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The Modified Atkins Diet

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SUMMARY

In 2003, a case series was published describing the benefits of a less restrictive ketogenic diet (KD) started as an outpatient without a fast and without any restrictions on calories, fluids, or protein. This "Modified Atkins Diet" (MAD) restricts carbohydrates to 10 g/day (15 g/day in adults) while encouraging high fat foods. Now 5 years later, there have been eight prospective and retrospective studies published on this alternative dietary therapy, both in children as well as adults. In these reports, 45 (45%) have had 50–90% seizure reduction, and 28 (28%) >90% seizure reduction, which is remarkably similar to the traditional KD. This review will discuss basics and tips to best provide the MAD, evidence for its efficacy, suggestions about the role of ketosis in dietary treatment efficacy, and its side effect profile. Lastly, the possible future benefits of this treatment for new-onset seizures, adults, neurologic conditions other than epilepsy, and developing countries of the world will be discussed.

KEY WORDS: Modified Atkins diet, Ketosis, Children, Epilepsy, Ketogenic.

The modified Atkins diet (MAD) was created at Johns Hopkins Hospital as an attempt to create a more palatable and less restrictive dietary treatment primarily for children with behavioral difficulties and adolescents that parents and neurologists were reluctant to start on the traditional ketogenic diet (KD). Recognizing that there is only limited evidence that high ratios, calorie and fluid restriction, fasting, and an inpatient diet initiation are necessary (Vaisleib et al., 2004; Bergqvist et al., 2005), the MAD was designed to mimic ketosis while providing similar but unlimited quantities of high fat (and protein) foods. As is commonly the case, parents and patients were the ones to first realize a stricter version of the Atkins diet controlled seizures either de novo or after loosening the restrictions of the KD and we first reported a case series of six children and adults in 2003 (Kossoff et al., 2003). Half of these patients had at least a 50% reduction in seizures.

Today it is no longer considered a new treatment; the MAD has been reported as efficacious in eight publications to date by centers in four countries (Kossoff et al., 2003, 2006, 2007; Kang et al., 2007; Carrette et al., 2008; Ito et al., 2008; Kossoff et al., 2008a, 2008b). This review will summarize its composition, evidence for efficacy, possible mechanism of action, side effects, tips to make it easy to implement and follow, and potential future uses.

DIET COMPOSITION

The composition of the MAD was recently elaborated upon in a prospective, crossover-design evaluation (Kossoff et al., 2007) with detailed 3-day food record provided by parents. The MAD was similar in fat composition to a 0.9:1 ketogenic ratio (fat:carbohydrate and protein) diet, with approximately 65% of the calories from fat sources. This is certainly less fat than a standard 4:1 KD (90% fat) but more than a typical diet (0.3:1, 35% fat) (Fig. 1). In children, the carbohydrates are limited initially to 10 g/day, with planned increases after 1 month to 15 g, then 20–30 g/day as tolerated based on seizure control. Adults are started at 15 g/day and can be increased to 20–30 g/day after 1 month. All carbohydrates are allowed, in contrast to the low glycemic index treatment which restricts carbohydrates to those with a glycemic index less than 50 (Pfeifer & Thiele, 2005). Carbohydrates can be given throughout the day or at one meal. We allow fiber to be ignored from the total carbohydrate count, but not sugar alcohols. The MAD protocol still in use today is provided in Table 1.

The diet is "modified" from the Atkins diet as the "induction phase" of the diet limiting carbohydrates is maintained indefinitely, fat is encouraged (not just allowed), and weight loss is not the goal (unless nutritionally indicated).

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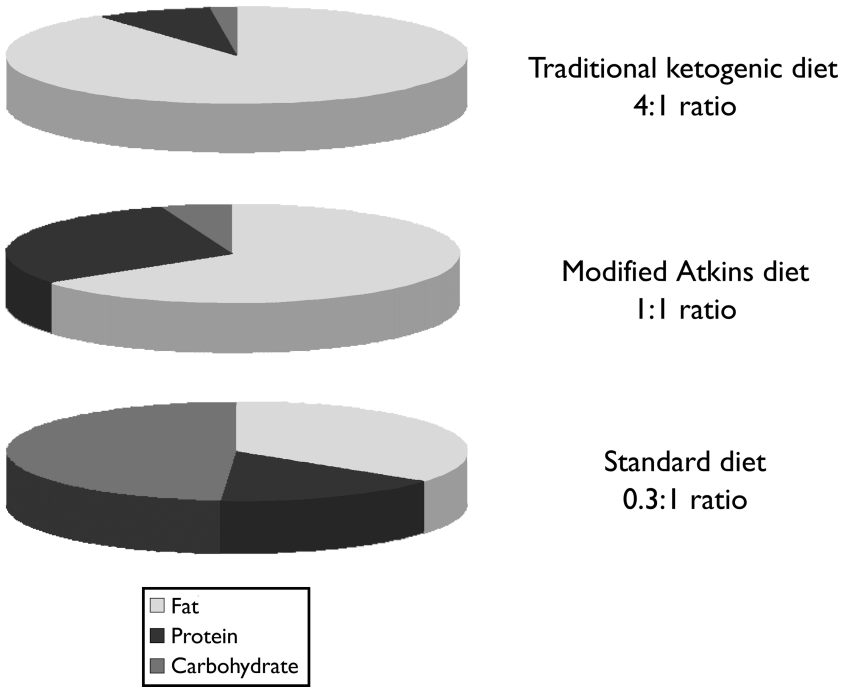

Figure 1.
Diet compositions. Ratio, grams of fat: protein and carbohydrate.
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Efficacy in Children and Adults

The first prospective study of the MAD in children was open-label and included 20 children with intractable daily seizures resistant to at least two anticonvulsants (Kossoff et al., 2006). This study was sponsored by the Dr. Robert C. Atkins Foundation, who paid for all study visits. In this study, efficacy was surprisingly high, with 13 (65%) having at least a >50% seizure reduction at 6 months, half of whom (35%) had >90% seizure reduction using an intent-to-treat analysis. No subject demographic correlated with a higher likelihood of success. When given the option to continue the diet beyond the 6-month study period, 14 of the 16 completing the study chose to remain on the MAD. A similar design study from South Korea of 14 children aged 2–14 years demonstrated slightly less likelihood of a >50% seizure reduction (43%), however, a higher incidence of >90% seizure reduction (36%) (Kang et al., 2007).

Several children in the first prospective study had planned increases in carbohydrate limits as the study progressed without resultant worsening of seizure frequency. To further test a hypothesis that carbohydrate limits were not critical, a randomized, prospective study compared 10 versus 20 g/day of carbohydrates at MAD onset, with a crossover to the opposite limit after 3 months (Kossoff et al., 2007). The hypothesis was proven correct at the 3-month crossover time point; increasing carbohydrates did not worsen seizure control despite improving tolerability and decreasing carbohydrates did not improve seizure frequency. However, there was a surprisingly higher incidence of >50% seizure reduction at 3 months with

Table 1. Modified Atkins diet protocol in current use at Johns Hopkins Hospital

- Carbohydrate counting book and web-sites for low-carbohydrate recipes provided
- Carbohydrates (any) restricted to 10 g/day for the first month (15 g/day for adults)
- Fats (e.g., 36% heavy whipping cream, oils, butter, mayonnaise) encouraged
- Low-carbohydrate multivitamin (Centrum Silver, Wyeth, Madison, NJ, U.S.A.) and calcium carbonate supplementation recommended
- Calendar provided in order to document seizures daily, urine ketones semiweekly, and weight weekly
- Medications unchanged for the first month, but changed if necessary to tablet or sprinkle (non liquid) preparations
- Low-carbohydrate, store-bought products (e.g., shakes, candy bars, baking mixes) discouraged for at least the first month then gradually introduced one at a time
- Children evaluated by phone after 1 month, then in clinic after 3 and 6 months
- After 1 month, carbohydrates can be increased by 5 g/month to the limit of 30 g/day. Additionally, low carbohydrate products can be tried and anticonvulsants reduced as tolerated (one change at a time).
- Complete blood count, complete metabolic profile (SMA-20), fasting lipid profile at baseline, 3, and 6 months

an initial carbohydrate limit of 10 g/day (60% vs. 10%, $p = 0.03$). This study suggests that a strict carbohydrate limit is important, but only during the first 1–3 months.

Even as far back as 2003, the MAD was foreseen as primarily of benefit for adolescents and adults not typically offered the KD. From 2005 to 2007, a prospective, open-label study of the MAD for adults with intractable epilepsy was performed with a study design nearly identical to the pediatric trial (Kossoff et al., 2008a). Thirty adults were enrolled and started on the MAD with 15 g/day of carbohydrate restriction. The dropout rate was high, with 10 (33%) discontinuing the MAD before the 3-month assessment point, even at times despite >90% seizure reduction. However, the MAD worked quickly (median 2 weeks), with 47% having a >50% seizure reduction by 3 months and 33% by 6 months. Only one patient became seizure-free. We now counsel adults that the MAD works quickly when effective, but is most likely to lead to a 50–90% seizure reduction (not seizure freedom).

One of the largest drawbacks to the use of diets in adults is a lack of dietitian expertise and a perceived complicated nature of using these diets by the average neurologist without KD experience. In order to disprove this and allow the use of the MAD for adults who need it, we are completing a prospective study of the MAD that enrolls, initiates, and maintains adults on this diet via the internet, with both emailed information and no direct dietitian involvement in day-to-day care. Results should be forthcoming soon.

At the time of the writing of this review, there have now been 100 reported children and adults started on the diet in eight publications worldwide. Forty-five (45%) have had 50–90% seizure reduction, and 28 (28%) >90% seizure reduction, which is remarkably similar to the traditional KD. Further adult and pediatric studies are underway.

Lessons Regarding Dietary Mechanisms of Action

Results from studies of the MAD have raised some interesting questions about why the traditional KD works. In the first pediatric study, ketosis correlated with seizure control after 1 month (86% vs. 40% with large ketosis in those who improved, $p = 0.04$). This correlation did not persist for the subsequent 5 months, however. The study of the MAD from Korea found higher seizure reduction in children with fewer fluctuations in serum ketosis (Kang et al., 2007). In the pediatric crossover study, although lower carbohydrate limits were associated with seizure reduction at 3 months, ketosis was not (Kossoff et al., 2007). In studies of the low glycemic index treatment, serum ketosis is also lower than seen with the KD and theorized not to be related to efficacy (Pfeifer & Thiele, 2005). The relative importance of ketosis, for the first month or beyond, remains to be proven.

An interesting and surprising finding of the first pediatric study was that a stable body mass index (BMI) (change <0.3 over the 6-month study period) correlated with seizure reduction whereas weight loss did not ($p = 0.004$) (Kossoff et al., 2006). This is in contrast to anecdotal and animal experience that weight loss and calorie restriction may have anticonvulsant benefits (Greene et al., 2001). However, at the 3-month period (not at 1 or 6 months) of the adult study of the MAD, a BMI decrease correlated with seizure reduction ($p = 0.03$) (Kossoff et al., 2008a). Again, the relative importance of weight loss and calorie restriction remains to be proven.

Side Effects

The MAD appears to be tolerable with limited adverse events in studies to date. An approximate 25–50 mg/dl increase in total cholesterol was noted in both Johns Hopkins pediatric and adult studies (Kossoff et al., 2006, 2007, 2008a), which was statistically significant and included an increase in LDL cholesterol in the latter two. Triglycerides did not increase in the adult study (Kossoff et al., 2008a). The only other significant laboratory abnormality found was blood urea nitrogen (BUN), likely a result of increased protein intake, although serum creatinine does not appear to increase. Weight loss can occur in children and adults who are overweight predominantly and may be desired. Although less restrictive than the KD, the MAD is still not an easy diet to maintain and should not be advertised as such.

The long-term side effects of the MAD have not been established, unlike the KD (Groesbeck et al., 2006). Considering the increased protein and decreased fat, one suspects the risk of growth impairment, kidney stones, dyslipidemia, and gastroesophageal reflux will be reduced in comparison to the KD. Should this be demonstrated in long-term studies, switching children on the KD to the MAD after several years of therapy (if the child still requires a dietary treatment) may be logical.

Tips for Successful Usage

The MAD can be initiated efficiently in an outpatient clinic setting with limited dietitian involvement at diet onset. Parent and/or patient education should take approximately 30–60 min and includes carbohydrate counting, reading food labels, and identifying and encouraging high fat foods. To allow the education to be limited to this short-time interval and to minimize the need for dietitian involvement while the patient is maintained on the MAD, the parent/patient is given an approximately 20-page information packet in clinic. This packet includes carbohydrate contents of common foods, recommendations for reputable websites with information and recipes (e.g., www.epilepsy.com), grocery store available low-carbohydrate products, online support groups, and sample daily menus. In addition, *The Ketogenic Diet: A Guide*

for Children and Others with Epilepsy is suggested due to commonly asked questions nonspecific to any dietary therapy and MAD chapters at the end of the book (Freeman et al., 2006). They are encouraged to read this information, go food shopping, and obtain the fasting baseline lab studies before actually beginning the MAD.

One other potential benefit of the MAD versus the traditional KD is that other family members can be on this diet as well as a supportive gesture. There may be additional health benefits for weight loss for family members as well. Although this is not mandatory, having the entire family eat a "low-carb lifestyle" likely improves MAD compliance.

If ketosis drifts downward or is lost and it appears to correlate with a loss of seizure control on a seizure calendar, we then obtain a 3-day food record to ascertain if the patient is consuming adequate amounts of fat and calories. To regain ketosis, patients can fast for one meal, replace one meal with a KetoCal (Nutricia, Gaithersburg, MD, U.S.A.) shake, or add medium-chain triglyceride (MCT) oil to the MAD recipes. The issue of when to discontinue the MAD and switch to the KD is unclear at this time, but we generally switch if ketosis is both relevant to seizure reduction in that individual patient and is difficult to keep elevated with the MAD. If ketosis drifts downward or is lost and it does not affect seizure control, the patient should stop checking urine for ketones.

The Future of the Modified Atkins Diet

When the next International Symposium of the Use of Dietary Treatments for Neurologic Disorders occurs in 2010 in Edinburgh, in whom will the MAD be used? We suspect the MAD will continue to be used in conditions that the KD is deemed too restrictive, as initially envisioned. The MAD may become a treatment of choice therefore for adults and possibly even supplant the KD in adolescents as well due to its ease of administration. We also predict that the MAD may become used increasingly for new-onset epilepsy conditions associated with high initial seizure frequencies (myoclonic-astatic epilepsy, absence epilepsy, juvenile myoclonic epilepsy). As the MAD works quickly and can be started in the clinic immediately, a parent may be willing to try this therapy (as opposed to the KD which requires a relatively time-intensive 4-day admission to initiate) for several weeks prior to starting anticonvulsants. In addition, as described in another review in this supplement, the MAD may be used in other neurologic conditions (e.g., brain tumors, autism, Alzheimer's disease) in which dietitians may have less time available to allocate to patients who do not have intractable epilepsy.

Lastly, we have experience with a 2-year-old child in Honduras without access to a dietitian or locally-trained KD experienced neurologist (Kossoff, 2008b). The MAD was started via email with local neurologist support and the child has had both a >90% reduction in seizures as well as a reduction in his cost of care by $5 per month due to elimination of two daily anticonvulsants. He remains on the MAD after over 2 years and his mother is helping to train several other families in its use with neurologist guidance. Further studies are being designed for developing countries using the MAD.

Conclusions

The past 5 years have seen the MAD progress from a new, potentially-effective, alternative KD to an established, mainstream therapy for children and adults with intractable epilepsy. Its use in 100 patients to date has led to interesting insights regarding the mechanisms of action of dietary therapies. The place of the MAD in comparison to the KD remains unclear, however, and will likely be clarified in the next 5 years. It appears to have definite benefits for both adults as well as children not believed to be able to handle the restrictions of the KD. The MAD may also have a role in future studies of new-onset epilepsy, neurologic conditions other than epilepsy, and in developing countries.

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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