

Clinical Experience of a Diet Designed to Reduce Aging

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ABSTRACT

Objective: Aging is associated with elevated levels of glucose, insulin, and triglycerides. Our objective was to assess the effect of a nutritional program designed to reduce these correlates of aging.

Design: This is a retrospective chart review of patients attending an outpatient metabolic management program including a high-fat, adequate-protein, low-carbohydrate diet, nutritional supplementation and periodic individual visits. Outcomes measured at baseline and follow-up included body weight, fasting serum glucose, insulin, leptin, lipids, and thyroid hormone.

Results: Thirty-one patients were identified with complete information. The mean age of patients was 57.6 ± 2.4 consisting of 53% female and 47% male patients. The average duration between follow up visits was 91.5 ± 8.5 days. Of the parameters measured at the follow-up visit, body weight, serum leptin, insulin, fasting glucose, triglyceride, and free T3 significantly decreased by $8.1 \pm 0.8\%$, $48.2 \pm 3.8\%$, $40.1 \pm 4.7\%$, $7.6 \pm 2.1\%$, $28.3 \pm 5.7\%$, and $10.8 \pm 1.8\%$, respectively. Furthermore, the triglyceride/high density lipoprotein ratio decreased from 5.1 ± 1.7 to

2.6 ± 0.5 .

Conclusions: In the context of an outpatient medical clinic, a high-fat, adequate-protein, low-carbohydrate diet with nutritional supplementation led to improvements in serum factors related to the aging process. Further research regarding this dietary approach and its relationship to aging is in order.

BACKGROUND

Since the discovery that caloric restriction extended the lifespan of rats 70 years ago¹, many model organisms such as yeast^{2,3}, nematodes⁴, fruit flies⁵, and mice^{6,7} have been subjected to some form of food restriction that resulted in extended lifespan. These and many other studies regarding the impact of caloric restriction on lifespan has generated such compelling evidence that the National Institute on Aging has initiated studies in non-human primates (rhesus macaques) examining caloric restriction on a number of metabolic and biological parameters including lifespan⁸.

Nevertheless, the mechanisms driving the increased lifespan by caloric restriction or weight loss are unclear. Data from *C. elegans*^{9,10}, *Drosophila*, and yeast¹¹ and, more recently, rodents¹² implicate the insulin/Insulin-like growth factor signaling pathways as a potential regulator of this process.

Moreover, the ongoing data collection on the physiologic effects of caloric restriction in rhesus macaques parallels rodent studies demonstrating reduced body and fat mass, improved gluoregulatory function, decreased blood pressure and blood lipids, and decreased body temperature¹³. Interestingly, centenarians have lower blood glucose, insulin, leptin, free T₃ and serum triglycerides than those who do not live to be over one hundred years old¹⁴. Therefore, the fundamental mechanism by which calorie restriction improves lifespan appears to alter these metabolic parameters.

In this paper, we examine the impact of a diet specifically designed to improve metabolic parameters independent of caloric intake. The diet is based on the premise that by reducing glucose and protein as substrates for oxidative metabolism and enhancing fatty acid oxidation, many of the same physiologic changes that are seen in calorie-restricted animals will also be seen in individuals following this type of diet.

METHODS

Design

This is a retrospective analysis of clinical information from patients attending a private practice. Patients were referred for the treatment of diabetes, cardiovascular disease, excessive weight, fatigue, and other chronic diseases of aging. All patients with sufficient baseline and follow-up parameters were included in this series.

Clinic procedures

On the first visit, a comprehensive history and basic physical examination was performed. Clinical information was obtained and dietary instruction was provided by a clinical team consisting of a naturopath, nutritionist, and physician. After the first visit, the patients were typically contacted by telephone after 2-4 weeks, and a return visit was scheduled for 2-3 months later for follow-up evaluation and labs.

Dietary recommendation

The diet included unlimited amounts of certain fats and oils, a restricted amount of

protein, and a very limited amount of carbohydrate. Patients were told to eat when they were hungry. Calories were not explicitly restricted; calorie intake was determined only by levels of hunger. Recommended sources of fat included raw nuts and seeds, avocados, olives and olive oil, flax oil and cod liver oil. The intake of protein was told to be limited to approximately 1.0 grams/kg lean body mass per day (increased for exercise to 1.25 grams/day). As a result, most patients were instructed to eat from 50-80 grams of protein per day. Recommended sources of protein included sardines, fish, eggs, tofu, chicken, turkey, wild meats, low-fat cheeses (cottage, ricotta, swiss), seafood, and veggie burgers. Only non-starchy, fibrous vegetables were acceptable: lettuce, greens, broccoli, cauliflower, cucumbers, mushrooms, onions, peppers, sprouts, asparagus, and seaweed. Though not explicitly stated, the general dietary intake as percent daily caloric intake from macronutrients for most people ended up by history to be approximately 20% carbohydrate, 20% protein, and 60% fat. For drinking, 6-8 eight ounce glasses of water and/or herbal tea were recommended. A written handout with a list of acceptable and unacceptable foods was provided.

Nutritional supplementation

Nutritional supplements to support fat metabolism and enhance insulin sensitivity were recommended to all patients to be taken on a daily basis: L-carnitine 2000mg, alpha-lipoic acid 400mg, coenzyme Q10 100 mg, 1 tbsp cod liver oil, magnesium 300mg, potassium 300mg, vitamin C 1000mg, vitamin E 800mg daily, and a multivitamin consisting of all essential B vitamins and minerals.^{15, 16}

Medication adjustment

If an individual was taking lipid-lowering or sulfonylurea medications, these medications were discontinued at the first visit before starting the diet. In those patients taking blood pressure medication, medication was adjusted or, altogether discontinued, if low normal blood pressures were observed dur-

Table 1a. Summary of patient demographics. This population of patients consisted of highly motivated, primarily Caucasian individuals. (Data is presented as \pm S.E.M.)

Baseline patient characteristics	
n:	31
Age (in years):	57.6 \pm 2.4
Sex:	53% female, 47% male
Follow up duration (in days):	91.5 \pm 8.5

ing the course of the intervention. Because these patients were seen in clinical practice, patients were responsible for purchasing their own supplements.

Outcome measures

At baseline and return clinic visits, body weight was measured on the same scale (Tanita Model TBF-300A, Tanita Corporation of America, Inc. Arlington Heights, Illinois). Baseline and follow-up laboratory measurements included body weight and sitting blood pressure. Laboratory parameters included serum glucose, insulin, leptin, total cholesterol, LDL, HDL, triglycerides (TG), free T₃ and thyroid stimulating hormone

Table 1b. Effect of dietary and nutritional supplement therapy on gravimetric measurements and fasting serum levels. Patient physicals were performed at the initial and final, follow up clinic visits. At each time, blood was drawn for the determination of fasting serum levels of the measured parameters. (* p <0.001; data presented as \pm S.E.M.).

Effect of Diet Program on Body Weight and Fasting Serum Levels			
Parameter	Baseline	Follow-up	% Change
Body weight (kg)	86.3 \pm 3.2	79.2 \pm 3.0*	-8.1 \pm 0.8*
Insulin (mg/dl)	22.2 \pm 2.9	11.1 \pm 0.9*	-40.1 \pm 4.7*
Glucose (mg/dl)	108.3 \pm 5.0	99.3 \pm 4.5*	-7.6 \pm 2.1*
Leptin (mg/dl)	16.5 \pm 2.5	8.2 \pm 1.4*	-48.2 \pm 3.7*
Triglyceride (mg/dl)	229.3 \pm 75.1	110.7 \pm 14.2*	-28.3 \pm 5.7*
High density lipoprotein, HDL (mg/dl)	55.4 \pm 3.5	53.5 \pm 3.0	-0.3 \pm 3.9
Creatinine (mg/dl)	1.02 \pm 0.03	1.01 \pm 0.03	0.5 \pm 1.7
Free T ₃ (pg/ml)	2.97 \pm 0.05	2.64 \pm 0.06*	-10.8 \pm 1.8*
Thyroid Stimulating Hormone (pg/ml)	2.53 \pm 0.25	2.57 \pm 0.22	8.9 \pm 8.1
Systolic blood pressure (mmHg)	136.6 \pm 3.7	121.7 \pm 2.3*	-10.2 \pm 2.1*
Diastolic blood pressure (mmHg)	86.5 \pm 1.7	76.4 \pm 1.7*	-11.4 \pm 1.8*

(TSH) following a 12 hour fast. The clinical data were abstracted from the medical charts and entered into a computer database without identifying information.

Statistical Analysis

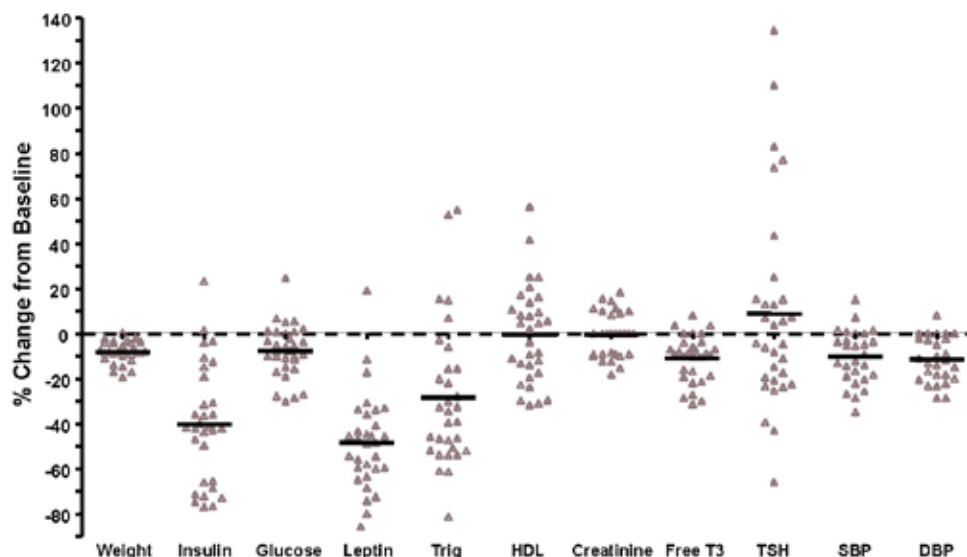
The primary analysis was a “pre-post” analysis comparing baseline to follow-up values using a paired t-test. Individual percent changes for each laboratory parameter were determined and used to calculate the mean percent change. This de-identified analysis of existing clinical data was approved by the Duke University Medical Center Institutional Review Board.

RESULTS

Patient demographics of those who had complete baseline and follow-up laboratory tests are displayed in Table 1a. The mean age was 57.6 \pm 2.4 years consisting of 53% female and 47% male patients. The average duration between baseline and follow up measurements was 91.5 \pm 8.5 days.

The recommendation of a high fat, adequate protein, low carbohydrate diet resulted in a significant loss of body weight by 7.1 + 0.8 lbs in this patient population (Table 1b; Figure 1). Accompanied by the weight

Figure 1. Directional impact of dietary intervention on clinical parameters of aging. The percent change from baseline is indicated for the averaged data taken from each patient. (* $p < 0.001$; data presented as \pm S.E.M.) Abbreviations: Gluc, glucose; Crea, Creatinine; Trig, triglyceride; HDL, high-density lipoprotein; TSH, thyroid stimulating hormone; FT3, free T3; Wt, weight; SBP, systolic blood pressure; DBP, diastolic blood pressure.



was a significant reduction in both systolic and diastolic blood pressure by $10.2 \pm 2.1\%$ and $11.4 \pm 1.8\%$ mmHg, respectively. Serum levels of leptin, insulin, fasting glucose, and free T3 significantly decreased from baseline levels by $48.2 \pm 3.8\%$, $40.1 \pm 4.7\%$, $7.6 \pm 2.1\%$, and $10.8 \pm 1.8\%$, respectively (Table 1b; Figure 1). In addition, despite the intake of predominantly fat, there was a significant decrease in triglyceride ($28.3 \pm 5.7\%$) in this patient group. The triglyceride/HDL ratio decreased from 5.1 ± 1.7 to 2.6 ± 0.5 . Serum creatinine and TSH did not change significantly.

DISCUSSION

This retrospective analysis of patients from a private clinic adhering to a high-fat, low carbohydrate, adequate protein diet demonstrated reductions in critical metabolic mediators including insulin, leptin, glucose, triglycerides, and free T₃. Moreover, the patient group, on average, lost significant weight even though they were not instructed to reduce calorie intake. These findings are consistent with other studies showing

weight loss and reductions in fasting serum insulin with a low carbohydrate, ketogenic diet^{17,18}. The ability of the diet to lower these parameters, especially TGs and body weight, seems counter to standard thinking considering the increased ingestion of fats. A possible explanation is that the resultant lower leptin and insulin was indicative of increased leptin and insulin sensitivity, resulting in increased β -oxidation, hypothalamic mediated increased satiety, and possibly subconsciously lowered caloric intake^{19,20}.

It has been known for some time that different dietary fats appear to have varying effects on insulin-sensitive tissues and this may differentially impact the metabolic parameters measured in this study^{21,22}. Numerous studies have demonstrated that reduced glucose (carbohydrate) substrates in the diet suppress hepatic de novo fatty acid biosynthesis, triglyceride production, and triglyceride secretion, while enhancing hepatic, adipose, and skeletal muscle fatty acid oxidation²²⁻²⁴.

Nonetheless, the impact of this dietary

approach on aging mechanisms can only be implied from comparisons with longevity studies that have examined the same metabolic parameters. Many aging studies have used calorie restriction as the means to impact aging. These types of studies become difficult in humans for the obvious reasons of dietary compliance, human lifespan duration, and the multiple and complex confounding factors. For this reason, investigators have examined the effectiveness of weight loss as a surrogate for caloric restriction on human mortality rates²⁵ but have found an increased mortality rate and reduced lifespan²⁶. The reason is that many of these studies did not distinguish between intentional and unintentional weight loss with the latter usually resulting from disease and, thus, increased mortality. It is now speculated that fat loss as opposed to weight loss decreases all-cause mortality in humans²⁵.

Patients in this study demonstrated a similar directional impact on the measured parameters when compared to studies using more established models of longevity such as caloric restriction. The patients in this study demonstrated significant weight loss along with a reduction in glucoregulatory mediators including insulin and leptin similar to those found in calorie-restricted primates^{27,28}. Moreover, calorie restricted primates demonstrated a positive relationship between food intake and leptin levels²⁹. Thus, although patients were not told to restrict calories, there may have been a reduction in caloric intake secondary to reduced hunger, with the decrease in circulating leptin reflecting an increase in leptin sensitivity^{19,30}. Interestingly, this study cohort exhibited a reduction in circulating free T₃, the secreted form of thyroid hormone thought to mediate most of thyroid actions. Paralleling this reduction in circulating free T₃, 9 patients of this study cohort that had basal body temperatures measured before and after intervention showed a significant decrease (p=0.004) in basal body temperature of 0.182 degrees C. Similar findings were reported in caloric restricted rodents,

monkeys, humans, and centenarians³¹⁻³⁴. It has been suggested that the reduction in T₃ and body temperature could alter the aging process by reflecting a reducing metabolic rate, oxidative stress, and systemic inflammation^{35,36}.

It is important to note that the dietary recommendation in this study is unique from other ketogenic diets in that this dietary intervention limits protein intake as well as carbohydrates (though not total fat intake). It has been demonstrated that the longevity effects of calorie restriction can be partially attributed to the reduction in protein intake³⁷. It has been shown that limiting dietary amino acids, specifically methionine, inhibits signaling through mammalian target of rapamycin (mTOR) thereby decreasing mitochondrial damage and protein translation^{38,39}. Future studies will be aimed at investigating the impact of a high fat, low carbohydrate with limited but adequate protein on mTOR signaling.

Because this was a retrospective analysis of a clinical practice, there may be bias introduced in the patient sampling procedure. This study reflects the effect of recommending this diet in a clinical practice, so food intake was not directly measured. In addition, this sample population may reflect the results in highly motivated individuals. Though the metabolic improvements occurred in patients who had both high and low weight loss, the improvements in metabolic parameters may be all or partially due to the weight loss. It should be noted, however, that the percent reduction in leptin particularly far exceeded the percentage of fat loss and may not be explained solely as a result of this fat loss. Also, it remains unclear as to the contributions of the suggested nutritional supplementation to the observed outcomes.

In conclusion, a nutritional program recommendation originally designed to treat chronic diseases of aging led to weight loss and metabolic changes currently thought to be beneficial in reducing the aging process. Further research regarding this dietary ap-

proach and its relationship to aging is in order.

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