Research Question:

Are simple cost-effective dietary interventions effective in reducing cardiovascular risk in middle-aged diabetic, hypertensive, and hyperlipidemic individuals?

A. Study Purpose and Rationale

It is well-known that atherosclerosis is a disease caused by accumulation of lipid, cellular, and fibrous components in vascular intima, both diffusely and focally throughout the body. Moreover, a large number of risk factors contribute simultaneously to formation of atherosclerotic plaques as well as to acute vascular events such as stroke, MI, or critical limb ischemia. Large clinical trials have centered around agents that could ameliorate those risk factors as well as reduce the rate of events. So far, statins have emerged as the greatest innovation in the last fifty years to this end, while aspirin has shown consistent benefit across countless studies in reducing cardiovascular events and mortality. The principle aim of this study is to examine the role, if any exists, for simple and cheap dietary interventions such as increasing free water or leafy green vegetable intake.

Diabetes mellitus has been demonstrated to be an independent risk factor in vascular disease, with both microvascular (i.e. peripheral neuropathy) and large-to-medium vessel sequelae (i.e. MI, stroke). Atherosclerosis is a disease of inflammatory vascular plaques, with the pathologic underpinnings of lipid and oxidized cholesterol that accumulates in vessel wall, recruiting macrophages and other inflammatory cells.

Hyperlipidemia, or dyslipidemia (that is to say, elevated cholesterol, especially that contained in lipid-rich LDL particles), is known to contribute to atherosclerosis. Conversely, low levels of LDL cholesterol and high levels of HDL are known to be protective, as triglyceride-rich LDL is thought to be the major offending particle that becomes trapped in vessel walls in atherosclerosis. A compendium of both basic science and clinical evidence has highlighted the utility in interventions that modify LDL-C and HDL-C. For example, carnivoran mammals experience orders of magnitude lower rates of atherosclerosis and its sequelae—stroke and MI—than rodents and primates, and have lipid profiles that would be quite perverse by human standards, with LDL-C in the teens or lower, and very high HDL-C. However, carnivorans that become hypothyroid (either experimentally or otherwise) experience reversal of these outstanding lipid profiles, accompanied by an incidence of stroke and MI approaching that of rodents and primates.

Lastly, hypertension is a known correlate with atherosclerosis, and increasing vessel wall tension that occurs with higher blood pressures effects vessel wall injury and greater lipid accumulation. Tight blood pressure control reduces the risk of stroke and MI. Currently, a vast array of antihypertensive agents exist – and control of blood pressure, regardless of mechanism, has shown this benefit.

It has been known for nearly seventy years that caloric restriction decreases both LDL and increases lifespan in experimental animals (this was initially discovered in rodents). Lifestyle interventions in humans, such as weight reduction, are known to increase HDL, and decrease LDL—though a number of studies do not indicate that material decreases in LDL can be accomplished through lifestyle intervention alone. Interestingly, weight loss in obese individuals achieved through bariatric surgery has been associated with a reduction in vascular events, even beyond what is achieved with medical therapy. Thus, one might reason that weight loss achieved through other mechanisms may serve a similar positive outcome.

It has been known for nearly fifty years that weight loss in overweight diabetic individuals improves insulin sensitivity. Mechanisms to physiologically explain these findings are just emerging, and include signaling mechanisms of intramuscular and hepatic fat on metabolism as well as gene

transcription. Nonetheless, weight loss is often difficult to achieve and impractical to control in human experimental studies. Unfortunately for those patients desiring facile interventions, surgical weight loss has historically been much more efficacious than medical weight loss, as few safe pharmacologic agents are available.

Hypertension, a significant risk factor for acute vascular events, can be treated pharmacologically with several classes of existing medications. First-line therapy consists of distal-acting diuretics, beta-blockers, and/or calcium-channel blocker. In diabetic individuals, or those with stable chronic renal disease and/or heart failure, angiotensin receptor blocking agents are utilized. Reductions in blood pressure are accompanied by reductions in atherosclerotic plaque burden as well as plaque rupture events including ACS.

This study will examine the effects of a discrete, cost-effective lifestyle intervention a number of easy-to-measure direct outcomes in hypertensive, hyperlipidemic, diabetic patients. Participants will be required to consume 2.5L water daily, as well as consume ½ pound daily of celery, carrots, broccoli, and/or cauliflower. It is our hypothesis that this intervention will have a measurable effect on blood pressure, lipid profiles, insulin sensitivity, weight, and/or subjective mood.

Hypothetically, there are a number of reasons why increased oral intake of fluids and fibrous low-calorie vegetables may improve biological parameters under study here. In terms of weight reduction, 2.5L of water and ½ pound of vegetables constitutes a substantial mass intake – 6 pounds daily – with very little calorie burden, and at a relatively low cost. The satiety effect alone of these items may cause reductions in the intake of other higher-calorie foods and beverages. Secondly, substantial free water intake will theoretically induce natriuresis by impairing renal concentration of urine due to dilution of plasma – with a concomitant drop in blood pressure. Free water intake may improve renal function in two ways: through increased circulating volume, increased glomerular filtration and renal plasma flow, and therefore decreased the energy burden on renal tubular transport. These physiologic changes may collaterally lead to decreased renin secretion, creating a tendency toward decreased vascular smooth muscle tone.

B. Study Design

The study will be a prospective controlled cross-over design with three phases in defined order, to examine the effect of combining these two lifestyle interventions on directly measurable outcomes. Participants aged 40 to 70 will be selected who have comorbid hypertension, hyperlipidemia, and diabetes. They will be selected among primary care patients in Washington Heights, New York City.

Each phase will last four months, the first and third phases involving observation only without intervention. During the second phase, the intervention phase, participants will not be asked to cease any lifestyle behaviors or diets, but will be required to add the following two items to their daily PO consumption: 2.5L water daily in divided doses of no greater than 750mL, and ½ pound daily of celery, carrots, broccoli, and/or cauliflower.

The crossover design is well-suited to the experimental question, and eliminates most possible confounding factors besides temporal ones that are likely to be patient-specific in any case. The three-phase “off-on-off” design is superior to a two-phase “off-on” one for a number of reasons – at only a slightly greater cost. Primarily, this design will provide better control for the “study participant” effect on lifestyle and behavior, whereby participants may alter their behavior either consciously or subconsciously as a response to enrollment and monitoring by medical professionals. Moreover, this third “off” phase should theoretically provide a 'chase' or 'wash-out' effect that will increase the study's impact and generalizability.

Written consent will be obtained prior to enrollment. Given the high prevalence of the medical conditions of interest (diabetes, hypertension, hyperlipidemia) in the Washington Heights population, enrollment is anticipated to take up to a year, given the power calculations below. With enrollment taking up to a year, and with the actual study duration of one year, it is anticipated that the investigators will be able to conclude all meaningful data collection within two years from the first enrollment.

Primary outcome measures will include blood pressure, hemoglobin a1c, lipid profiles, and mood as assessed by the Goldberg depression test. As weights and other vital signs will be recorded for each participant at all data collection points (which occur every four months), these can be followed as well.

All patients beginning the study will have an enrollment exam with data collected pertaining to each outcome measure. At four months time, a second round of data collection and counseling session will precede the intervention phase – phase two. At eight months, participants will have a third round of data collection, and will be asked to return terminate the dietary interventions that began at four months. After twelve months, the final round of data collection will be conducted, and the study will terminate, with no additional follow-up.

Data collection will consist of vital signs, including bilateral blood pressure, heart rate, respiratory rate, and oxygen saturation. Patients will also provide blood for analysis for each data collection, in the overnight fasting state; lipid panel, finger-stick glucose, and hemoglobin a1c will be analyzed. CBC and chemisitries will also be drawn and examined at each data collection, for routine surveillance on each individual's overall health status. Notably, investigators will be interested in the effect of increased free water intake on serum sodium and potassium – as there may be a propensity for this intervention to effect a “beer potomania”-type of hyponatremia.

This crossover design will allow for paired statistical analysis, greatly reducing the number of patients needed to enroll and achieve statistical significance. Moreover, the third phase will improve the impact and interest of the study, regardless of the result.

The number needed to enroll will depend on the parameters measured and their expected deviations across measurements:

Blood pressure (SBP or DBP): goal to power to a 0.5mm Hg difference, with 5mm Hg deviation
Cholesterol (non-HDL): goal to power to a 2mg/dL difference, with 20mg/dL deviation
Hemoglobin A1c: goal to power to a 1% difference, with 10% deviation
Weight: goal to power to 1lb difference, with 10lb deviation
Goldberg depression test: goal to power to 0.5 point difference, with 5 point deviation

In all above cases, the study aims to power to a tenfold greater deviation than effect size.

$N = 2 + 8(10)^2 = 802$

We will thus aim to enroll about 1000 participants.

C. Study Procedure

Most of the pertinent procedure is elaborated above. See below timeline for study participant interventions and data collections:

	< phase 1	> < phase 2	> < phase 3 >
-1m	0m	4m	8m 12m
E	D	D,S	D,T D

Key:
E = initial enrollment, signing of consent
D = data collection point
S = start of interventions
T = stop point of intervention
m = month

Data collection will consist of vital signs, including bilateral blood pressure, heart rate, respiratory rate, and oxygen saturation. Patients will also provide blood for analysis for each data collection, in the overnight fasting state; lipid panel, finger-stick glucose, and hemoglobin a1c will be analyzed. CBC and chemistries will also be drawn and examined at each data collection, for routine surveillance on each individual's overall health status.

Start of interventions will consist of counseling sessions on how to implement interventions. Each participant will receive one click counters and one BPA-free 750mL liquid containers. Meal vouchers will be provided during the entirety of phase 2 that stipulate purchase of the requisite vegetables. Where necessary, weekly home delivery of vegetables will be arranged by the study.

D. Study Drugs

Water, raw carrots, broccoli, cauliflower, celery.

E. Mechanical Devices

N/A

F. Questionnaires

Goldberg depression test; see online at:
http://www.netdoctor.co.uk/interactive/interactivetests/goldberg.php

G. Study Subjects

Inclusion Criteria:

40 < age < 70
history of hypertension
or on antihypertensive agents
history of hyperlipidemia
or on lipid-lowering agents
history of diabetes
preference for patients with suboptimal medical control of one of the above

Exclusion Criteria:

malignancy
schizophrenia or bipolar disorder
cognitive impairment
pregnancy
meeting any of SIRS criteria at study outset
cirrhosis
heart failure
renal failure (CKD > stage II)
serum sodium < 135mM at study outset

H. Recruitment of subjects

Patients will be recruited from New York-Presbyterian Hospital / Columbia University Medical Center, and from The Allen Hospital. Primary care physicians will be informed of the study and encouraged to consider whether their patients would be appropriate for the study.

I. Confidentiality of Study Data

All data will be de-identified and stored securely.

J. Potential Conflict of Interest

N/A

K. Location of Study

This study will be conducted in the outpatient clinics at New York-Presbyterian Hospital / Columbia University Medical Center.

L. Potential Risks

The major risks of study participation include physiologic burden of increased free water intake. Participants will be required to take daily free water load as divided doses, and they will be provided with a 750mL container to reduce the likelihood of this effect. Nonetheless, hyponatremia may occur, and will be monitored by serum chemistry studies performed with each data collection point. Participants will also be counseled regarding possible symptoms of hyponatremia or fluid overload, and

told to present to clinic if they occur.

M. Potential Benefits

Improvement in any or all outcome measures could be a possible benefit of study participation – this includes but is not limited to improved blood pressure, lipid profile, glycemic control, weight, or subjective feeling of enhanced well-being.

N. Alternative Therapies

Alternative therapies include Mediterranean-like diet, regular exercise, and all medications indicated for treatment of the diseases: diabetes, hypertension, hyperlipidemia.

O. Compensation to Subjects

Participants will receive $62.50 each, at each data collection point. Thus, each will be compensated a total of $250 over the course of the one-year study.

P. Costs to Subjects

Participants will not incur costs associated with participation in this study.

Q. Minors as Research Subjects

N/A

R. Radiation or Radioactive Substances

N/A

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(BALL et al., 1947; Belalcazar et al., 2013; Crockford and Salmon, 1970; Davis et al., 1983; Espeland et al., 2013; Hoeg et al., 1986; Kang et al., 2010; Look AHEAD Research Group et al., 2013; Mohammadpour and Akhlaghi, 2013; Samuel et al., 2010; Sjöström et al., 2012)