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William R. Ware, PhD - Editor

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Welcome to our 200th issue! This month the focus is almost entirely on various aspects of diabetes and prediabetes. However, because of the current interest in the H1N1 virus, we begin with a brief commentary on the potential role of vitamin D in preventing influenza. Rather than discuss this at length, especially when the key paper was discussed earlier in the Newsletter, I have elected to link the reader with the excellent and authoritative website of the Vitamin D Council. This is an especially useful source since it provides links to a number of important papers, many of which are available full text at no charge. Readers should find the article by Dr. Cannell written for the council website to be of considerable interest in connection with the current threat represented by H1N1.

The main topic is of great importance in the context of preventive medicine since diabetes is associated with serious vascular problems that adversely impact peripheral circulation, the eyes and the kidneys and as well increase the risk of adverse cardiovascular events and mortality. It is becoming clearer all the time that it is important to identify this disease in its earliest stages and take preventive action to attempt to halt progression and achieve regression. By the time the diagnostic flags are waving their warning, it is much more difficult to intervene. Thus it is important to be aware of the early warning signals and if the appropriate tests are not routinely requested by ones physician, to specifically ask for them.

We start with a convenient method for assessing the risk of developing diabetes from data that should be readily available. This is followed by a review of a paper that examined the trajectories of two diagnostic measures of diabetes and highlights how fast progression can occur once a threshold has been crossed. The use of glycated hemoglobin as an indicator of prediabetes and as a diagnostic for diabetes itself is of growing interest as indicated by the consensus of a new international expert committee.

Primary prevention is of course most important, and thus some recent work involving intensive lifestyle modification is of great interest. The combination of the right diet and exercise has the potential for large reduction in the risk of incidence of diabetes. For men, once one has elevated markers suggesting prediabetes or the metabolic syndrome, the treatment of low testosterone levels appears to offer a considerable potential for benefit. This is discussed along with reference to a new book by an expert at Harvard which provides a comprehensive discussion of the use of supplementary testosterone under certain circumstances and how this does not impact the risk of prostate cancer.

In keeping the diabetes theme, this issue also has a Research Review on carbohydrate restriction. This follows and is related to the review on fat and saturated fat which appeared in the June Newsletter.

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Wishing you good health,

William R. Ware, PhD, Editor

Highlights

H1N1 INFLUENZA AND VITAMIN D

While this issue focuses on prediabetes and type 2 diabetes uppermost in the minds of many readers is no doubt swine flu and the H1N1 virus. The media has built up an atmosphere of fear associated with what will happen come winter since, while no one knows, there is a chance that the virus will develop lethal properties and present a much greater danger than it has so far exhibited.

Readers of this newsletter may recall an earlier discussion of a landmark paper on vitamin D and influenza, which, among other things, attributed the seasonal and latitude variation to population vitamin D status. With this in mind, it my have struck some readers as odd that on TV and in the print media, the silence regarding the role that vitamin D might play in the prevention of an H1N1 infection has been profound. Mainstream focus is on vaccines and prescription anti-virals, period. While a whole issue could be easily be devoted to the subject of vitamin D and the flu, the extensive material on the website of the Vitamin D Council (http://www.vitamindcouncil.org/) does such a good job of providing an up-to-date to most of the important questions that instead readers are referred to this resource. This subject is well worth studying since it is not as simple a matter as one might suppose, even given the remarkable success of vitamin D supplementation in preventing flu and colds as seen in randomized and other intervention trials. In particular, attention is drawn to the article by Dr. J.J. Cannell, M.D., who is an internationally recognized vitamin D expert, coauthor of the paper mentioned above, and the Director of the Vitamin D Council. The title of the article is *H1N1 Flu and Vitamin D* and is listed currently among items on the home page. This may change so the URL is http://www.vitamindcouncil.org/newsletter/h1n1-flu-and-vitamin-d.shtml. Readers are also referred to the "Research" section under the research area subheading "Influenza" for an impressive set of links to the literature on vitamin D and influenza. Some of these links will yield full text and in particular the landmark paper *Epidemic Influenza and Vitamin D* and as well an equally important paper *On the Epidemiology of Influenza*. Dr. Cannell is the lead author in these papers, and both are co-authored by experts in either vitamin D or epidemiology. Attention is also directed to the paper on cod liver oil and vitamin A toxicity and the adverse impact on vitamin D efficacy which is also available in full text.

To your editor, it appears we have reached the point where all readers and their family members who do not know their current 25-hydroxy-vitamin D level should have the blood test. One of the reasons is that while the current recommendation of Cannell and many others is 4000-5000 IU of D3 per day, for some individuals this will not bring the serum level up optimum. Opinions vary on what is optimum, but start at 50-70 ng/mL (divide numbers in nmol/L by 2.5 to get ng/mL). This is not a simple matter because of the seasonal variation, and the goal should be to remain within or the above-optimum range throughout the year. Thus the result of the blood test must be considered in the light of when the sample was drawn. In general, the seasonal increase starts strongly in early spring, but this depends on the latitude. See the Vitamin D Council website for a discussion of optimum levels, deficiency seasonal variation and related topics. Also, it is important that one get the right blood test. The test for 1,25 dihydroxy-vitamin D is the wrong test and tells one next to nothing, but it is sometimes ordered by mistake or out of ignorance. Finally, the so-called reference ranges or "normal" values that come with laboratory reports should be ignored. In Canada, one of the major testing laboratory companies gives sufficiency as 30-100 ng/mL and toxicity as > 100 ng/mL. The former is misleading since 30 ng/mL is considerably below the threshold for optimum, and the toxicity level, according to modern opinion, is too conservative.

Finally, according to the July 27, 2009 Toronto Globe and Mail, The Public Health Agency of Canada is sponsoring a study of the 25-hydroxy-vitamin D levels in individuals diagnosed with H1N1. The goal is to determine if there is an association between the severity of the disease and the vitamin D status. The outcome and the resultant recommendation should prove interesting for a number of reasons. Furthermore, the medical scientists involved should have a wide range of 25-hydroxy-vitamin D levels with which to work, given that severe vitamin D deficiency is widespread, increasing, and acquiring the vitamin from sun

exposure, which of course is what we evolved to do, is under constant attack from the dermatology community. Witness the latest campaign against getting just a suntan.

NEW DATA ON PREVALENCE OF VITAMIN D DEFICIENCY AND VIEW OF AMERICAN ACADEMY OF PEDIATRICS

Shocking new numbers just appeared from a new study which indicate that 61% of those between 1 and 21 years in the U.S. have vitamin D levels, as measured by 25-hydroxyvitamin D that are classified as insufficient (15-29 ng/mL), and 9% have levels so low as to be described as deficient (< 15 ng/mL). For non-Hispanic black individuals and Mexican Americans the prevalence of deficiency and insufficiency was even higher. For example, for non-Hispanic black girls 1-6, 7-12 and 13-21 years of age, 85%, 97% and 98% had levels < 30 ng/mL respectively. For levels < 15 ng/mL, the corresponding prevalence figures were 10%, 28% and 59%, i.e. more than half of the female adolescents in this ethnic group were outright deficient. In all groups, the problem became more severe with increasing age.[1] One of the study authors, Dr. Michael Melamed from Albert Einstein College of Medicine, was quoted in the Washington Post (August 3, 2009) as saying "At first we couldn't believe the numbers. I think it's very worrisome." A study published in the same issue of *Pediatrics* found that low levels of vitamin D in U.S. adolescents were strongly associated with hypertension, hyperglycemia, and the metabolic syndrome, *independent of adiposity*. The distribution of 25-hydroxyvitamin D levels in the cohort was such that they used > 26 ng/mL as the threshold for the highest quartile, i.e. insufficiency was very common.

In late 2008, the American Academy of Pediatrics published guidance concerning recommended vitamin D supplementation in infants, children and adolescents. They abandoned the long-standing recommendation of 200 IU/day in favour of 400 IU/day. They recognized deficiency at a blood level < 20 ng/mL of 2-hydroxyvitamin D and insufficiently in the range of 20-32 ng/mL. Apparently on the basis of just one cited study which showed that 400 U/day of vitamin D would maintain levels above 20 ng/mL in exclusively breast fed infants, they recommend for infants, children and adolescents an intake of 400 IU/day. It is well known that 400 IU/day is totally inadequate for many adults and thus probably for adolescents if the goal is sufficiency or optimal levels, so presumably the recommendation is to avoid profound deficiency but not even eliminate insufficiency. The recommendation does not take into account age, skin color or latitude of residence. More importantly, it does not take into account seasonal variation. Also, they strongly support the recommendation advising decreasing sunlight exposure with protective clothing and sunscreens. However they recognize that 10-15 minutes of sun full-body sun exposure in the summer will generate 10,000-20,000 IU. Readers of the paper are left to ponder the discrepancy between 400 IU/day and 20,000 IU/day.

The "optimum" blood levels quoted above, i.e. 50-70 ng/mL, which may still be too conservative, are clearly off the radar screen of experts in pediatrics and are so far above what is seen in infants, children and adolescents, that it is hard to be optimistic that optimum levels will be reached any time soon. The impact this will have not only general health but also the susceptibility to influenza will probably be significant. Finally, one wonders why the goal is sufficiency and not optimization of vitamin D levels and why the need for distinguishing between deficient and insufficient when both are highly undesirable.

PROBIOTICS AS PROTECTION AGAINST THE FLU

Some readers many have seen reports in the media regarding the success of a probiotic mixture on the incidence and duration of cold and flu-like symptoms in young children. The two bacterial strains used belonged to the families *Lactobacillus acidophilus* and *Bifidobacterium animalis.* However, specific strains were used in the study recently published in *Pediatrics*[2] which do not appear to be available through the usual consumer outlets such as health food stores or the internet. The trial involved 6 months of dietary probiotics which was found to be safe and effective in reducing the incidence and duration of fever, runny nose, and cough, the use of antibiotics and as well as the

number of days of school missed. The children were 3 to 5 years of age. Family members of these two bacteria can be found in probiotic preparations available over the counter or on the internet, but one does not know if the strains used in the commercial preparations are as effective or even effective at all in this context.

The subject of probiotics with special reference to gut problems will be the subject of an upcoming review. It turns out that specific strains demonstrated to have significant benefit in treating irritable bowel syndrome are in fact commercially available without prescription and even present in one brand of widely available yogurt. The two are *Bifidobacterium infantis* 35624 and a preparation called VSL#3. The former is one of three active bacteria in the yogurt brand *Activa* which, according the website of the manufacturer Danone, appears to be available in a large number of countries. It is important to know that many yogurts contain no probiotic bacteria due to pasteurization and that large numbers of probiotic bacteria must be ingested to produce benefit, numbers measured in billions per dose.

DIABETES DIAGNOSIS AND PREVENTION UPDATE

Diabetes is a worldwide and rapidly growing problem. There are an estimated 54 million Americans with prediabetes. It is thought to be linked to the obesity epidemic and the belief that high carbohydrate diets which include highly refined carbohydrates like sugars and refined flour are essential to our energy requirements and eating pleasure. Many individuals, including no doubt some readers of this newsletter, have a prediabetic condition and do not even know it. Their physician checks for diabetes, but may be more focused on targeting this disease, not preventing it. Another important component is the amazing success of the food industry in making scientifically designed and highly addictive foods which promote serious overeating, which becomes uncontrollable and a true physiological addiction.[3] Obesity and its morbid variety result. Once one has diabetes the future is bleak, including problems with the nervous system in the extremities (peripheral neuropathy), poor circulation in the extremities, slow healing, especially in the extremities, a higher risk of cardiovascular disease, and the ultimate problem, an increased risk of amputation. Blindness is also a risk. One needs to reflect that for someone with this disease, simply pulling a hangnail on a toe may result in an infection which becomes a medical emergency and a significant risk for gangrene. It is estimated that there is one diabetes related amputation operation every 2 hours worldwide. It is the rare individual who cannot grasp the impact of foot or leg amputation on the quality of life, even though it is a routine operation performed every day worldwide. This is also true of peripheral neuropathy where walking becomes painful and the feet turn blue. Thus both the diagnosis of prediabetics and the prevention of the progression of mildly abnormal glucose metabolism to frank diabetes is an important issue. This area appears to be receiving increase attention and some of the studies will be reviewed this month.

PREDICTING RISK OF DEVELOPING TYPE 2 DIABETES

There continues to be interest in developing models and systems for estimating or scoring the risk of developing type 2 diabetes. One study just published has developed a scoring system for U.S. adults age 45-65.(Kahn *et al* [4]). A group of almost 13,000 individuals was enrolled and followed. A risk score was developed from baseline parameters and a 15-year follow-up. On the basis of the diabetes cases observed, a score was created that reflected the risk based on the most important factors. This was then validated using the other 25% of the cohort. The researchers developed a basic model which included family history, hypertension, race, age, smoking, waist circumference, height, resting pulse and weight. An enhanced model omitted smoking, added alcohol as a positive factor, as well as fasting glucose, triglyceride, HDL and uric acid levels. While the first model had the merit of not requiring a blood test, it was significantly outperformed by the enhanced model which did. There seems little advantage in not requiring a fasting blood test given the supreme importance attached to serum cholesterol by mainstream medicine, the measurement of which requires fasting. Most American adults probably know if they have high cholesterol, and might even know the

numbers, but probably have no idea regarding their fasting blood glucose unless they are diabetic. In the enhanced model, fasting glucose at baseline was the single largest contributor to the score. In addition, the combination of a large waist circumference and high triglycerides contributed a large risk component. This is consistent with the view that type 2 diabetes is not so much an isolated impairment of glucose regulation as a complex metabolic consequence of the accumulation of "out of place" fat, i.e. around the waist.

A second study also just published examined 64 potential blood markers as useful and significant risk factors for the development of type 2 diabetes.[5] They narrowed the field to just six, adiponectin, C-reactive protein, ferritin, an interlukin-2 receptor, glucose and insulin. The model based on these parameters performed well, but the predictive power does not appear superior the more conventional approach outlined above and it has the disadvantage of requiring a blood test not routinely ordered in check-ups and physical exams. However, the factors found most significant highlight the role of inflammation and oxidative stress in the development of type 2 diabetes. Ferritin is an antioxidant which functions by binding iron. Adiponectin is involved in the metabolic syndrome and inflammation and a low level is known to be associated with type 2 diabetes. Also, oxidative stress associated with high glucose and low insulin levels, and elevated levels of interlukin-2 receptor are an indicator of increased oxidative stress. Thus while interesting, this study does not appear to lead directly from bench to bedside.

In the study of Kahn *et al* the enhanced model involved 12 factors. It is of interest to compare the score system of Kahn *et al* with a scoring system based on data from the recent Framingham Offspring Study.[6] This study generated a 7-item assessment algorithm. This approach is simpler than that of Kahn *et al* and was structured as follows.

If the following have "yes" for an answer, award the indicated points:

- Fasting glucose level 100-126 mg/dL 5.6-7.0 mmol/L) 10
- BMI 25.0-29.9 (overweight) 2
- BMI ≥ 30.0 (obese) 5
- HDL < 40 mg/dL for men, < 50 mg/dL for women 5
- Parental history of type 2 diabetes 3
- Triglycerides ≥ 150 mg/dL 3
- Blood pressure ≥ 130/85 m Hg 2

(To convert HDL to mmol/L, divide by 38.7, whereas for triglycerides, divide by 88.6)

The total then is interpreted as follows:

Total Score	8-year risk of diabetes (%)
≤10	≤3
15	7
20	18
≥25	>35

The standard statistical test used for comparison of screening methods (the c-statistic) indicates that this simple scheme works as well or better than either the method of Kahn *et al* or the method incorporating the unconventional biomarkers. The fasting glucose range used in the Framingham Score is regarded by many as an indicator for the prediabetic state. Triglycerides, HDL cholesterol and fasting blood sugar are normally measured in routine physical exams. Individuals who ask for and keep copies of the lab reports can easily use the above data to estimate risk. From the HDL and triglyceride values in mg/dL, one can estimate insulin resistance. A ratio of TG/HDL > 3.5 is used in many studies as the threshold. The ratio in the Framingham Score of 150/40 already exceeds this.

PROGRESSION PATTERNS FOR SOME MARKERS OF DIABETES RISK

As an individual progresses from normal to being a diabetic is it is expected that some risk markers will change with time and ultimately cross a threshold where a diagnosis is declared. The problem of diagnosing diabetes was the subject of a review in the Dec08/Jan09 issue of this newsletter. Today two different criteria are applied: (a) fasting glucose > 126 mg/dL (7 mmol/L) or (b) a blood glucose level two hours after a 75 g oral glucose challenge of > 200 mg/dL (11.1 mmol/L). The second is the so-called oral glucose tolerance test (OGTT) which traditionally was the test used for a definitive diagnosis of diabetes, but its inconvenience in the view of some has argued for the simpler single test of fasting glucose. In a recent study, Tabak *et al* [7] examined the time course of these two parameters and in addition a measure of insulin resistance as one progresses from normal to diabetic, and made a comparison with those who remained free of diabetes. The results are quite interesting.

This was part of a prospective cohort study of British civil servants (Whitehall II). Sixty-five hundred individuals were followed for a mean of almost 10 years. Data on fasting glucose, the results of the OGTT, and a measure of insulin resistance (HOMA) were periodically collected. When diabetes was diagnosed using either of the two criteria mentioned above, then the earlier date was examined to establish the trajectory of these parameters leading up to the point of diagnosis. The results were compared with the time course of these parameters for individuals who did not develop diabetes. The FPG or the OGTT 2-hr glucose level trajectories were initially linear. In data covering 13 years, the average behaviour of the FPG in those destined to become diabetic initially increased linearly up to two years prior to diagnosis and then it shot up dramatically. For this cohort, the value at 13 years before diagnosis was 5.5 mmol/L and at two years prior to diagnosis it had only increased to about 5.8 mmol/L. Then it increased sharply to about 7.4 at the time of diagnosis. For the OGTT results, the glucose also increased in a linear fashion from an initial value of about 6.1 mmol/L at 13 years before diagnosis to about 6.3 mmol/L at 6 years prior to diagnosis, and then jumped to about 7. 5 mmol/L for 4 years prior to shooting up to over 12 mmol/L at the time of diagnosis. By comparison, individuals who were never diagnosed with diabetes maintained a constant FPG at about 5.75 and an OGTT glucose level that increased linearly and slowly from about 5.0 to 5.8 mmol/L. Thus for both of these measures, the average levels at 13 years prior to diagnosis were normal and increasing minimally, but those destined to develop the disease were somewhat higher and increasing faster.

What makes this trajectory study especially interesting is that in looking back over the 13 years prior to diagnosis, the two criteria only increased strongly in the last two years and for the FPG, the value two years prior to diagnosis was still too low to ring alarm bells. The same can be said for the OGTT test, although the jump six years before diagnosis to a somewhat higher value might be considered by some as alarming. The authors suggest that these results are consistent with the multi-stage model of the development of diabetes. The initial state is a long compensatory period when insulin secretion increases to compensate for insulin resistance with little change in FPG. This is followed by a stable adaptation when the beta-cell (cells responsible for insulin production) mass is decreasing in spite of beta-cell adaptation. Finally there is a transient unstable period with the rapid development of overt diabetes. They identify the adaptation period as that seen in individuals who have FPG values increasing faster in those destined to develop diabetes as compared to those who remain free of the disease. The authors also suggest that when prediabetes is recognized clinically, the individual is already in the steep part of the trajectory, and prevention would be more effective before this unstable period, and that more research is needed to identify people at this stage. Measures that would keep one on the linear part of the trajectory should significantly delay or prevent type 2 diabetes. It is noteworthy that the OGTT appears to give a significantly earlier warning of the impending diabetes.

If these trajectories are realistic and not confounded, they suggest that the OGTT gives an earlier warning than FPG. However, it is unrealistic to expect that a yearly OGTT will ever become standard practice, given that has essentially been abandoned already, presumably because the "inconvenience" is deemed more compelling than preventing the progression of prediabetes to the full-blown disease. The authors comment that the data already exists for validating the predictive properties of the yearly FPG since many organizations such as HMOs have patient records going back a number of years. Some readers may also have collected such

data over the years and can examine it in the light of this paper. To convert mg/dL of glucose to mmol/L, divide by 18.

INTERNATIONAL EXPERT COMMITTEE TAKES A POSITION ON GLYCATED HEMOGLOBIN (HbA1c)

The oral glucose tolerance test is deemed too inconvenient for modern individuals or their physicians, a point of view which speaks volumes regarding the prevalent philosophy of preventive medicine. Historically it was more or less the gold standard for the diagnosis of diabetes. Glycated hemoglobin (HbA1c) on the other hand represents the ultimate in convenience. It is expressed as the percentage of hemoglobin glycated. No fasting is required for the blood test and it averages glycemia over an extended period, ironing out fluctuations which can confuse the issue. All that is required of the physician is checking off a box on the blood work requisition. An international expert committee was formed by the American Diabetes Association, the European Association for the Study of Diabetes and the International Federation of Diabetes examined the current evidence associated with the use of HbA1c in diagnosing type 2 diabetes (type 1 generally makes its presence known in a easily recognized and definitive fashion). Their report has just appeared.[8] HbA1c is routinely used only after one has diabetes since it provides an easy way to monitor the success of blood glucose control.

As discussed in the research review on type 2 diabetes diagnosis in the Dec08/Jan09 issue of this Newsletter, criteria are somewhat arbitrary and strongly influenced by the association between glucose levels and long-term complication of hyperglycemia such as retinopathy. In this consensus report the authors display three plots of the prevalence of retinopathy as a function of fasting plasma glucose (FPG), the two-hour OGTT glucose level, and HbA1c for three different groups of individuals (Egyptians, Pima Indians, a high risk ethnic group, and 40-74 year old participants in NHANES III, a large cross sectional study of the U.S. population). All three plots are essentially flat until a threshold is reached, after which the prevalence strongly increases. Data for FPG, the OGTT and HbA1c superimpose in all three plots and define a threshold for HbA1c of about 6% and for FPG around 110 mg/dL (6.1 mmol/L). For the NHANES population, going from a FPG of 110 to 120 mg/dL or an HbA1c from 5.9 to 6.2% increases the prevalence of retinopathy from about 4% to about 16%!

The expert committee concluded from their review of the literature that diabetes should be diagnosed when HbA1c exceeds 6.5% if confirmed with a repeat test. This recommendation differs from the past position of the American Diabetes Association. The HbA1c test is also recommended for children when diabetes is suspected. They state that impaired fasting glucose and impaired glucose tolerance fail to capture the continuum of risk and predict these two measures will be phased out of use as HbA1c become standard. They point out that individuals with HbA1c levels between 6 and 6.5% are at the highest risk of progressing to diabetes. The test does not require fasting, which should give it great appeal to those concerned with the convenience issue. It also provides a clear warning, apparently securely evidence-based, of big trouble ahead and should prompt aggressive preventive action.

TYPE 2 DIABETES PREVENTION

One of the most recent studies on this subject to report comes from data from the Diabetes Prevention Program, a multicenter program in the U.S. All participants had impaired glucose tolerance at baseline with 2-hour oral glucose tolerance test levels from 140 to 198 mg/dL (7.8 to 11 mmole/L). The endpoint was regression from this prediabetic state to normal glucose regulation. Fasting plasma glucose ranged from 95 to 124 mg/dL (5.3-6.9 mmol/L). Three interventions were used: (1) intensive lifestyle modification (ILS), (2) drug therapy (metformin) plus standard lifestyle recommendations, or a placebo plus standard lifestyle recommendations. The ILS goal was to achieve and maintain a weight reduction of at lease 7% of initial body weight through a healthy, low calorie, low fat diet and physical activity of moderate intensity such as a brisk walk for at least 150 minutes per week. What advice was given regarding

macronutrient balance and carbohydrate type is not clear from the paper or the study website.

It was found that ILS and especially greater weight loss had a significant and independent effect on regression to normal glucose metabolism. At the end of 3 years, 40% of the lifestyle group had achieved normal glucose regulation, as had 25% of the drug group and 18% of the placebo group. Normal glucose regulation was defined as FPG < 100 mg/dL (5.6 mmol/L) and 2-hour glucose < 140 mg/dL (7.8 mmol/L). The authors comment that weight loss appears to be the most important component of ILS for predicting regression with every 1 kg lost associated with a 16% reduction in diabetes risk, but in the study in question, ILS also had an impact on regression independent of weight loss. This was regarded as an indication of the benefits from healthy eating and exercise in restoring normal glucose regulation even at constant weight. It is interesting that the results for the non-drug intervention were clearly superior to metformin, the most common drug treatment for glucose control.

A review just published on lifestyle intervention and the prevention of type 2 diabetes is of interest in this context. Eight randomized controlled trials and one prospective trial found an average of 52% (range 67-29%) relative risk reduction for type 2 diabetes from exercise and diet.[9] Not included was the study by Mozaffarian *et* al[10] discussed in the June 2009 Newsletter which reported up to an 89% relative risk reduction for the development of diabetes with lifestyle modifications. With regard to the specifics of dietary modification, the reviewers conclude that a high fiber and low saturated fat diet are important in both reducing diabetes risk and inducing weight loss. Noteworthy is the absence of any serious consideration of the nature or amounts of carbohydrate consumed. The studies reviewed, which reported in the period 1991 to 2008, were apparently strongly influenced by the fat is bad school of thought. Thus macronutrient composition of diets targeted at diabetes prevention remains an open question, but what appears well established is the critical importance of weight loss and control. The role of carbohydrate restriction for diabetics and prediabetics is discussed in a research report included in this newsletter.

ELEVATED FASTING BLOOD GLUCOSE, DIABETES AND CORONARY ARTERY PLAQUE

A recent study has examined the association between elevated blood glucose and coronary artery atherosclerosis.[11] Non-invasive CT scanning (cardiac CT angiography) was used to quantify calcified, non-calcified and mixed coronary artery plaque in individuals with normal fasting glucose, impaired fasting glucose and diabetes. Subjects (43% female) had a mean age of 48 and were not obese. It was found that subjects with impaired fasting glucose or diabetes had greater plaque burden, more severe coronary blockage and higher coronary artery calcium scores than normal subjects. Even after adjusting for confounding factors, fasting glucose was strongly associated with significant coronary blockage and greater plaque burden. Important factors associated with the presence of coronary calcification, aside from fasting blood glucose, were smoking and C-reactive protein and female gender put one at higher risk. The Prevalence of mixed plaque (< 50% calcification) also was also dependent on blood glucose levels but the statistical analysis failed to reveal odds ratios for non-calcified plaque. Consistent with a large body of evidence,[12] the association of coronary plaque burden with LDL cholesterol was negligible as was the association with triglycerides. HDL did not appear in the statistical analysis. But diabetes puts one in the high-risk category for coronary heart disease and frequently prompts statin treatment even though LDL lowering does not impact the coronary plaque burden. The authors state that dyslipidemia was significantly associated with mixed plaques, but if one looks at the odds ratios, one finds for triglycerides and LDL values of 1.003 and 1.011, i.e. negligible risk elevation. These are to be compared to normal fasting vs. impaired fasting glucose which gave an odds ratio of 1.85 and normal fasting glucose vs. diabetes which yielded 2.11. Also, in this context dyslipidemia is generally means elevated triglycerides *and* depressed HDL.

These results are of considerable interest because they examine the impact of elevated glucose on atherosclerosis observed directly rather than coronary heart disease defined by severe angina, a fatal or non-fatal heart attack or the need for revascularization (angioplasty or a coronary artery bypass). The latter endpoints feature acute events, whereas the plaque burden measures a critical

feature of the disease directly as it develops. There do not appear to be studies that examined the impact of normalizing blood glucose on the progression of coronary plaque. Randomized trials with statins in general fail to slow the progression,[12] although a small non-randomized trial on diabetics suggests that statins may have some benefit here, perhaps through their anti-inflammatory action.[13] The reader is referred to the Research Report in this issue for a discussion of lowering blood sugar levels with carbohydrate restriction and exercise.

TREATING LOW TESTOSTERONE BENEFITS MEN WITH TYPE 2 DIABETES

Men with the metabolic syndrome and type 2 diabetes frequently have low testosterone levels. A study just published in the *Journal of Andrology*[14] examined the hypothesis that elevating low testosterone levels would improve the features of the metabolic syndrome and as well, blood sugar control. In a 52-week randomized trial, supervised diet and exercise (D&E) and diet and exercise plus transdermal testosterone (D&E+T) were compared in 32 men with low testosterone who had the metabolic syndrome and newly diagnosed type 2 diabetes. It was found that serum testosterone levels, HbA1c, fasting plasma glucose, HDL-cholesterol and triglyceride concentrations, and as well waist circumference improved in both treatment groups. In the group with added testosterone, these measures were significantly further improved compared to D&E alone. All D&E+T patients achieved an HbA1c goal of < 7% and 88% reached an HbA1c of < 6.5%, a commonly used threshold for the diagnosis of diabetes. Using the National Cholesterol Education Program definition of the metabolic syndrome, they found 81% of the patients randomized to the D&E+T program no longer qualified for the designation of metabolic syndrome as compared to 31% in the D&E group. In addition, it was found that testosterone treatment improved insulin sensitivity and decreased levels of C-reactive protein.

In a perspective just published in the *International Journal of Impotence Research,* Maggio and Basaria discuss the evidence indicating that low serum testosterone is a risk factor for diabetes, metabolic syndrome, inflammation and dyslipidemia and in addition, low testosterone is an independent risk factor for cardiovascular and all-cause mortality.[15] They call for long-term randomized intervention trials to confirm the present evidence concerning the effect of testosterone therapy on cardiovascular risk factors, mortality and all-cause mortality.

Many readers will immediately wonder—what about the connection between testosterone and prostate cancer. In a recent book on testosterone by Dr. Abraham Morgenthaler from Harvard Medical School (*Testosterone for Life*, McGraw Hill, 2009) an entire chapter (Chapter 7) is devoted to a discussion of this topic. It turns out that the almost universally held belief of the dangers of testosterone therapy in men with low levels is incorrect and correcting this problem is safe for the prostate. Morgenthaler is a leading expert on this subject and has recently published a number of papers concerning testosterone therapy and the prostate. Men interested in pursuing this subject should consider reading Morganthaler's book, having their testosterone levels measured, and then having a discussion with their physician if a low level is detected. The book provides detailed information to help interpreting the blood test results.

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RESEARCH REVIEW

CARBOHYDRATE RESTRICTION

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INTRODUCTION

Judging dietary modifications is complex. There are many potential endpoints to examine, including initial weight loss, long-term weight loss maintenance, changes in blood lipids, and changes in markers of insulin resistance and carbohydrate metabolism. The latter relate to the various aspects of diabetes and the prediabetic state. One can also look at overall mortality and the incidence, progression and mortality associated with specific diseases. The diet literature is vast and contains a mixture of results ranging from nonsense to significant. This review will feature carbohydrate restriction, which is more or less synonymous with low-carbohydrate diets, and how this relates to diabetes, prediabetes and the metabolic syndrome. Heart disease is indirectly related through its association with diabetes and the metabolic syndrome.

In the Research Review on saturated fat, it was pointed out that while this type of fat is considered sufficiently dangerous that many organizations recommend aggressively reducing its percentage contribution to total energy intake, the review presented extensive documentation for the assertion that this recommendation was not evidence-based and in fact may not be justified at all. But the recommendation to lower saturated fat is part of

the low-fat movement that started 30-40 years ago and resulted in the food industry manufacturing a vast collection of low-fat foods which found a ready market among a frightened population. Then, as has been documented in the literature and in the articles and the comprehensive book *Good Calories, Bad Calories* by Gary Taubes, the search for evidence came up empty handed. Saturated fat and the other types of fat were neutral or beneficial. Even the notion that the omega-6 polyunsaturated fats were bad because they were inflammatory has now come under criticism with the American Heart Association now recommending not avoiding this particular type of fat. But the low-fat diet has been the centerpiece of much nutritional advice coming from mainstream medicine and the academic and professional nutritional community. They would now appear to be in a position where their advice is not as evidence-based as they would like us to believe, and already subtle changes are seen in recommendations—i.e. more flexibility and less emphasis on low-fat. But overall, it must be a hard pill to swallow. This is especially true now that it has become difficult to demonize the low-carbohydrate diet on the basis of its increased fat content, given that the fat is bad hypothesis now lacks that important imprimatur, solid evidence.

Strongly related to the above history is the rebirth of interest in carbohydrate restriction and the attempt to give the low-carbohydrate type diet a level of respectability that it heretofore has lacked. It is worth reminding readers that it was not that long ago when Dr. Robert Atkins was hauled up before a U.S. congressional committee and accused of being a public enemy for suggesting that low-carbohydrate diets were healthy and the way to lose weight and decrease the risk of heart disease and diabetes. While this attack by the government and the "fat is bad" community failed, there was the terrible press after his death which suggested that he died because he followed his diet, but this was not true. One of his strongest opponents was in fact an organization with a fancy and convincing title which was apparently a front for an animal rights group of vegetarians. Nevertheless, over the years, brave investigators have nibbled away at the credibility of the anti-low-carb community and created a much more balanced view of what might be called the macronutrient distribution problem in human nutrition.

The low-fat revolution resulted in motivating individuals to increase dramatically their carbohydrate intake, frequently with little regard for the type of carbohydrate involved. Low-fat foods were purchased with abandon in spite of the fact that many had high levels of sugar and refined carbohydrates. Some nutritional scientists present a catalogue of what they believe were unintended and very unfavourable results. These include strongly elevated triglycerides, depressed HDL levels, increased levels of small, dense atherogenic LDL particles, decreased insulin sensitivity, glucose intolerance, prediabetes and type 2 diabetes, elevated risk of cardiovascular disease, increased inflammation, hyperglycemia, and hyperinsulinemia and finally the so-called metabolic syndrome or syndrome-X. Added on to this remarkable list was a trend toward either being overweight or obese. While it is true that some of these adverse results could have been avoided by very carefully and knowledgably selecting carbohydrates used to replace fat or by weight loss, the general public was ill prepared to do this nor was the food industry seen to provide much help. Even "whole wheat bread" was not really whole grain bread, but many had no idea there was any difference. The supermarkets reached the point where a substantial fraction of what they sold and in fact are still selling would not have been recognized a century ago as food at all. The age of ersatz food had arrived.

The above state of affairs is no doubt responsible for the growing appearance in the literature of calls for a reconsideration of the low-carb or carbohydrate restricted approach to eating, with special reference to the obese, those with the dyslipidemia characterized by low HDL and high triglycerides, the prediabetics and those with type 2 diabetes. This was in general what was being recommended 10-20 years ago, not only by Atkins, but also by the other authors of low-carb diet books, and as well endocrinologists like Dr. Diana Schwarzbein and specialists in the treatment of diabetes such as Dr. Richard K. Bernstein. Even the Optimum Weight for Life program at Children's Hospital in Boston has moved strongly in this direction under the guidance of Dr. David Ludwig, who appears to view the basic philosophy as simply endocrinology 101.

Of special significance is the use of carbohydrate restriction for diabetics and prediabetics. The failure of the ACCORD trial discussed in this Newsletter prompted Westman and Vernon[1] to ask "Has carbohydrate-restriction been forgotten as a treatment for diabetes mellitus?" They describe a typical approach to glucose control by diabetics called "cover the carbohydrate" where high carbohydrate diets are consumed and then intensive medication therapy used to attempt to achieve blood sugar control. They even comment that they frequently see individuals who are instructed to eat high carbohydrate diets and counteract the effects with injectable glucose lowering therapy, which they regard as an open invitation to serious hypoglycemia which can have permanent

adverse effects including increased mortality. What is interesting about these observations is that diabetics are being advised, presumably by either their physicians or nutritionists, to consume diets high in carbohydrates which aggravate the swings in serum glucose. There are many issues here including increased risk of vascular damage, kidney damage, ocular damage, and limb amputation. ACCORD was halted after the intensive insulin arm of the study showed enhanced mortality in spite of achieving, to some extent, blood glucose control.

Westman and Vernon also quote from the famous *Principles and Practice of Medicine, 9th Edition,* by Osler and McCrae. William Osler became famous at McGill, Johns Hopkins and finally as Regius Professor at Oxford. The edition cited, coauthored by McCrae, was published in 1923, just after Osler's death in 1919 and only two years after the discovery of insulin. Osler was considered the high priest of early 20th century medicine. In this text, the treatment of diabetes consisted of a diet 75% fat, 17% protein, 6% alcohol and only 2% carbohydrate with a daily energy intake of about 1800 calories. This was about 9 g/day of carbohydrate which makes the modern carbohydrate restriction diets at 50-100 g/day appear very liberal. Taubes in his book *Good Calories, Bad Calories,* presents a detailed history of the treatment of both diabetes and obesity in this early period in the evolution of modern medicine and finds the same picture of severe carbohydrate restriction as the basic therapy employed. One presumes that in these much earlier times, carbohydrate restriction had been found to "work."

This review will examine carbohydrate restriction, especially with regard to prediabetes, type 2 diabetes, and the so called atherogenic dyslipidemia associated with the metabolic syndrome, a blood lipid picture that some considered consider vastly more alarming than elevated LDL. Readers of this Newsletter who are diabetic should worry about limiting adverse vascular effects which can be deadly and destroy the quality of life. Prediabetics should worry about reversing the trend toward diabetes. Those with the metabolic syndrome should worry about getting rid of this condition. And finally, everyone else needs to worry about maintaining normal glucose metabolism and low levels of inflammation. In discussing carbohydrate restriction, these are among the issues we will discuss.

CARBOHYDRATE RESTRICTION

Carbohydrate restriction implies a low-carbohydrate diet, although the amount of carbohydrate restriction may well exceed that of some low-carbohydrate diets which in fact involve a rather small reduction to yield a diet still relatively high in this macronutrient. Frequently, discussions of low-carbohydrate diets involve the percentage of energy intake represented by this macronutrient rather than the absolute number of grams. For example, an intake of < 200 g/day of carbohydrate has been termed by some a low-carbohydrate diet, whereas others think it should be defined as the range of 50-150 g/day. For an 1800-calorie diet, this would represent 11% to 33% of energy intake. However, levels below 33% are generally necessary to force the body to burn ketones, the so-called ketogenic diets.[2] Low-carbohydrate diets almost always result in lower energy intake due to the impact on satiety and appetite from the higher percentage or absolute amounts of fat and protein.[2]

There are three principal issues: (a) the influence of carbohydrate restriction on serum markers related to or alleged to be related to cardiovascular risk, which should include the risk of atherosclerosis and its progression; (b) the impact of carbohydrate restriction on carbohydrate metabolism, fat metabolism and storage and insulin sensitivity; and (c) weight loss.

CARBOHYDRATE RESTRICTION AND CARDIOVASCULAR RISK FACTORS

With regard to the first issue, Krauss *et al*[3] published a key paper in 2006. In a controlled diet experiment, after a one-week normalization period with a basal diet consisting of 54% of energy from carbohydrate, four diets were used. The distribution of macronutrients is shown in the table. During the next 3 weeks no attempt was made to control weight. Then a 1000-calorie reduction was instituted for 4 weeks to reduce weight followed by a four-week period of weight stabilization by calorie adjustment, while keeping the energy distributions constant. Data was not provided regarding the distribution of energy intake by macronutrient at baseline.

Macronutrient distribution in four dietary interventions[3]

Diet	% CHO	% FAT	% PROTEIN	% SF
• Low-Fat	54	30	16	7
• CR (39% CHO)	39	29	29	8
• CR (26% CHO)	26	46	29	9
• CR (26%CHO + SF)	26	45	29	15

At the end of the study, all four diets resulted in a decrease in triglycerides (TG) and at the end of the study the high saturated fat diet showing the largest decline of over 40% whereas in the low-fat diet, TGs were down about 23%. Prior to weight loss, the corresponding numbers were 35% and 10%. The low-carbohydrate high-saturated fat diet was also the most effective in elevating HDL by the end of the study (on average 5 mg/dL) but even in the absence of weight loss, this diet gave the largest increase (3 mg/dL) whereas the low-fat diet showed a small decrease prior to weight loss and then returned to close to baseline at the end of the study. The low-carbohydrate high-saturated fat diet was also the most successful in reducing the APO B/APO A-1 ratio, a marker of cardiovascular risk, and essentially all the decrease came prior to weight loss; whereas with the low-fat diet, change was small prior to weight loss and decreased by the end of the study. The low-carbohydrate high-saturated fat diet had the most favourable (less atherogenic and less dense) effect on the LDL diameter both prior to weight loss and at the end of the study whereas the low-fat diet only showed a change after weight loss. The same was true of the total cholesterol to HDL ratio, which some consider to be a much stronger risk factor than LDL. These results are shown graphically by Feinman and Volek.[4] The results with the low-carbohydrate diet but without the increase in saturated fat were also superior to the low-fat diet for these lipid parameters. These data show that the low-carbohydrate diet was the most effective in improving so-called atherogenic dyslipidemia (low HDL, high TGs) and the APO ratio, *with or without weigh loss*. High saturated fat made the results even better.

In a letter to the editor, Westman *et al* [5] congratulate Krauss *et al* for presenting one of the strongest cases to date for dietary carbohydrate restriction and provide a number of references to other studies which found results that were similar for one or more aspects studied by Krauss *et al*, i.e. a satisfactory level of consistency. They also point out that given the difficulty in loosing weight, the data of Krauss *et al* support the notion that carbohydrate restriction is the default diet for the treatment of atherogenic dyslipidemia. Most of the beneficial effects were seen prior to the weight loss phase of the study.

Many diet studies examine the impact on LDL cholesterol. But in the context of primary prevention, non-invasive coronary artery imaging suggests that there is no connection between LDL and coronary artery plaque burden or progression and LDL does not drive atherosclerosis.[6] In these imaging studies it was also observed that among the various lipid risk factors, only elevated HDL and a low APO B/APO A-1 ratio were frequently found to have a beneficial influence on the rate of progression. The carbohydrate restricted diet with or without high saturated fat significantly changed these two markers in the right direction. In addition, the results of Krauss *et al* also fail completely to support the notion that elevated intake of saturated fat is bad in the context of atherogenic dyslipidemia. Quite the contrary, saturated fat appears to enhance the benefits of carbohydrate restriction. Incidentally, the increase in fat that Krauss *et al* used for the high saturated fat diet compared to the low-fat diet corresponds to the opposite of the decrease recommended by mainstream medicine and nutrition where a reduction from 15% to 7% is advised.

Two recent randomized studies with significant reductions in energy from carbohydrates and energy intake showed the expected pattern of increasing HDL and decreasing triglycerides. One study had a decreased over 12 months from 46 to 34% in energy from carbohydrates, an increase from 36 to 44% for fat, and an energy decrease of about 300 cal. An increase was seen in HDL of about 5 mg/dL and a decrease in triglycerides of almost 30 mg/dL with no significant change in LDL.[7] In another study, carbohydrate intake decreased over 24 months from 51 to 41% of energy, fat increased from 32 to 39%, energy intake decreased by 550 cal. HDL increased by 8.4 mg/dL and triglycerides decreased by 24% with no significant change in LDL. Westman *et al* [2] have reviewed earlier studies where low-fat diets with carbohydrate intake ranging from 51-62% of energy were

compared with low-carbohydrate diets with carbohydrate intake at 8 to 37%. The same general picture appears where the low-carbohydrate diets resulted in large decreases in triglycerides, large increases in HDL, very small changes in LDL and weight loss ranging from 5 to 12 kg. These diets had energy intakes between 1300 and 1800 cal. For the low-fat diets with energy intakes ranging from 1100 to 1600 cal, the changes in blood lipids were much smaller as was the weight loss. These studies ran from 6 to 12 months. Thus the evidence appears compelling that low-carbohydrate diets improve the blood lipid picture associated with dyslipidemia.

In a review calling for a critical reappraisal of carbohydrate restriction, Accurso *et al*[8] summarize the situation as of 2008. It was concluded that substitution of fat for carbohydrate is generally beneficial for markers for CVD and these beneficial effects of carbohydrate restriction do not require weight loss.

When Atkins put forward the low-carbohydrate notion and his highly carbohydrate restricted diet, mainstream medicine was up in arms claiming it was very dangerous. This was in keeping with the "fat is public enemy number one" dogma and also consistent with a lack of much understanding concerning diet and cardiovascular risk. It was simply assumed on the basis of weak and inconsistent evidence that increasing fat consumption to compensate for the drop in carbohydrates would produce a significant increase in the risk of heart disease. At this time the dogma reigned supreme and low-fat diets and low-fat foods were promoted by the so-called experts in the absence of much if any evidence. But now there is a large body of evidence concerning this issue and the time has come, as Accurso *et al* point out, for a dispassionate examination of what appears to be a better alternative, no matter how distasteful it is to those who have based their whole careers on the "fat is bad" dogma.

CARBOHYDRATE RESTRICTION, CARBOHYDRATE METABOLISM AND DIABETES

The second issue associated with carbohydrate restriction and low-carbohydrate diets concerns carbohydrate metabolism, insulin sensitivity (or resistance, the other side of that coin) and fatty acid metabolism, all of which concern aspects of the metabolic syndrome. As carbohydrate metabolism becomes dysfunctional, first the prediabetic state and then diabetes occur. A low-fat diet (< 7% of energy) in combination with regular exercise is the current recommendation for preventing or treating diabetes.[9] This appears counter intuitive considering that dietary carbohydrate is the major determinant of post-meal blood glucose levels. The American Diabetes Association, in its latest dietary guidelines, even suggest that if table sugar is added to the meal plan, all one needs to do is cover its impact with insulin or other glucose-lowering medications.[9]

Westman *et al* recently discussed the impact of insulin on the treatment of diabetes in the early 20th century.[10] As mentioned above, a very low carbohydrate, high fat diet was employed for the treatment of type 1 diabetes using urine glucose levels as an indicator of efficacy, and this was the approach recommended in the principal medical text book of the time. After insulin was discovered, insulin injections were viewed as the ultimate solution, but studies consistently show that diabetics achieve poor blood sugar control and adverse vascular effects are widespread. In recent times, one approach has been to attempt to modify the impact of a high carbohydrate intake by emphasizing low glycemic index foods. A recent meta-analysis of a number of studies on both type 1 and type 2 diabetics suggests that this approach has a very limited impact on glycated hemoglobin A1c levels, the standard measure of long-term glucose control.[11] However, as part of the Cardiovascular Health Study, Mozaffarian *et al*[12] have examined the combined impact of lifestyle factors which included both low glycemic foods and exercise on the incidence of diabetes in later life in lean individuals and found dramatic decreases in the risk of developing diabetes. This was discussed in the June 2009 Newsletter.

As discussed in a recent Research Report on the diagnosis of diabetes, fasting glucose, the glucose tolerance test, and the blood levels of glycated hemoglobin A1c (HbA1c) are all used to access the short and long term status of glucose metabolism. As Accurso *et al*[8] discuss in their recent review, carbohydrate restriction slows glycemic (blood sugar) responses and insulin response. In one study of obese diabetics, 14 days on a low-carbohydrate diet with an intake of about 1000 cal resulted in a drop in HbA1c (7.3% to 6.8%), and insulin sensitivity increased by 75%. In another study of a similar group, a very low-carbohydrate diet reduced blood glucose levels to normal over 48 weeks. The authors cite other studies that had similar if not greater impact on both HbA1c and glycemic control and even moderate carbohydrate reduction was reported to improve glycemic control by 40-55%. Carbohydrate restriction has been reported by several investigators to cause diabetic patients to reduce or eliminate medication. Feinman and Volek[13] point out that the reduction or elimination of glycemic control medication is a pre-requisite for establishing the merits of the low-carbohydrate approach in the

treatment of diabetes. They cite three studies, as of 2008, which in fact demonstrate that this is what happens. Indeed, carbohydrate restriction is so effective that when combined with glycemic control drugs it can result in dangerous hypoglycemia. Finally, glycemic control has been shown to dramatically reduce the levels and excursions of both insulin and glucose over a 24-hour period as compared to the usual high-carbohydrate diet diabetics are apparently encouraged to eat, with these very favourable results seen after only 2 weeks on a low-carbohydrate diet.[8] These beneficial effects directly impact prediabetics as well and can result in normal glucose metabolism and thus dramatically reduce the risk of developing diabetes. Also, in both the prediabetic and diabetic, these changes in glucose metabolism reduce the risk of vascular complication, which is really the name of the game.

A retrospective case study published in 2003 illustrates the power of carbohydrate restriction in this context.[14] Fourteen patients with diagnosed diabetes (13 type 2, 57% female, age 35-52) were counseled to reduce their carbohydrate intake to 20 g/day. Once glycemic control was achieved 5 g per day of carbohydrate was added until urinary ketones were no longer detectable. This fixed the final level of carbohydrate intake. Oral hypoglycemic agents were discontinued at the start of the intervention, and insulin used only if necessary to keep blood glucose in the 150-200 mg/dL range. The median follow-up was 8 months. Ten of the 14 had an initial HbA1c which averaged 10.9% with a range of 16.8-9.5%, i.e. all very high, typical of diabetics and dangerous in terms of vascular damage. The dietary intervention reduced the HbA1c in all 10 to less than 6.5% (average 5.5%, range 4.7-6.3%). An HbA1c of 6.5% is the latest suggested cut-off for the diagnosis of diabetes and near the threshold for the onset of adverse vascular effect of hyperglycemia. Another patient went from 12.0 to 6.8% in 2 months, and one started at 12.7 and reached 7.6% in 13 months. Only 2 patients out of 14 failed to respond, and 10/14 no longer had an HbA1c diagnostic of diabetes. These changes occurred in some patients with minimal weight loss and all were either obese or morbidly obese. Triglycerides dropped on average by 50.3% and HDL increased. While it is recognized that one study which was not randomized is of limited value, these results are similar to other studies and provided the motivation for Westman and Vernon to suggest that carbohydrate restriction was superior to insulin therapy and is in fact the protocol they use clinically with success.[1]

Richard K. Bernstein, M.D., in his book *Diabetes Solution* (Little Brown, New York, 2003), also promotes carbohydrate restriction, regards the target HbA1c levels recommended by the various diabetes associations as being absurdly high, and aims in his clinic to achieve values well below that indicative of diabetes. This book is highly recommended for anyone with diabetes.

As part of the now famous Nurses' Health Study, it has been demonstrated that diets rich in vegetable sources of protein and fat may modestly reduce the risk of diabetes. The authors comment that in a previous investigation of the same cohort, it was found that a score reflecting a diet high in fat and protein and low in carbohydrates was not associated with increased risk of coronary heart disease in women.[15]

CARBOHYDRATE RESTRICTION AND WEIGHT LOSS

Diet and weight loss constitute a complex subject. Issues include starting weight, fat distribution, energy derived from each macronutrient, presence of concomitant exercise and its intensity, duration of the study, and gender. Adherence to an assigned diet is a big issue. Benefits aside from weight loss are generally measured by markers of perceived cardiovascular and metabolic risk and inflammatory markers. The matter is complicated by the fact that 20-30% of obese individuals are what is called metabolically healthy, i.e. they do not differ significantly in a variety of metabolic markers from healthy non-obese individuals. Other issues include presence or absence of diabetes and menopausal state.

Problems can be found with most studies. These involve duration which is too short to be very meaningful, small or very small numbers of participants, failure to document adherence, and comparison of diets that do not involve meaningful differences in a given macronutrient. With carbohydrate restricted diet studies, one finds a number that employed unrealistically low-carbohydrate intake such that long term maintenance of the diet would probably be impossible and extrapolating the results to more realistic but still quite low-carbohydrate intake is unclear. Other studies claiming to compare low- and high-carbohydrate diets actually end up comparing two relatively high-carbohydrate diets.

A common characteristic of diet studies is that during the first few months the mean weight change is 4-8 kg, but by the end of a year it approaches the baseline mean value. When two or more distinctly different diets are compared, a difference in weight loss may be seen which is generally greater during the first few months and the diets then tend to converge in the long term to a smaller and similar weight loss. One rarely sees a diet study where the weigh continuously declines throughout the study. But there are also the extremes not reflected in the averages—some find it easy to continuously lose weight and some find it almost impossible. If one had to generalize, it is probably necessary to conclude that losing significant amounts of weight is difficult for many individuals.

The latest large randomized weight reduction trial to date reported in February 2009 and was heralded by the media as proving that all diets have the same effect on long-term weight loss regardless of their macronutrient composition, including high carbohydrate low-fat and low-fat high-carbohydrate.[16] The diets were designed to be low-fat and average-protein, low-fat and high-protein, high-fat and average-protein, and high-fat and high-protein. In these 4 diets, the carbohydrate intake target as a percentage of total energy was 65%, 55%, 45% and 35%, respectively. However, it turned out that carbohydrate, fat and protein targets were never met and all four diets were in fact very similar during the execution of the study. Thus it would be a mistake to attach any significance to the weight-loss aspect of this study. While a number of other parameters were measured, when everyone is actually on the close to the same diet, the results are also not interesting. Some would no doubt argue that this study did not merit publication because the execution proved seriously flawed.

A second randomized trial that compared low-carbohydrate, Mediterranean and low-fat diets over 2 years has also recently reported.[17] In terms of weight loss it was found that the Mediterranean and low-carbohydrate diets were effective alternatives to the low-fat diets. In the low-carbohydrate diet, carbohydrates were only decreased from 51 to 41%, but overall energy intake was decreased by 550 cal, whereas in the Mediterranean diet there was no significant change in the percentage of energy from carbohydrates and the energy decrease was about 370 cal. Both produced a weight loss at 24 months of about 6 kg whereas the low-fat diet with a decrease in energy of 570 cal and a constant percentage of energy from carbohydrates yielded a weight decrease of only 3 kg at 24 months.

A number of other studies could be cited but for the most part they were of short duration or involved unrealistically low-carbohydrate intake which could not be part of a long-term diet. Nevertheless, these short-term studies with severe carbohydrate restriction produced, as would be expected, large decreases in triglycerides and large increases in HDL. Thus the overall picture is consistent and suggests carbohydrate restriction offers a satisfactory protocol for modest weight loss and has an excellent impact with regard the atherogenic dyslipidemia which may enable this intervention to play a significant role in the prevention of cardiovascular disease. It is unfortunate that Robert Atkins did not live to see his ideas repeatedly confirmed.

CARBOHYDRATE RESTRICTION AND THE METABOLIC SYNDROME

Carbohydrate restriction improves the features of the metabolic syndrome and it has been suggested by Volek and Feinman that in fact the syndrome could be defined by the response to carbohydrate restriction.[18] This point of view is of considerable interest since the metabolic syndrome carries a predisposition to diabetes, cardiovascular disease and other pathologic states. However, most formal guidelines and clinical papers have not emphasized carbohydrate restriction as a recommended approach in treating either the syndrome or its individual components. This may be due to a fear of conflict with the fat is bad dogma.

The usual definition of the metabolic syndrome used in North America is that any three of the following criteria must be met: (1) waist circumference > 102 cm in men and 88 cm in women; (b) triglycerides ≥ 150 mg/dL (1.7 mmol/L); HDL cholesterol < 40 mg/dL in men and < 50 mg/dL (1.0 and 1.3 mmol/L); blood pressure ≥ 130/85 and blood glucose > 110 mg/dL (6.1 mmol/L). Volek and Feinman[18] present 13 carbohydrate restricted diet studies that favourably impacted triglycerides, HDL and glucose in both normal weight and obese men and women, as well as reducing weight and in some studies, systolic blood pressure. They also demonstrate on the basis of three studies that for short term low-fat vs. ketogenic (very low carb) diets, only the latter result in favourable changes in the lipid parameters. More recent studies discussed above support this observation.

In a recently published paper, Volek, Feinman and coworkers reported on a detailed study over 12 weeks of a carbohydrate restricted diet vs. a low fat diet.[19] The study involved 40 subjects with elevated triglycerides and

low HDL. Carbohydrate intake in the restricted diet was individually determined by the intake that resulted in a low level of ketosis. Foods consumed included unlimited amounts of beef, poultry, fish, eggs, oils and heavy cream, moderate amounts of hard cheeses, low-carbohydrate vegetables and salad dressings, and small amounts of nuts and seeds. The low fat diet was designed to provide < 10% of calories from saturated fat and< 300 mg of cholesterol. Foods encouraged included whole grains, fruit, vegetables, vegetable oils, low fat and lean meat. The results demonstrated that a diet restricted in carbohydrates can provide a more comprehensive improvement in the clinical risk factors associated with the metabolic syndrome than a low-fat diet at reduced caloric intake. Furthermore, the carbohydrate restricted diet showed more favourable responses to alternative indicators of cardiovascular risk such as post-meal lipidemia, the Apo B/Apo-A1 ratio, and the LDL particle size distribution, i.e. a decrease in the small dense LDL particles viewed by some a the atherogenic component of the total LDL. The carbohydrate diet also improved glycemic and insulin control.

There is growing recognition that atherogenic dyslipidemia presents an independent risk factor for coronary heart disease and may account for the large number of individuals with normal or low LDL that experience heart attacks. The connection is probably stronger with events than the progression of atherosclerosis where the evidence that elevated triglycerides and low HDL are associated with risk is weak but still suggestive.[6] It is interesting to look at recent calls for action and intervention.[20,21] One group uses the phrase “Residual Risk Reduction Initiative.” These mostly discuss pharmaceutical interventions using fibrates or niacin or the increased consumption of long-chain omega-3 fatty acids such as are derived from marine sources. But when dietary interventions are discussed, no mention is made of carbohydrate restriction and the major study discussed is one which reduced carbohydrates only from 58 to 48% of total energy.[22] Yet the changes in HDL and triglycerides that result from a diet more restricted in carbohydrates are comparable to what can be achieved with fibrates and/or niacin.[23]

There are two potential explanations: (a) the call for action is coming from medical scientists who have strong links with the pharmaceutical industry and think in terms of drug interventions, and (b) carbohydrate-restricted diets have not made it to mainstream medicine and, because they generally involve an increase in fat and even saturated fat, go against the fat is bad dogma which is still very much alive and well as suggested by the constant refrain that one must reduce fat intake. The trouble is that many individuals who qualify for treatment of atherogenic dyslipidemia or the metabolic syndrome will receive a long term drug program recommendation and not even be made aware of the merits of carbohydrate restriction. If dietary recommendations involve only the reduction of saturated fat from 15% to 7% of energy, restricting dietary cholesterol and reducing fat in general, then the dietary approach will probably fail and the recommendation of a pharmaceutical approach will gain credibility as the only answer. This is especially true if a large weight loss is also used as the target. This is unfortunate since it is not the only answer. Furthermore, while most diets produce only modest declines in weight after one or two years, the carbohydrate restricted diet can produce dramatic reductions in dyslipidemia with these modest weight loses an in fact eliminate the diagnosis of the metabolic syndrome.

EGGS AND THE CARBOHYDRATE RESTRICTED DIET

With the advent of the fat is bad era and the belief that dietary cholesterol was also bad, the nutritional and medical establishments took a very dim view of the egg, since the typical egg yolk contains 200 mg of cholesterol. This appears to lack justification given that for 70% of the population, dietary cholesterol does not significantly elevate serum cholesterol and for those responders, dietary cholesterol elevates both LDL and HDL and the ratio remains constant suggesting no increase, according to the conventional wisdom, in CHD risk. Also, if one does not believe that fat is bad, then the fat in eggs is also not an issue. Furthermore, research does not support a consistent relation between egg intake and increased CHD incidence and egg consumption has been shown to promote the formation of large LDL particles thought to be much less atherogenic.[24]

Two recent papers report results on the impact of egg consumption on lipid parameters and inflammation in subjects on carbohydrate-restricted diets. The first study found that adult men on a carbohydrate-restricted diet who consumed eggs had a significant increase in HDL compared to those consuming an egg substitute. The former had a 12% increase in HDL compared to the latter who experienced a 1.2% decrease, both without a significant change in LDL levels. Mean HDL levels went from 47.6 to 57.1 mg/dL after 12 weeks on the diet containing eggs. This diet provided an additional 640 mg/day of cholesterol. TG levels were significantly decreased in both groups and the addition of eggs to the diet did not alter the positive effects of carbohydrate restriction on features of the metabolic syndrome.[25] A second study from the same group found that adding eggs

to the carbohydrate-restricted diet made a significant contribution to the anti-inflammatory effects of the diet, perhaps due to the lutein in eggs.[26]

Current mainstream recommendations call for reducing dietary cholesterol. These results suggest exactly the opposite, at least in the context of a low-carbohydrate diet. Furthermore, eggs contribute to healthy diets, providing protein, dietary carotenoids, lecithin, lutein, zeaxanthin and choline. As Herron *et al* point out, eggs are particularly appropriate in elderly populations, especially since elevated total cholesterol appears to be a risk factor only in middle-aged individuals.[27]

CONCLUSIONS

In the context of the prevention of coronary heart disease and the prevention and treatment of diabetes as well as the prediabetic state, carbohydrate restriction would appear to the approach of choice, especially if the desire is to avoid pharmaceutical intervention if at all possible. Furthermore, carbohydrate restriction can beneficially impact both blood lipids and glucose metabolism even in the absence of significant weight loss, whereas even the smaller benefits achievable from the low-fat diet generally require weight loss. Furthermore, carbohydrate restriction has the potential to reverse prediabetes and diabetes and eliminate the need for glucose lowering medication. The fear that carbohydrate-restricted diets would have an adverse impact on the blood lipid profile does not appear evidence-based. Quite the contrary, this type of diet has the potential to reverse the dyslipidemia of the metabolic syndrome and its impact on LDL, if one believes that to be significant, is minimal. The severity of carbohydrate restriction depends on the goal of the intervention. Fortunately, most of the parameters involved are easily measured. If on is trying to reverse diabetes or prediabetes, then HbA1c and fasting glucose are of interest. Both are routine and one can be done at home. Assessing the metabolic syndrome involves only one measurement that cannot be done at home, the blood lipid profile, but this again is a routine measurement although now the focus is on triglycerides and HDL, not on LDL and total cholesterol. Thus if one is armed with a scale, a tape measure, a blood glucose meter and a blood pressure measuring device, aside from two blood tests, the success of a dietary intervention can be followed at home.

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