin A (ie, vegetables, especially dark leafy greens). Higher vitamin A levels in the blood correlate with decreased (proinflammatory) tumor necrosis factor (TNF) and higher (anti-inflammatory) IL-10. Blood levels of vitamin A can be used as a marker of what your patients are eating.¹⁴

IMCJ: Blood levels of vitamin A may not accurately reflect consumption of β -carotene. Two common SNPs in the gene that encode the enzyme β -carotene 15,15'-monooxygenase (*BCMO1*), which is responsible for conversion of β -carotene to retinoic acid, lessen the body’s ability to convert β -carotene into vitamin A by as much as 70%. These SNPs, *R267S* and *A379V*, are present in less

than 45% of the population in Great Britain. Furthermore, a number of other factors can inhibit the conversion or render the amount of carotenoids absorbed insufficient to produce or maintain adequate levels of vitamin A, even in individuals who are not carriers of the *R267S* and/or *A379V*.^{iv}

Mediterranean Diet Improves Fatty Acid Profile. Blood and tissue levels of saturated fat and omega-6 fatty acids go down; levels of monounsaturated fats and omega-3 fatty acids go up. Changes are seen in as few as 28 days.

Clinical application: Within 1 month, you can see measurable changes in your patients’ fatty acids in the blood.^v

Mediterranean Diet Increases Endothelial Nitric Oxide Production. More endothelial nitric oxide (NO) results in less inflammation, more vasodilation. Leafy greens are rich in nitrates.

IMCJ: Richest sources: 100 to 250 mg/100 g fresh weight of celeriac, Chinese cabbage, endive, fennel, kohlrabi, leek, or parsley. More than 250 mg/100 g fresh weight of red beetroot, spinach, rocket, lettuce, celery, cress, or chervil.¹⁵

Clinical application: Flow mediated dilation can be used to verify beneficial effects of Mediterranean diet. NO levels can also be checked using salivary NO indicator strips.^{vi}

Mediterranean Diet Increases Telomerase Activity and Telomere Length. Leukocyte telomere length (LTL) and rate of telomere shortening are known biomarkers of aging. A study of 217 elderly subjects stratified according Mediterranean diet score (MDS) found longer LTL and higher telomerase activity in those with higher adherence to a Mediterranean diet compared with others. Linear regression analysis including age, gender, smoking habit, and MDS showed that MDS was independently associated with LTL and telomerase activity levels.¹⁶

ii. See, for example, <http://nutripath.com.au/product/cytokine-panel-blood-serum-sst-level-1-or-2-test-code-4002-4004/>.

iii. For a full discussion of the effects of key sirtuin regulatory proteins, see Pizzorno L, “Resveratrol, Niacin, Nicotinamide Riboside: Key Players in Activating Sirtuins to Mimic Calorie Restriction & Extend Lifespan, Part II, Longevity Medicine Review,” available at <http://www.lmreview.com/articles/view/resveratrol-niacin-nicotinamide-ribose-key-players-in-activating-sirtuins-to-mimic-calorie-restriction-extend-lifespan-part-ii/>.

iv. For a full discussion of these issues, see Pizzorno L, “Common Genetic Variants and Other Host-related Factors Greatly Increase Susceptibility to Vitamin A Deficiency, Longevity Medicine Review,” available at <http://www.lmreview.com/articles/view/common-genetic-variants-and-other-host-related-factors-greatly-increase-susceptibility-to-vitamin-a-deficiency/>.

v. For a full discussion of these issues, see Pizzorno L, “Common Genetic Variants and Other Host-related Factors Greatly Increase Susceptibility to Vitamin A Deficiency, Longevity Medicine Review,” available at <http://www.lmreview.com/articles/view/common-genetic-variants-and-other-host-related-factors-greatly-increase-susceptibility-to-vitamin-a-deficiency/>.

vi. See Neogenis Labs for more product information, available at <http://www.neogenis.com/nitric-oxide-indicator-strips.html>.

Clinical application: Leukocyte telomere length testing, which will soon be available not just for large clinical trials, but individual patients, may be used to verify beneficial effects of dietary recommendations.^{vii}

Mediterranean Diet Lowers Caveolin-1. Caveolae are cholesterol and sphingolipid-enriched microdomains abundant in vascular endothelial cells. They are responsible for mediating signal transduction across the plasma membrane and can negatively influence endothelial function. Endothelial cell dysfunction is characterized by a decrease in NO bioavailability and increased production of reactive oxygen and nitrogen species (ROS/RNS).

Caveolin-1 has recently been shown to negatively regulate the rate-limiting enzyme (guanosine triphosphate cyclohydrolase) responsible for de novo synthesis of tetrahydrobiopterin (BH₄), a required cofactor for NO production by eNOS. BH₄ also plays a critical role in preventing eNOS uncoupling, which leads to RNS formation via the production of superoxide. Caveolin-1 signaling prevents BH₄ synthesis, thus blocking NO production and increasing RNS. Caveolae are also involved in the regulation of enzymes associated with several key signaling pathways that determine intracellular redox status. The Mediterranean diet can affect the expression of caveolin-1 receptor, transforming patients' health at the cellular level. Nutrients abundant in the Mediterranean diet (eg, omega-3 fatty acids and several polyphenolic compounds) beneficially alter caveolae-associated cellular signaling. These compounds improve endothelial cell function by decreasing the formation of ROS/RNS and increasing NO bioavailability, both of which are associated with altered caveolae composition.^{17,18}

Mediterranean Diet's Beneficial Effects Results From a Complex Combination of Factors, Not Only One! It's not 1 constituent or even 1 food group:

- (1) Polyphenolic compounds interact with sirtuin.
- (2) When SIRT1 is activated, NF-κB, which would otherwise turn on all the proinflammatory cytokines, goes down.
- (3) If polyunsaturated fatty acids (PUFAs) are in fish, NF-κB goes down, TNF goes down, and integrin-vascular cell adhesion molecule and vascular cell adhesion molecule expression in the subendothelial space (which leads to plaque formation) go down.
- (4) Eating lots of greens boosts nitrate levels leading to NO production, blood vessel relaxation, and improved endothelial function.

The Paleo Diet: Loren Cordain, PhD, Professor Emeritus, Department Health & Exercise Science, Colorado State University

The Paleo diet is based on the supposition that ancestral hunter gatherers diets, which contained minimally processed wild plants and animals, but no dairy

or grains, provide optimal nutrition for contemporary humans. Only 330 generations have come and gone since we were all eating hunter-gatherer diets.

IMCJ: Today's version of the Paleo diet is based on lean meat, fish, fruits, leafy and cruciferous vegetables, root vegetables (with restricted potato intake), eggs, and nuts.¹⁹

As is the case with the Mediterranean diet, no single Paleo or vegetarian (plant-based) diet exists, but the 3 main dietary options do have important differences and similarities.

The Mediterranean diet differs from the Paleo diet in that the former includes daily bread, pasta, rice, whole grains, potatoes, beans and legumes, cheese and yogurt, and highly salted foods (cheese and olives). Meat is only consumed on a monthly basis.

IMCJ: Correction regarding both meat and dairy foods. As Dr Guarneri noted, the Mediterranean diet includes "Moderate fish and poultry, low red meat, dairy, and saturated fats."

Because of these differences, the Paleo diet may be superior to the Mediterranean diet. Several studies suggest this:

- (1) A systematic meta-analysis, published 2014, that reviewed and analyzed the effect of the Mediterranean diet on cardiovascular risk factors in 33 cross-sectional, 9 cohort, and 16 intervention studies, found: "Most of the studies showed favorable effects of Mediterranean diet on CVD, although a certain degree of controversy remains in the respect of some issues, as obesity." In other words, the Mediterranean diet reduces CVD, but healthier diets may exist.²⁰
- (2) In a 3-month study, 1 of the studies included in another meta-analysis, the Paleo diet was found to be superior to Mediterranean diet in lowering HbA_{1c}: "8 studies met the inclusion criteria, 7 examined fasting blood glucose (n = 972), 6 examined fasting insulin (n = 1330) and 3 examined HbA_{1c} (n = 487). None of the interventions were significantly better than the others in lowering glucose parameters. The Mediterranean diet reduced HbA_{1c} significantly compared to usual care but not compared to the Paleolithic diet."²¹
- (3) Another 12-week study, in which the Paleo diet (described earlier) was compared with a "Mediterranean-like" diet based on "whole grains, low-fat dairy products, vegetables, fruits, fish, oils and margarines," found the Paleo diet superior to the Mediterranean-like diet. This study involved 29 patients with ischemic heart disease plus either

vii. See Telome Health, available at <http://www.telomehealth.com/>.

glucose intolerance or type 2 diabetes. Those randomized to the Paleo diet showed a 26% decrease of area under curve. Glucose compared with a 7% decrease in the Mediterranean diet-like diet group.¹⁹

Further analysis of data from the above study found the Paleo diet more satiating per calorie than Mediterranean-like diet in these individuals with ischemic heart disease. The Paleolithic group was as satiated as the Mediterranean group but consumed less energy per day (5.8 MJ/d vs 7.6 MJ/d). Leptin decreased by 31% in the Paleolithic group and by 18% in the Mediterranean group.²²

IMCJ: Leptin is a hormone made by fat cells that regulates the amount of fat stored in the body by adjusting both the sensation of hunger and energy expenditures. Upon satiety, leptin is secreted and circulates through the body, eventually activating leptin receptors in the hypothalamus. Energy expenditure is increased both by the signal to the brain and directly via leptin receptors on peripheral targets. Leptin's effects are opposed by those of ghrelin, the "hunger hormone."

Epidemiological Studies Show Inconsistent Results for the Mediterranean Diet's Effects on Obesity and Weight Loss

A meta-analysis of 21 epidemiological studies, including 7 cross-section, 3 cohort, and 11 intervention studies, reviewed the evidence on the effects of the Mediterranean diet on overweight/obesity. Of these, 13 found Mediterranean diet adherence significantly related to less overweight/obesity or more weight loss. Eight studies found no evidence of this association: "Although the results are inconsistent, the evidence points towards a possible role of the Mediterranean diet in preventing overweight/obesity, and physiological mechanisms can explain this protective effect."²³

Why Might the Paleo Diet Be Superior to the Mediterranean Diet and Plant-based (Vegetarian) Diets?

The Paleo Diet Does Not Contain Grains. Both the Mediterranean diet and the vegetarian diet do and, therefore, have a higher carbohydrate load, which translates into a higher glycemic load. Commonly eaten grains (eg, wheat, barley, and rye) contain gluten, which we now know may produce adverse effects in a much larger percentage of the population than in only those with or who are susceptible to celiac disease.²⁴ Grains are acid-producing.^{viii}

The Paleo Diet Is Richer in Branched Chain Amino Acids. BCAAs (leucine, isoleucine, valine) are found in larger quantities in animal foods. Leucine, in particular, is an appetite suppressant.

IMCJ: Correction. Leucine is abundant in a vegetarian diet. Soybeans contain 2.97 g/100 g of leucine; beef contains 1.76 g/100 g. Eggs, cheese, peanuts, almonds, sesame seeds, and pumpkin seeds are all good sources of leucine.^{ix}

Mediterranean and Vegetarian Diets Are Less Micronutrient Dense Than the Paleo Diet. Nutrient density compared to calories rankings per food group: (1) vegetables, (2) seafood, (3) lean meats, (4) fruits, (5) whole milk, (6) whole grains, and (7) nuts and seeds. Displacement of fruit, vegetables, lean meats, and seafood by milk and grains, the latter typically highly processed and thus almost completely depleted of nutrients, lowers the overall micronutrient density of the diet.²⁵

A Vegetarian Diet Is Lower in Absorbable Zinc, Iron, and B₁₂, and It Has a Higher Salt Content Than a Paleo Diet. Plant foods are devoid of B₁₂; B₁₂ deficiencies elevate plasma homocysteine.

Clinical application: The best way to evaluate B₁₂ levels is with holotranscobalamin II and methylmalonic acid (MMA).²⁶

IMCJ: This has been confirmed by further research.²⁷ MMA can now be assessed in dried blood spots, rather than plasma or serum. Dried blood spots offer a minimally invasive specimen collection method with no need for the blood processing steps, thus a simpler, more efficient and field-applicable method of assessing B₁₂ status than plasma.²⁸

Vegetarians Are at Risk of Long-chain Omega-3 Insufficiency. Vegetarian diets contain only α -linolenic acid (ALA), no long chain omega 3s (docosahexaenoic acid [DHA], eicosapentaenoic acid [EPA]). The conversion rate of ALA to EPA, DHA is very low, placing vegetarians/vegans at risk of omega-3 insufficiency.^{29,30}

IMCJ: There is considerable variation in ability to convert ALA to EPA/DHA, another instance of genetic individuality; see highlights from Dr Fuhrman's presentation later in these highlights. Algae-derived long chain omega-3 supplements are now readily available and have produced a robust response in vegans, increasing their levels of DHA/EPA to those seen in a cohort of omnivores (recently deployed soldiers) within 4 months: 3.7% in the vegans, 3.5% in the soldiers. Daily supplements provided 172 mg DHA and 82 mg EPA. And the range of postsupplemental omega-3 values in the vegans was wide, rising to above 8% in 2 participants.³¹

viii. For a full discussion of the ways in which metabolic acidosis adversely affects health, see Pizzorno J, Frassetto LA, Katzinger J, "Diet-induced acidosis: Is it real and clinically relevant?" *Br J Nutr.* 2010;103(8):1185-1194.

ix. See National Nutrient Database, Release 26, available at <http://ndb.nal.usda.gov/ndb/nutrients/report?nutrient1=504&nutrient2=&nutrient3=&fg=&max=25&subset=0&offset=325&sort=c&totalCount=4922&measureby=g>.

Vegetarian Diets Are Low in Zinc and Iron Because These Bind to Phytate in Whole Grains and Legumes.

With regard to zinc, phytate is abundant in diets that include unrefined cereals, pulses, and whole grains as staples, and it forms poorly soluble complexes with zinc in the gastrointestinal tract, resulting in reduced zinc absorption or reabsorption. The World Health Organization estimates zinc bioavailability based on the molar ratio of phytate to zinc in the diet. It has been suggested that the requirement for dietary zinc may be as much as 50% greater for some vegetarians.³²

IMCJ: Regarding iron, intake in vegetarians is typically similar or even slightly better than that of nonvegetarians, and incidence of iron-deficiency anemia is common among both vegetarians and nonvegetarians. The issue is one of iron bioavailability. Nonheme iron is sensitive to both inhibitors and enhancers of iron absorption. Inhibitors include phytates, calcium, and the polyphenolics in tea, coffee, herb teas, and cocoa. Vitamin C and other organic acids in fruits and vegetables substantially enhance nonheme iron absorption and reduce the inhibitory effects of phytate. Soaking and sprouting beans and grains as well as leavening of bread diminishes phytate levels and enhances iron absorption.³³

Vegetarian Diets Are Iodine Deficient and Soy Contains Antinutrients That Impair Iodine Uptake.

Urinary iodine excretion was assessed in 15 vegans, 31 lacto- and lacto-ovovegetarians, and 35 adults on a mixed diet. One-fourth of the vegetarians and 80% of the vegans were found to be iodine deficient (iodine excretion value below 100 mg/L) compared with 9% in the persons on a mixed diet.³⁴

IMCJ: More recent studies indicate that vegetarian diets need not lead to iodine deficiency, and vegans may, in fact, suffer excess iodine intake. Environmental perchlorate and thiocyanate (inhibitors of thyroid iodine uptake) are seen as a more serious concern than soy products. A review including 14 trials in which the effects of soy foods or isoflavones on thyroid function were assessed in healthy subjects found no effects or only very modest changes in thyroid function.³⁵ The most recently published research indicates that “U.S. vegetarians are iodine sufficient. U.S. vegans may be at risk for low iodine intake, and vegan women of child-bearing age should supplement with 150 µg iodine daily.”^{36,37}

Blood levels of vitamin D are lower in vegetarians and vegans than in meat eaters.³⁸ Vitamin D inadequacy is of special concern for vegans. Diet and lifestyle behaviors of 100 vegans in the United States were analyzed. Despite adequate intakes for most protective nutrients when compared with reference values, 0% intake adequacy was found for vitamin D.³⁹ Wheat germ agglutinin may suppress vitamin D metabolism by sitting on the nuclear pore via which vitamin D enters cells.⁴⁰

Legumes Contain Antinutrients That Increase Likelihood of Mineral Deficiencies. These include saponins, lectins, phytate, α-amylase inhibitors, and polyphenols (tannins, isoflavones, protease inhibitors, raffinose oligosaccharides, cyanogenetic glycosides, favaism glycosides).⁴¹

IMCJ: Legumes are inexpensive low GI, protein-rich foods, and are excellent sources beneficial phytochemicals and fiber. Soaking and discarding the soaking water before cooking will remove a significant amount of phytates, tannins, and raffinose. Total carbohydrate content is also lowered, but the amount of resistant starch (which helps support the growth of beneficial bacteria in the large intestine) is not.⁴²

Home cooking strategies can greatly increase the mineral bioavailability of legumes: In addition to soaking and discarding the soaking water, adding vitamin C-containing fruits will enhance non-heme-Fe absorption, and heating will destroy heat-labile antinutritional factors (eg, goitrogens, thiaminases).⁴³

The Plant-based “Nutritarian” Diet: Joel Fuhrman, MD

The goal is an optimal diet that will not only reduce incidence of type 2 diabetes and CVD, but enable a healthy lifespan that extends well into the 90s, free of obesity, diabetes, CVD, and cancer.

Low-calorie, high-nutrient intake prolongs lifespan by enhancing cellular repair mechanisms, reducing inflammatory response, suppressing genetic alterations, decreasing free radicals, inhibiting production of cross-linking agents, slowing the metabolic rate, enhancing DNA repair, and removing/lessening the production of toxins, free radicals and AGEs.

The characteristics of an optimal diet are:

- (1) Health expectancy = nutrients/calories.
- (2) Slows the aging process.

Three principles define the optimal diet:

- (1) High micronutrient density per calorie intake.
- (2) A broad spectrum of plant foods consumed to promote complete micronutrient adequacy.
- (3) Consumption of foods that are hormonally favorable (ie, will not drive up levels of estrogen, insulin, IGF-1).

The nutritional quality of the foods consumed, not the percentage of calories from fat, protein, or carbs, is key.

The 30 or so vitamins and minerals we recognize represent only a tiny fraction of the nutrients (beneficial phytochemicals) in real foods (eg, each strawberry contains more than 700 nutrients; broccoli contains more than 1000 nutrients).

The standard American diet (SAD) could not have been better designed to kill us by al Qaeda; it promotes

chronic disease and suppresses immune function. The SAD is 55% processed foods; 30% animal products; 11% vegetables, fruit, nuts and beans; and 4% whole grains. One-half of the 11% of vegetables consumed are ketchup and French fries. The amount of colorful vegetation consumed by Americans is less than 5% of the total diet.

Processed foods provide macronutrients with virtually no micronutrients, antioxidants, or phytochemicals. Processed grains push up insulin, but a piece of conventionally produced chicken is not nutritionally much better than a piece of white bread when you consider conventionally raised chickens' lack of micronutrients (antioxidants and phytochemicals). In addition, products from conventionally raised animals have negative hormonal effects: The SAD's animal products push up IGF-1, the hormone most closely linked with colon, breast, and prostate cancers, and rapid tissue aging.

Green vegetable consumption is a major determinant of Nrf2 activity.

IMCJ: The Nrf2 antioxidant response pathway is “the primary cellular defense against the cytotoxic effects of oxidative stress.”⁴⁴ BG-12 has been shown to have beneficial effects in preclinical models of neuroinflammation, neurodegeneration, and toxic oxidative stress, which appear to be mediated predominately through its activation of Nrf2, and is currently being investigated for use in the treatment of multiple sclerosis. Nrf2 binds to and activates the antioxidant response element (ARE), which increases the expression of several antioxidant enzymes and regulates the expression of many phase II-genes. Nrf2 is sequestered in the cytoplasm where activation by ROS provokes its release and translocation to the nucleus, where it activates ARE-dependent genes. Nrf2-regulated genes include those that direct production of glutathione S-transferases (GST), γ -glutamyl cysteine ligase (gGCL), NAD(P)H:quinone oxidoreductase 1 (NQO1), and heme oxygenase 1 (HO1).⁴⁵

ANDI (Aggregate Nutrient Density Index) Scores—designed by Fuhrman—are a listing of whole foods ranked by micronutrient per calorie density.^x

IMCJ: The Mediterranean-type diet espoused by the World's Healthiest Foods, a nonprofit Web site, developed by Salugenecists, Inc, for the George Mateljan Foundation, is based on the same concept of nutrient density.^{xi} The profile for each of the World's Healthiest Foods includes a nutrient-density chart that highlights the nutrients for which the food is either an excellent, very good, or good source.

Olive oil may not be optimal for sedentary people because it is too caloric. Fuhrman recommends (fiber-rich) walnuts rather than olive oil.

IMCJ: Clarification: One tablespoon of olive oil contains 126 calories; one-quarter cup of walnuts contains 164 calories.⁴⁶

High glycemic load increases cancer risk: “The whiter the bread, the sooner you're dead.” Almost all natural foods, except white potato, are low glycemic load. It is when they are processed that their glycemic load goes up.

Excess protein shortens lifespan and promotes cancer. A primary reason is that protein intake is a key determinant of IGF-1 levels in humans. In calorie-restriction-with-adequate nutrition studies, it's primarily IGF-1 that drops and extends lifespan. Dairy products raise IGF-1 more powerfully than other animal products.

Low protein intake is associated with major reduction in IGF-1, cancer, and overall mortality. The Paleo diet contains excessive amounts of meat; the Mediterranean diet contains less meat, but contains dairy products and grains, so neither can be considered optimal.

Data from NHANES III, a nationally representative, cross-sectional study, on 6381 adults aged 50 and older (mean age = 65 y) followed for 18 years, found a 75% increase in overall mortality, and a 4-fold increased risk of cancer deaths in the highest protein category.⁴⁷ What they considered high (20% or more) was lower than what the average American eats. Americans are currently getting at least 23% of their calories from protein. The low protein category was 5% from animal protein. The Paleo diet might push that percentage up to 40% to 60% of protein. And this might push up breast cancer rates.

IMCJ: Regarding Levine et al,⁴⁷ there are 2 qualifications: (1) “These associations were either abolished or attenuated if the proteins were plant derived”; and (2) “Conversely, high protein intake was associated with reduced cancer and overall mortality in respondents over 65. ... These results suggest that low protein intake during middle age followed by moderate to high protein consumption in old adults may optimize healthspan and longevity.”⁴⁷

Regarding IGF-1: In contrast to the findings in animal studies, *low* IGF-I activity in humans is not associated with longevity but with an increased risk of CVD, diabetes, and all-cause mortality. However, *high* IGF-I activity in humans is associated with an increased risk of developing cancer.⁴⁸

In a recent prospective study, serum IGF-I levels were measured in 2901 elderly men (aged 69 to 81 y) who were followed an average of 5.1 years. The association between serum IGF-I and risk of CVD events was nonlinear. Analysis revealed a U-shaped association between serum IGF-I levels and CVD events. Low as well as high serum IGF-I (quintile 1 or 5 vs quintiles 2-4) were significantly associated with increased risk for CVD events (hazard ratios [HR] of 1.25 and 1.35, respectively), and these associations remained after adjustment for prevalent CVD and multiple risk factors.⁴⁹

x. See <https://www.drfuhrman.com/library/andi-food-scores.aspx/>.

xi. The concept is explained fully at “What are the World's Healthiest Foods,” available at <http://www.whfoods.org/genpage.php?name=faq&dbid=20>.

A study published in 2012 by the same group of researchers⁵⁰ had found that both low and high serum IGF-I levels are risk markers for increased cancer mortality in older men. For low serum IGF-I (quintile 1), the HR was 1.86; for high serum IGF-I (quintile 5), the HR was 1.90. Only low serum IGF-I was associated with increased CVD mortality (HR = 1.48) in this study. These associations remained after adjustment for multiple covariates and exclusion of men who died during the first 2 years of follow-up.

Other research conducted in Germany, on a study population of 1988 men and 2069 women aged 20 to 79 years, who were followed up on average 8.5 years, found men with *low*, but not high, IGF-I levels had an almost 2-fold higher risk of all-cause mortality (HR = 1.92), CVD mortality (HR = 1.92), and cancer mortality (HR = 1.85) compared with men with normal IGF-I levels. Low IGFBP-3 levels were also associated with higher all-cause mortality in men (HR = 1.87) and women (HR = 1.63).⁵¹

Debate

At this point in the presentations the panel entered open discussion.

Dr Cordain stated that studies often do not differentiate between free and bound IGF-I, and it is free IGF-I that affects epithelial cell growth and may increase risk of cancer. In addition, the ratio of free IGF-I to IGF-binding protein 3 may be a much better indication of risk. Dr Fuhrman responded that the same factors that raise IGF-I also raise free IGF-I and lower IGF-binding protein 3.

Clinical application: Check patient's ratio of free IGF-I to IGF-binding protein 3.

IMCJ: The range of IGF-I considered "normal" varies significantly by age and sex, and what is considered the "normal range" at various ages (Tanner stages) can be quite wide.^{xii} In sum, optimal levels of IGF-I are highly individual, a further confirmation of the need for truly personalized medicine: "For each individual there is probably a specific optimal 'setpoint' for the insulin/growth hormone/IGF-I axis which co-determines survival."⁵²

Advocates of high-protein diets point to the Inuit and Eskimos as examples of healthy populations that consumed high protein diets. In fact, however, the HORUS study identified severe atherosclerosis even in relatively young individuals eating wild meats. Mortality from stroke was higher than that seen in modern Western populations. These populations lived long enough to reproduce; they did not attain optimal lifespan.

Large prospective cohort studies indicate a vegetable-based low carbohydrate diet is superior to an animal-based low carbohydrate diet. A total of 130000 participants were examined from the Nurses' Health Study and Health Professionals' Follow-up Study—85 168 women, aged 34 to 59 years at baseline, followed for 26 years, and 44 548

men, aged 40 to 75 years at baseline, followed for 20 years. The low-carbohydrate, animal-based model resulted in 23% increased death rate from all causes in men and women (HR = 1.23), 14% increase in cardiovascular mortality, and 28% increase in cancer mortality (HR = 1.28). A low-carbohydrate, vegetable-based diet was associated with 20% lower death rate from all causes, and 23% lower death rate due to CVD.⁵³

Dr Fuhrman stated that meta-analyses confirm animal products boost IGF-I and risk of breast cancer.

IMCJ: The research, albeit inconsistent, suggests an association between high IGF-I and not only breast, but prostate cancer. Evidence from more than 40 case-control studies and 12 cohort studies does not support an association between dairy product consumption and the risk of breast cancer.⁵⁴ Four meta-analyses and literature reviews have concluded that a positive association exists between circulating levels of IGF-I and IGF-binding protein-3 (IGFBP-3) and breast cancer risk for premenopausal but not postmenopausal women. Recently, a large prospective study reported an association with IGF-I and IGFBP-3 concentration for breast cancer risk in older women (>50 y) but not in younger women.⁵⁵

Meat consumption, particularly that of red or processed meats, increases cancer risk: The most recently published paper (2014) investigating the association between animal products and breast cancer is a prospective study of 88 803 premenopausal women from the Nurses' Health Study II who were followed for 20 years. IGF-I levels were not ascertained. Higher intake of red meat was associated with a 22% increased risk of breast cancer, but higher intakes of poultry, fish, eggs, legumes, and nuts were not related to breast cancer overall. When evaluated by menopausal status, higher intake of poultry was associated with a 27% lower risk of breast cancer in postmenopausal women. Estimating the effects of exchanging different protein sources, substituting 1 serving/day of legumes for 1 serving/day of red meat was associated with a 15% lower risk of breast cancer among all women and a 19% lower risk among premenopausal women. Substituting 1 serving/day of poultry for 1 serving/day of red meat was associated with a 17% lower risk of breast cancer overall and a 24% lower risk of postmenopausal breast cancer. Furthermore, substituting 1 serving/day of combined legumes, nuts, poultry, and fish for 1 serving/day of red meat was associated with a 14% lower risk of breast cancer overall and for premenopausal breast cancer.⁵⁶

The World Cancer Research Fund and American Institute of Cancer Research report, which is based on an extensive review of the existing evidence by an international panel of experts, concluded that a high intake of red or

xii. See Mayo Medical Laboratories, insulin-like growth factor 1 and serum, available at <http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/35099>.

processed meats is a convincing and probable cause of colorectal cancer. Risk of colorectal cancer was estimated to increase by 29% for every 100 g/day increase in red meat and by 21% for every 50 g/day increase in processed meat consumption.⁵⁷

Numerous studies on bowel cancer have confirmed that red meat increases risk, and high-fiber plant foods decrease risk.^{58,59} Consumption of red meat, particularly if cooked at high temperatures or until well done, has also been shown to increase risk of prostate cancer. Of interest, individuals who are carriers of a SNP in the *PTGS2* gene are less able to detoxify meat mutagens and thus at higher risk of prostate cancer from red meat consumption.⁶⁰

Clinical application: Patients at risk of breast, prostate, or colorectal cancer should be informed that high intake of red or processed meats intake may increase cancer risk. Replacing red meat with a combination of legumes, poultry, nuts, and fish may reduce cancer risk.

Although controversy exists over what percentage of caloric intake is advisable for animal products, Fuhrman believes the data indicates that somewhere between 0% to 15%, probably 5% to 10%, will afford people the best protection against cancer.

Optimal Plant-based diet guidelines are:

- (1) Eat high on the nutrient-density line.
- (2) Unlimited: Green vegetables: all raw vegetables, non-starchy cooked vegetables, fresh fruit, beans/legumes.
- (3) Limit daily: cooked starchy vegetables, whole grains, raw nuts and seeds
- (4) Limit weekly: fish, fat free dairy, wild meat and fowl, eggs.
- (5) Rarely: red meat, refined grains, full fat dairy, cheese, refined oil, sweets.

Fuhrman suggests a “greens and beans” diet. Legumes were found to be the only the group whose frequent consumption reduced risk of mortality in elders (aged 70 y and older) among 5 cohorts in Japan, Sweden, Greece, and Australia. The legume food group showed a 7% to 8% reduction in mortality HR for every 20 g increase in daily intake regardless of ethnicity. No other food group was found to be consistently significant in predicting survival.⁶¹

In the Adventist Health Study, beans eaten 3 times a week reduced risk of colon cancer by 33% after adjusting for meat intake. Daily consumption of cooked green vegetables reduced risk 24%, and consumption of brown rice once per week reduced risk by 50%.⁶² Beans contain inositol pentakisphosphate (IP-5), which has significant antiangiogenic and antitumor effects.⁶³

IMCJ: Legumes are an excellent source of resistant starches and dietary fiber, the substrates for fermentation in the digestive tract to produce short-chain fatty acids (eg, butyrate,

which is the major energy source for colonocytes). Butyrate not only nourishes the colonic mucosa, but by promoting cell differentiation, cell-cycle arrest and apoptosis of transformed colonocytes helps prevent colon cancer. SCFA in general, and butyrate in particular, enhance the growth of lactobacilli and bifidobacteria and play a central role on the physiology and metabolism of the colon.^{64,65,66,67}

Panel Consensus: Dietary Recommendations

More vegetables and low GI fruits.

- (1) No packaged processed foods.
- (2) Few or no white potatoes because they are high GL and also contain glycoalkaloids that are toxic in a dose-dependent manner.
- (3) No hydrogenated/trans fats.
- (4) No refined grains.

Small amounts of unrefined, minimally processed grains are recommended. If the patient is not wheat-sensitive, then examples would be sprouted grains and wheat berries. If the patient is gluten sensitive, gluten-free steel cut oats, quinoa, black or brown rice, millet, sorghum are recommended.

Dr Fuhrman suggested to pick intact whole grains that you would cook in water (eg, black rice, quinoa, steel cut oats). Dr Guarneri recommends Steel cut oats in the morning, quinoa if eaten later in the day. Dr Cordain prefers no grains. Humans do not have a grain requirement. There is no nutrient in grains we cannot get from other foods, and gluten is the tip of the iceberg of problems caused by grains. Guarneri and Fuhrman agreed: Grains are not essential for human health.

Dr Gardener asked, “What is the optimal percentage of calories from animal products: meat, dairy, and fish?” This question was asked with the assumption of no more corn-fed, soy-fed, factory-farmed, environment-destroying animal products (ie, if you have the best natural animal products such as beef, poultry, pork).

Dr Fuhrman responded that less than 10% of calories from animal products in the longest-lived populations, but evidence suggests we can push this to 5% or lower with right supplementation. Having worked with Dean Ornish, MD, in the 1990s, Dr Guarneri has seen 10%—if done correctly—reverses plaque, but if not done correctly, becomes a high GI disaster. Guarneri recommends no beef, poultry or pork, and only a small amount of wild fish, salmon, and trout that are locally sourced and seasonal. Dr Cordain explained that when hunter gatherers have been measured in studies, approximately 55% of their caloric intake has been found to be from animal products (eg, wild game including marrow and organs); however, this is in the context of a high fruit and vegetable consumption.

Dr Gardener then asked, “Do we need omega-3 supplements?” A recently published study has revealed that humans exhibit broad genetic variability in their

ability to convert ALA to EPA and DHA; however, humans' conversion of ALA to EPA is typically quite minimal, and conversion to DHA is virtually nil.⁶⁸ Richest dietary sources of ALA include flaxseed, echium, walnut, and algal oil; only algal oil has been found to produce increases in blood levels of DHA. A review published 2014 that included 10 key intervention studies published over the last 10 years found that ALA from nut and seed oils was not converted to DHA at all, but ingestion of microalgae oil led to significant increases in erythrocyte and plasma DHA.

Clinical application: If the diet chosen is vegetarian or vegan, or if the individual does not regularly consume omega-3-rich fish or take supplemental EPA and DHA, check blood levels of omega-3 fatty acids. Algal oil supplements can be recommended for vegetarians/vegans.⁶⁹

The Biology of (Processed) Food Addiction

Mark Hyman, MD, chairman of IFM, presented the development of views regarding diet and calories.

Current View: The Calorie Hypothesis

Obesity is related to lack of will power. Just eat less, exercise more. The calorie restriction model fails because:

- (1) Compensatory mechanisms defend against weight loss by decreasing energy expenditure and increasing appetite.
- (2) High-GI carbohydrates (added refined sugars, especially sugar sweetened beverages, refined grains, starches) light up the nucleus accumbens—the brain's addiction center—promoting compulsive overeating of processed, high GI foods.
- (3) Multiple factors regulate metabolism: dietary composition, microbiome, toxins, infections, allergens, nutrient status, mitochondrial dysfunction, and hormonal and neurotransmitter dysregulation.

Alternative Views

Poor Diet Quality, Not Calories, Is the Driver of Obesity⁷⁰:

- (1) All calories are not created equal in the human system.
- (2) Food is not just calories; it is information and instructions that change your metabolic state.
- (3) Diets don't work because they are not addressing fundamental driver of excessive calorie intake: physiological addiction to refined carbs and sugars. A biochemical, not psychological problem.

Sugar Is 8 Times More Addictive Than Cocaine. Experimental research on animals, especially rats, has revealed deep commonalities between overconsumption of sugars and drug addiction⁷¹:

- (1) Sweet tastants and drugs of abuse both stimulate dopamine signaling in the ventral striatum, a brain-signaling pathway critically involved in reward processing and learning.
- (2) Cross-tolerance and cross-dependence are seen between sugars and drugs of abuse (eg, animals with a long history of sucrose consumption become tolerant to the analgesic effects of morphine); naloxone (an opiate antagonist) triggers in rats with sugar overconsumption some of the behavioral and neurochemical signs of opiate withdrawal; and recent neuroimaging studies in humans have discovered neuroadaptations in the brain of obese individuals that mimic those previously observed in individuals addicted to cocaine and other drugs of abuse.
- (3) Virtually all rats preferred saccharin over intravenous cocaine, a highly addictive drug; the same preference was observed with an equipotent concentration of sucrose, a natural sugar.

Overeating Behavior Can Be Compulsive, Resembling Drug Addiction⁷²:

- (1) Compulsive overeating behavior in obese rats.
- (2) Excessive "palatable" food consumption resistant to disruption by aversive conditioned stimulus (electric shock).
- (3) Striatal dopamine D₂ receptors (DR2) down regulated (similar to drug addicts).
- (4) Knock down of DR2 accelerated addiction reward, compulsive behavior.
- (5) Humans: DR2 activation is blunted in obese adults.

Hungry Visceral Fat Is An anabolic Driver of Overeating Behavior⁷³:

- (1) Visceral fat biology: Being fat makes you overeat.
- (2) "Hungry fat cells suck fuel out of your blood like a vacuum cleaner," secrete hormones and cytokines that promote weight gain and inflammation.
 - a. Hormones (adiponectin, resistin, insulin, leptin, MSH).
 - b. Cytokines (IL-6, IL-1, TNF- α , etc).^{74,75}
- (3) Availability of metabolic fuels regulates hunger and food intake.
- (4) Fuels: glucose, nonesterified fatty acids, and ketones are tightly controlled at 4 to 6 kcal/L.

Insulin Release Surges in Response to High GI Foods Causing Dysfunctional, Obesity-Promoting Metabolism.

- (1) Insulin is an anabolic hormone that drives circulating fuel into storage, decreasing metabolic fuel availability.
- (2) Insulin stimulates lipogenesis and inhibits lipolysis.
- (3) Insulin treatment increases weight gain in humans and animals.

In sum, anabolic changes in adipose tissue precede overeating:

- (1) Calorie restricted diets exacerbate metabolic dysfunction leading to more overeating.
- (2) Decline in energy expenditure and increase in hunger triggers starvation response.

Dietary composition is more important than calories to understand how to address the obesity epidemic. Both human and animal studies confirm this.

A Low Glycemic Load Diet Higher in Fat and Protein Improves Metabolic Rate and Energy Availability. Eight obese young adults were fed a standard hypocaloric diet to produce 10% to 15% weight loss, then provided isocaloric low-fat (60% of energy from carbohydrate, 20% fat, 20% protein), low-GI (40%-40%-20%), and very low-carbohydrate (10%-60%-30%) diets in randomized crossover design for 4 weeks. The low-fat diet lowered energy availability and metabolic rate. The very low carbohydrate diet had the highest energy availability and metabolic rate.⁷⁶

Changes in Dietary Composition Produce Obesity in Genetically Normal Animals Independent of Calorie Intake. Rats fed to maintain identical body weight developed 70% more body fat on a high-GL versus a low-GL diet. The high-GL diet resulted in lower muscle mass despite lower calorie intake. High-GL fed animals develop hyperphagia *after* onset of hyperinsulinemia.⁷⁷ Body weight decreased in rats with isocaloric diets that were low GL. The low-GL diet improved hepatic gene expression that favors catabolism. Excessive fat deposition driven by high GL diet precedes and promotes hyperphagia. Overeating is driven by loss of metabolic fuels sequestered in adipose tissue.⁷⁸

Increasing Percentage of Calories From Fat Will Not Increase Risk of CVD. Sugar, Not Fat, Is Linked to CVD. A large meta-analysis of 76 studies on fat shows no link with CVD, except trans fats.⁷⁹ A large meta-analysis on sugar found a significant link to CVD: HR for CVD was 1.3 for the lowest and 2.75 for highest sugar consumption.⁸⁰

New View: The Diet Quality Hypothesis

- (1) Diet quality affects fat storage availability of metabolic fuels.
- (2) High-GL foods drive sequestration of energy into fat.

- (3) This leads to perceived deficit of metabolic fuels, lowered energy expenditure, and increased energy intake.
- (4) People have more control over WHAT they eat than HOW much they eat.
- (5) The optimal diet should have a low GL; high micronutrient, phytonutrient, and fiber content; and higher healthy fat. This will lower fat cells' anabolic drive, increase energy expenditure, reset neuro-hormonal responses to food, normalize brain chemistry and dopamine receptor status to regulate appetite, and automatically decrease excessive food intake.

Conclusion

Back to that patient in your office awaiting your dietary prescription. It appears that regardless of whether the diet is Mediterranean, Paleo, or vegetarian/vegan, the key issue is the quality of foods consumed. Any of these dietary approaches can be utilized to provide “a low glycemic load; high micronutrient, phytonutrient and fiber content; higher healthy fat diet” that contains:

- (1) More vegetables and low-GI fruits.
- (2) No packaged processed foods.
- (3) Few or no white potatoes.
- (4) No hydrogenated/trans fats.
- (5) No refined and fewer grains.

And, regardless, of which diet you—in consultation with your patient—choose, a wide assortment of biomarkers can be used to verify its efficacy. Key labs that should provide insight within 1 month: insulin sensitivity, hs-CRP, triglycerides, and homocysteine.

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