Clinical Use of a Carbohydrate-Restricted Diet to Treat the Dyslipidemia of the Metabolic Syndrome

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ABSTRACT

Background: The metabolic syndrome is characterized by an atherogenic dyslipidemia identifiable using lipoprotein subclass analysis. This study assesses the effect of a carbohydrate-restricted diet on the dyslipidemia of the metabolic syndrome in a clinical setting.

Methods: This is a retrospective chart review of patients attending a preventive medicine clinic using lipoprotein subclass analysis (by NMR spectroscopy) to identify the atherogenic dyslipidemia. If present, patients were counseled to begin a carbohydrate-restricted diet (<20 g/day). Patients already on statin therapy were included only if the medication dose was not changed. The outcomes were changes in body weight, fasting serum lipid profiles and serum lipoprotein subclasses.

Results: Of 122 patients identified, 80 patients had complete pre- and post-treatment data. The mean (±SD) age was 66 ± 9 years, baseline weight was 85 ± 12 kg, BMI was 28.1 ± 3.6, 73% were male, 99% were Caucasian. Sixty-five percent were taking statin medication. Carbohydrate-restriction led to a 13% reduction in total cholesterol, 16% reduction in LDL cholesterol, 38% reduction in triglycerides, and a 13% increase in HDL cholesterol (all p values < 0.001). Carbohydrate-restriction also led to a reduction in LDL particle concentration of 28%, a reduction in small LDL of 82%, a reduction of large VLDL of 62%, and an increase in large HDL of 30% (all p values < 0.001).

Conclusions: A carbohydrate-restricted diet recommendation led to improvements in lipid profiles and lipoprotein subclass traits of the metabolic syndrome in a clinical outpatient setting, and should be considered as a treatment for the metabolic syndrome.

INTRODUCTION

Dietary carbohydrate, especially refined carbohydrate, has been implicated as a contributory factor in many health problems including obesity and cardiovascular disease.1 Because obesity, elevated triglycerides and reduced high density lipoprotein (HDL-C) are recognized as components of the metabolic syndrome, and can be made worse by a low-fat/high-carbohydrate diet, a carbohydrate-restricted diet might be appropriate as a treatment for these conditions.2-4

The measurement of serum lipids to predict cardiovascular risk is has been enhanced by the measurement of lipoprotein subclasses. One

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method to determine lipoprotein subclasses which uses NMR spectroscopy technology has been predictive of recurrent coronary events in several studies. Based on these studies, the criteria most predictive of coronary events is an elevated low-density lipoprotein cholesterol (LDL-C) particle concentration (>1400), and at least 2 of the following: reduced LDL-C size (<20.5 nm), reduced large HDL-C concentration (<21), or elevated large very low-density lipoprotein cholesterol (VLDL-C) concentration (>27). This dyslipidemia is similar to the hypertriglyceridemia and low HDL-C pattern characteristic of the metabolic syndrome.

Based on the theory that the LDL particle itself, as opposed to the cholesterol within the particle, is the causative agent for atherosclerosis and coronary artery disease, we began using the lipoprotein subclass profile routinely in our clinical practice and attempted to aggressively lower the LDL particle concentration. This review summarizes the effect of recommending a carbohydrate-restricted diet on the lipoprotein subclass profile in medical outpatients.

**MATERIALS AND METHODS**

**Design**

This is a retrospective cohort study of clinical information from outpatients attending an internal medicine practice in Hilton Head, South Carolina (J.T.H.). Charts were included if lipoprotein traits of the metabolic syndrome were present and a recommendation of a carbohydrate-restricted diet was made. Charts were excluded if lipid-lowering medication was changed during the diet treatment, or if follow-up lipoprotein subclass profiles were not available.

**Diet instruction**

The carbohydrate-restricted diet recommendation was to reduce the intake of carbohydrate grams to fewer than 20 g per day until the development of urinary ketones (detectable by urine ketone strips). The diet generally includes unlimited amounts of animal foods (meat, chicken, turkey, other fowl, fish, shellfish), hard cheese, unlimited eggs, salad vegetables (1–2 cupfuls per day), and low carbohydrate vegetables (e.g., broccoli, cauliflower, kale, spinach, cabbage, or asparagus) (1–2 cupfuls per day). Once weight loss or risk factor reduction was achieved, carbohydrate was gradually reintroduced into the diet while monitoring the rate of weight loss.

**Medications**

Most patients (65%) were already receiving statin medication prior to introduction of the diet. To be included in this analysis, the medication dosage had to remain the same throughout the diet period. The doses used were the equivalent of simvastatin 20–40 mg daily.

**Outcomes**

At an initial clinic visit, a history and physical examination and laboratory tests were performed. At return visits, body weight and vital signs were measured. Before the diet instruction, and then periodically, a fasting lipid profile and lipoprotein subclass analysis was collected. After overnight fasting, blood was collected for serum lipoprotein profile determination (total cholesterol, HDL-C, triglyceride, LDL-C) using direct measurement techniques (LipoScience, Inc., Raleigh, NC). Lipoprotein subclasses were determined by nuclear magnetic resonance assay testing (LipoScience, Inc.). This assay measures the distinctive nuclear magnetic resonance signals broadcast by lipoprotein subclass particles of different size. The measured amplitudes of these signals give the subclass concentrations. VLDL-C subclass levels are expressed in milligrams per deciliter units of triglyceride, and those of LDL-C and HDL-C subclasses in units of milligrams per deciliter units of cholesterol. The following subclasses, with subpopulation designation and estimated diameter ranges, were quantified: large VLDL (V6, V5; 60–200 nm), medium VLDL (V4, V3; 35–60 nm), small VLDL (V2, V1; 27–35 nm), intermediate density lipoprotein (IDL) (23–26.9 nm), large LDL (L3; 21.3–23 nm), medium LDL (L2; 19.8–21.2 nm), small LDL (L1; 19.0–19.7
large HDL (H5, H4, H3; 8.2–13 nm), small HDL (H2, H1; 7.3–8.1 nm). From the initial 15 subclass concentrations, weighted-average LDL particle sizes (nm) and LDL particle concentration (nanomoles/L) were calculated.

Analysis

Clinical data were collected by the medical staff at the time of the visit. Data were abstracted from the medical charts and entered into a computer database. Patient identifiers were removed and the data were analyzed by the Duke investigators. Two of the Duke investigators conducted a site visit to the outpatient clinic. This de-identified analysis of existing clinical data was approved by the Duke Institutional Review Board.

Descriptive statistics calculated included means and standard deviations of continuous variables and proportions for categorical variables. Because this study used a "pre-post" design and the comparison of interest was the change from baseline to follow-up, a paired t-test was used to test for statistical significance. For between-group comparisons (statin or no-statin), a two-sample t-test was used comparing the change from baseline to follow-up between groups. A p value of <0.05 was used for statistical significance.

RESULTS

One hundred twenty-two patients were identified with the atherogenic dyslipidemia and were treated with a carbohydrate-restricted diet. Seven patients were excluded because they were taking medication other than a statin for lipid-lowering purposes. Thirty-five patients had missing data, leaving 80 patients for the analysis. Sixty-five percent of patients were on pre-existing statin therapy. The demographic characteristics, duration of follow-up and weight change were similar between the two groups (statin or no statin) (Table 1).

Carbohydrate-restriction led to an improvement in the means of all components of the fasting lipid profile, regardless of the use of statin lipid-lowering medication (Table 2). There were reductions in total cholesterol, triglycerides, and LDL-C, and an increase in HDL-C (all p values < 0.001). There were also significant improvements in many of the lipoprotein subclasses (Table 3). There were reductions in LDL particle concentration, large VLDL (diet + statin only), medium VLDL (diet + statin only), small VLDL (diet only), small LDL, and an increase in large HDL. The only significant difference between groups was for large LDL: carbohydrate restriction alone led to an average decrease in large LDL (−2.4%), while diet with pre-existing medication led to an average increase in large LDL (+40.7%).

DISCUSSION

In this clinical case series we observed beneficial effects of using a carbohydrate-restricted diet for the atherogenic dyslipidemia that accompanies the metabolic syndrome. The large and consistent improvements seen in the lipids and lipoprotein subclasses enhance the validity of these results, despite the lack of a control group. However, because there is no control

<table>
<thead>
<tr>
<th>Table 1. Patient Characteristics</th>
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<tbody>
<tr>
<td><strong>Characteristic</strong></td>
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<tr>
<td>N</td>
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<tr>
<td>Age, years</td>
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<tr>
<td>Gender, male</td>
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<tr>
<td>Race, Caucasian</td>
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<td>Weight, kg</td>
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<tr>
<td>BMI, kg/m²</td>
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<tr>
<td>Duration of follow-up, days</td>
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<td>Weight change, kg</td>
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group, no conclusions can be directly made about its effectiveness in comparison to other treatments.

This report extends prior research regarding a carbohydrate-restricted diet because of the relatively long duration of follow-up, inclusion of normal weight patients with other medical co-morbidities, and concomitant use of statin lipid-lowering therapy. Published reports of the use of carbohydrate restriction have typically studied healthy obese volunteers and have followed subjects for only 6 months.10-14

It is notable that among these patients, large changes in serum lipids were seen without large changes in weight. Most studies regarding carbohydrate-restriction have examined the effect of the diet when accompanied with weight loss.10-15 In this study, the patients were not obese at baseline, which may explain the lack of weight loss. Other preliminary evidence suggests that these metabolic changes will be seen even without significant weight loss.15 The effect on lipoprotein subclasses appears similar to that of niacin, gemfibrozil, and rosiglitazone.16-18 Gemfibrozil has shown to be effective to reduce major cardiovascular events.19 In our clinical experience, the carbohydrate-restricted diet is approximately as potent as the combination of simvastatin 40 mg daily and niacin 2000 mg daily for triglyceride and HDL treatment.

### Table 2: Effect of Carbohydrate Restriction on Fasting Lipid Profiles

<table>
<thead>
<tr>
<th>Test</th>
<th>Carbohydrate-restricted diet (n = 28)</th>
<th>Carbohydrate-restricted diet + pre-existing statin (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline, mean (SD)</td>
<td>Follow-up, mean (SD)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>209.5 (35.7)</td>
<td>177.5 (34.6)</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>140.9 (118.2)</td>
<td>78.9 (33.3)</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>50.1 (15.3)</td>
<td>56.4 (14.2)</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>108.5 (29.0)</td>
<td>102 (24)</td>
</tr>
<tr>
<td>Triglyceride/HDL ratio</td>
<td>4.4 (1.1)</td>
<td>3.3 (0.7)</td>
</tr>
<tr>
<td>Non-HDL cholesterol, mg/dL</td>
<td>159.4 (29.6)</td>
<td>121.2 (29.4)</td>
</tr>
<tr>
<td>Triglyceride/HDL ratio</td>
<td>3.3 (3.4)</td>
<td>-1.7 (1.0)</td>
</tr>
</tbody>
</table>

*aAll changes from baseline to follow-up are statistically significant.
There are no statistically significant between group differences.

### Table 3: Effect of Carbohydrate Restriction on Fasting Lipoprotein Subclasses

<table>
<thead>
<tr>
<th>Test</th>
<th>Carbohydrate-restricted diet (n = 28)</th>
<th>Carbohydrate-restricted diet + pre-existing statin (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline, mean (SD)</td>
<td>Follow-up, mean (SD)</td>
</tr>
<tr>
<td>Large VLDL, mg/dL</td>
<td>38.1 (90.9)</td>
<td>13.1 (16.8)</td>
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<tr>
<td>Medium VLDL, mg/dL</td>
<td>42.0 (42.0)</td>
<td>20.2 (21.6)</td>
</tr>
<tr>
<td>Small VLDL, mg/dL</td>
<td>22.8 (15.5)</td>
<td>11.0 (8.1)</td>
</tr>
<tr>
<td>Intermediate DL, mg/dL</td>
<td>2.1 (5.9)</td>
<td>2.0 (4.9)</td>
</tr>
<tr>
<td>LDL particle size (nm)</td>
<td>20.6 (0.8)</td>
<td>21.1 (0.6)</td>
</tr>
<tr>
<td>Large LDL, mg/dL</td>
<td>55.0 (50.4)</td>
<td>53.7 (43.5)</td>
</tr>
<tr>
<td>Medium LDL, mg/dL</td>
<td>37.7 (32.7)</td>
<td>46.5 (34.6)</td>
</tr>
<tr>
<td>Small LDL, mg/dL</td>
<td>39.3 (33.9)</td>
<td>63.15 (15.6)</td>
</tr>
<tr>
<td>Large HDL, mg/dL</td>
<td>27.8 (15.2)</td>
<td>33.5 (15.0)</td>
</tr>
<tr>
<td>Small HDL, mg/dL</td>
<td>22.4 (6.6)</td>
<td>22.9 (5.5)</td>
</tr>
<tr>
<td>LDL particle concentration</td>
<td>1553.4 (292.6)</td>
<td>1212.4 (301.7)</td>
</tr>
</tbody>
</table>

* p value < 0.01 for baseline to follow-up change.
** p value < 0.001 for baseline to follow-up change.
*** p value = 0.02 for between group differences
This testing technique allows direct measurement of small LDL-C, which is thought to be a major factor in the pathogenesis of atherosclerosis. However, the use of these serum tests for the prevention of atherosclerosis is not yet widely recommended. There is extensive clinical data that measurement of total cholesterol, LDL-C and HDL-C is useful in predicting atherosclerotic disease and acute coronary syndromes. However, an LDL-C of >130 mg/dL is present in as few as 25% of premature CHD cases. Moreover, treating a high LDL-C with statin therapy confers only approximately a 30% reduction in coronary artery events in both primary and secondary prevention. Emerging evidence suggests that this lack of correlation of LDL-C and CHD is probably because LDL-C can be carried by large or small lipoprotein particles, and it is the small dense LDL particles that are correlated with increased cardiovascular risk. Small LDL particles are more readily oxidized than large LDL particles, and small LDL particles are able to filter into the subendothelium of the artery wall easier than large LDL particles. The smaller the LDL particles, the more particles are needed to carry any given amount of LDL-C.

Several studies have shown that the number of LDL particles (LDL particle concentration) is superior to LDL-C and apolipoproteins in predicting CVD endpoints (MI, stroke, CHD death) and subclinical CVD endpoints (carotid stenosis, coronary calcification, coronary lumen diameter). Different associations with HDL subclasses and CHD are also evident. Of the five subclasses of HDL, the three largest HDL fractions show an inverse correlation with CHD, whereas, the two smaller subclasses of HDL confer none of the protection of the larger subclasses. Because of the observed improvement in these surrogate markers for atherosclerosis, this dietary approach needs to be evaluated in larger outcome studies.

This review has several limitations. Because this was a retrospective analysis of a clinical practice, there may be bias introduced in the patient sampling procedure. If this is an unbiased estimate of the true treatment effect, then the carbohydrate-restricted approach appears as strong or stronger than the typical effect of gemfibrozil, which has an effect of lowering the triglycerides by about 25% and raising the HDL by 7%. This study reflects the effect of recommending this diet in a clinical practice. Because no formal adherence evaluation was done, we cannot be certain that the patients actually followed these recommendations. If there was noncompliance, it is possible that our findings actually underestimate the effect of carbohydrate-restriction.

In conclusion, a carbohydrate-restricted diet recommendation led to an improvement in the lipid profile and lipoprotein subclass abnormalities associated with the metabolic syndrome. Similar effects were seen with or without lipid-lowering therapy, but the combination of diet and medication may be needed to achieve target goals, particularly for LDL-C, in clinical practice. Due to the improvements in triglycerides and HDL, a carbohydrate-restricted diet program will probably be effective in the treatment of the metabolic syndrome.

REFERENCES

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