What Effect Do Isocaloric Low-Fat, Low-**Carbohydrate and Moderate-Fat Diets Have on Obesity, Inflammation and Coronary Artery Disease?**

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Background: Two-thirds of all Americans are either overweight or obese, accounting for almost 10% of all US medical expenditures. States with a greater incidence of overweight/obesity also have greater rates of cardiovascular disease. Cardiovascular disease remains a major cause of morbidity and mortality and has been shown to be due to inflammation by Fleming, et al. Numerous risk factors, including obesity, have been implicated as irritants for this inflammatory cardiovascular disease process. This study was designed to determine the effect of three different isocaloric diets designed to promote weight loss on (1) inflammatory cardiovascular disease risk factors, (2) coronary blood flow and (3) weight loss/BMI.

Method: One hundred and twenty men (62) and women (58) between 30-59 years of age with BMIs greater than 30 were enrolled into one of three dietary and exercise programs. Participants were randomly assigned to a 1500-1600 kcal/day low-fat, low-carbohydrate or moderate fat diet for 12 months. Dietary adherence was assessed using dietary recall, urine ketone testing and measurement of respiratory quotient. Weight, BMI, and 14 cardiovascular lipid and coronary blood flow health risk indices were monitored at baseline, 6 weeks, 3, 6 and 12 months. These indices were measured again 4 months post-study to determine residual effect. Fasting blood work included total cholesterol, LDLc, HDLc, triglycerides (TG), TC/HDL, VLDLc, TG/HDL, CRP, IL-6, Lp(a), fibrinogen and homocysteine. Objective measurement of coronary blood flow using nuclear imaging was made at baseline and 1 year to determine the effect of these dietary changes on heart disease. **Results:** Dietary adherence resulted in statistically significant (p<0.001) reductions in body weight and BMI for each of the three dietary regimens. Coronary blood flow improved on both the moderate-fat and low-fat diets. Effect sizes (R, R2) for differences between diets and their fat content were significant (p<0.000001) for all indices of inflammation. Interleukin-6 increased on lowered-carbohydrate diets and decreased with low-to-moderate fat diets. These changes in IL-6 corresponded to changes seen in coronary blood flow. **Conclusions:** Appropriate diet and exercise with time intensive counseling can lead to effective weight reduction and maintenance for most people. Long-term adherence to lowered-carbohydrate diet significantly increased cardiovascular risk as measured by inflammatory CVD risk markers and coronary blood flow. Long-term adherence to lowto-moderate fat diet significantly reduces CVD risk and improves coronary blood flow. Obesity, like cholesterol, is clearly one of several risk factors promoting an inflammatory effect on coronary arteries and the subsequent development of heart disease. The benefit of weight loss can be compromised if the dietary changes made promote an increase in inflammatory coronary artery disease.

Inflammatory Heart Disease Can Result From **Excessive Consumption of Protein**, **Carbohydrates and/or Fat!**



Changes in Weight & BMI.







• The average weight loss was 14-16 kg for the vegan group, 11-16 kg for the LMF group and 11-20 kg on the lower carb group. (upper left) • BMI decrease was present for all isocaloric groups independent of fat

Obesity & Heart Disease.

- Recent estimates of the impact of obesity on heart disease vary from study to study.
- Despite differences in these papers, obesity is clearly associated with heart disease, diabetes, cancer and other

The Question Remains: Can Dieting and **Exercise Break the Cycle of Obesity**, **Inflammation & Heart Disease?**

- Given the prevalence of both obesity and heart disease, and
- Given the relationship between Inflammation, Obesity & Heart Disease.
- This study looks at the effect of isocaloric diets of varying fat content to determine their effect on weight, the inflammatory irritants which lead to heart disease and changes in coronary blood flow itself.

Randomized Subgroups.

- 120 obese (BMI > 30) men (n=62) and non-pregnant women (n=58), ages 30-59, were randomly assigned to one of three diets for 12 months, with additional follow-up 4 months after the study was completed.
- The diets were isocaloric (1500-1600 kcal/d) and included a vegan group, lower carbohydrate high fat group and low to moderate fat group.
- Each group was then subdivided into 2 parts, with 1/2 receiving a 2.5 mg folate, 25 mg B6 & 1 mg B12 supplement, and 1/2 receiving no supplement.



content. (upper right)

Changes in Lipids

- Initial improvement was noted for all isocaloric dietary groups during the first three months of the study.
- After the first three months, the greatest improvement was noted among those following the low to moderate fat regimen, with less improvement noted followinlg the vegan regimen and worsening of lipids on the lowered carbohydrate approach.

Change in Lipids









Insulin Resistance

for people on higher fat diets.

 Insulin resistance improved for all isocaloric diets during the first three months of the study.

• Insulin resistance worsened thereafter



Homocysteine

- Markers of inflammation showed worsening of inflammation independent of caloric content or weight loss.
- The lower carb high fat and vegan diets without vitamin supplementation was associated with increased levels of homocysteine consistent with a folate, B6



major health problems.



Obesity confusion

Estimates from recent Centers

for Disease Control and Preven-

tion studies on the number of

deaths linked to obesity have

varied widely since March 2004.

Estimated number of deaths

400 thousand deaths

linked to obesity

300 --

The Estimates From These Studies Do Not Take Into **Account Other Health Problems Including Inflammation!**



Inflammation is The Link Between: **Obesity & Heart Disease?**



• In 1995 Fleming proposed that cardiovascular disease resulted from 12 arterial irritants which lead to inflammation within the walls of the

Dietary and Exercise Guidelines

- Dietary regimens (1500-1600 kcal/d)
- 1. Vegan diet excluded beef, poultry, pork, fish, et cetera. No dairy or eggs.
- 2. Low to moderate fat diet excluded no food group. Total fat content not to exceed 15-20% of diet (20-25 gms NSF, < 5gm SF).
- 3. Lowered carbohydrate diet < 100 gms/d.
- Exercise regimen (30 minutes, 3x/week)
- Bicycle, walking, swimming
- Indoors or outdoors

Self-Efficacy Counseling

- Participants received self-efficacy counseling every 6 weeks throughout the study for both diet and exercise.
 - Information
 - Counseling for problem solving
 - Motivation
- Measurement of outcomes (except for coronary blood flow which was measured at baseline and again at one year) at 6 time intervals throughout the study.

Measurement of Outcomes

		Measuremen	t of Variables		
Baseline	6 weeks	3 months	6 months	1 year	4 months after study
		Type title here			completion
MPI	Weight, BMI, RQ	Weight, BMI, RQ	Weight, BMI, RQ	MPI	Weight, BMI, RQ
Weight, BMI, RQ	FLPA	FLPA	FLPA	Weight, BMI, RQ	FLPA
FLPA	CRP, IL-6, Hcy, Fib, Lp(a)	CRP, IL-6, Hcy, Fib, Lp(a)	CRP, IL-6, Hcy, Fib, Lp(a)	FLPA	CRP, IL-6, Hcy, Fib, Lp(a)
CRP, IL-6, Hcy, Fib, Lp(a)				CRP, IL-6, Hcy, Fib, Lp(a)	

• Anthropomorphic information (height, weight (lbs/kg) and BMI). • Dietary compliance

- RQ using Med Graphics gas exchange
- Ketone urine strips for low carbohydrate group
- Blood work (fasting) for
- lipids, inflammothrombotic variables, and insulin resistance (TG/HDL).*

* McLaughlin T, et al. Use of metabolic markers to identify Overweight individuals who are insulin resistant. Ann Intern Med. 2003;139:802-9.

deficiency in the high fat group and a B12 deficiency in the vegan group.

Cytokine Markers of Inflammation

- Interleukin 6 (upper panel) improved with both vegan and low to moderate fat diets, while increasing on higher fat diets.
- CRP (lower panel) improved for all groups except those who did not receive vitamin supplementation on the high fat diet.





These Cytokine Markers of Inflammation Match Changes in Myocardial Perfusion





- Changes in perfusion imaging were analyzed for extent and severity of blood flow as shown in the upper left panel, yielding an ischemic index.
- Increased ischemic index (upper right) indicates worsening of coronary blood flow.
- Only those following LMF diets demonstrated a significant (p<0.05) improvement in coronary blood flow.

Conclusions to Isocaloric Diets Which Resulted in Equivalent Weight Loss, But Differences in Inflammation & Heart Disease.

• Independent of sex differences, the major factor involved in weight loss was an reduction in calories following one of three isocaloric diets, following self-efficacy counseling.

coronary arteries impairing CFR and subsequently causing ischemic coronary artery disease.

- Numerous investigators have focused on CRP as a marker of this inflammation. However, CRP while sensitive for inflammation is not specific for coronary artery disease.
- The importance of tissue cytokines and obesity are emphasized in the Unified Theory of Vascular Disease and provide the link to understanding Obesity & Heart Disease.

Unified Theory of Vascular Disease Accounts for Both Cytokine Activation of Inflammation & Obesity



Fleming, RM. Ch. 64 The Pathogenesis of Vascular Disease. The Textbook of Angiology, JB Chang editor, Springer-Verlag, New York, NY. 1999:787-798.

Results of Study

- There were no differences in outcomes between men and women.
- Each bar graph shows the results of those following a vegan diet without (s) and with (c) vitamin supplement, then the low to moderate fat diet without and with vitamin supplement and finally the lower carbohydrate group without and with supplement.

Dietary Adherence Demonstrated





Baseline 6 Weeks 3 Months 6 Months 1 Year 4 Months After

• Starvation or a lack of RCHO leads to the burning of fat as a primary fuel source. When fat is the primary fuel source, the RQ (VCO2/VO2) approaches 0.70. When protein is the primary fuel source the RQ is 0.80. When carbohydrates are the primary source of fuel for the body, the RQ nears 1.0.

• Changes in respiratory quotient objectively verify dietary changes, confirming successful adherence using self-efficacy counseling.

- During the initial phase of weight loss, lipids improved. This initial period of improvement lasts for approximately 3 months. After this time, further change in lipid levels is determined by the fat content in the diet. - Diets with higher fat levels (lower carbohydrate diet>vegan diet>LMF diet) are associated with worsening lipid levels over time, independent of weight loss.

Inflammation & Weight Loss = **Worsening Ischemic Heart Disease.**

- As interleukin 6, homocysteine and myocardial perfusion imaging demonstrate
- Inflammation is associated with worsening ischemic heart disease
- This inflammation can occur in the face of weight loss when there is either a deficiency in folate, B6 or B12, and/or there is an excess of saturated fat in the diet.
- Weight loss in the presence of worsening inflammation will result in an increased potential for myocardial infarction and injury.

Inflammation, Obesity & Heart Disease.



- Since obesity itself (adipocytes) promotes inflammation through the production of inflammatory cytokines, which can lead to a worsening of ischemic heart disease, reduction of overweight/obesity must be addressed to reduce the incidence of heart disease.
- However, since diets which are either high in saturated fat or deficient in certain vitamins can also lead to inflammation, independent of weight loss from caloric restriction, the successful treatment of obesity and heart disease requires an approach which reduces both weight and inflammation.