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VIEWPOINT

Efficacy of higher protein diets for long-term weight control. How to assess quality of randomized controlled trials?

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How to assess evidence

What evidence is required to conclude that a certain diet composition is preferable to another for preventing weight gain, inducing weight loss and supporting long-term weight maintenance, i.e. preventing weight regain? This is an important question, as 60–80% of the adult populations in developed countries are either overweight or obese, but the evidence-based science seems to be difficult to separate from politics, economic, ethical, and environmental interests.

In evidence-based medicine it is typically the *totality* of evidence that is considered, i.e. animal studies, human mechanistic and experimental studies, observational studies, and randomized controlled trials (RCT's). In this hierarchy of study designs RCT's are given more weight, and meta-analyses of RTC's are considered the most powerful level of evidence of "cause and effect" relationships.

The effects of proteins on energy balance: well-known mechanisms

Over the last 20 years numerous studies have demonstrated that energy from protein is more satiating than energy from other macronutrients, and that the effect can in part be attributed to protein ingestion triggering release of satiety hormones such as GLP-1 and PYY [1]. In addition, higher protein diets have a greater acute thermogenic effect [2] and they also promote a more sustained increase in energy expenditure over the long-term due to preservation or increase in lean body tissue [3]. The general consensus is that the physiology supports a role for dietary protein in promoting a reduction of fatness and preserving lean body tissue.

Assessing the efficacy of higher protein diets

Multiple RTC's have shown diets with reduced carbohydrate and increased protein contents to have greater efficacy for reducing body fat, both when diets are part of a calorie controlled program and when the diets are offered *ad libitum*, i.e. allowing the satiety effect to influence spontaneous energy intake [3–5]. Many of the studies have tested various popular diets claiming weight loss without any imposed energy restriction (e.g. South Beach Diet, Dukan, Atkin's,

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Paleolithic diet) [6], all characterized by less carbohydrate, more liberal fat intake, and an increase in protein content to 25–50% of calories from protein.

Several meta-analyses of RTC's comparing normal with higher protein diets have been published and they have all, with few exceptions, concluded that higher protein diets are superior to produce and maintain weight and fat loss, are better to preserve lean body and muscle mass, and also generally have beneficial effects on risk factors of type 2 diabetes and cardiovascular disease [3–5].

Recognising the efficacy of higher protein diet?

Although there seems to be convincing evidence to support that higher protein, lower carbohydrate diet should be recommended for weight control, some scientists have pointed out the lack evidence for long-term efficacy. It has even been suggested, based on observational studies, that there may exist an adaptation to the satiety effect of protein so that higher protein diets in the long-term may produce weight gain [7]. However, there is no biological mechanism to explain such a paradoxical effect of protein, and it is more likely that the observational studies suffer from residual confounding.

In this issue of the journal a systematic review and meta-analysis of long-term studies of diets recommending lower carbohydrate and increased protein by Clifton et al. provides us with a missing link [8]. This is a much more comprehensive analysis than the one by Schwingshackl and Hoffmann published recently [9], and Clifton et al. find that the diet change has significant and persistent effects on weight, fat mass, and fasting triglyceride after 12 months, but the effect is small. However, the small effect could clearly be attributed to the tendency not to adhere to the diets over time. A 3 times greater effect on fat mass was found in those studies where a difference between the diets of 5% energy from protein was still maintained at the end of the study, which was nearly 1 kg better than the normal-protein diets. So, just an increase in dietary protein content from say 16 to 21% of energy is enough to produce a reduction in body fat that may be of relevance for public health. This finding is equivalent to the finding of the Diogenes study [10]. One should note that most of the trials included in the meta-analysis had an active intervention of less than 12 months duration [8], so the final visit was a follow-up where the participants had been without contact to diet instruction etc. for months. In many, if not most studies, the participants did not see the study as a treatment option resulting in a life-long change of diet, but rather as one opportunity to test a diet and learn something to be used occasionally.

With this meta-analysis we now have evidence that those who stick to the higher-protein diet maintain weight and fat loss benefits in the long-term.

Study retention does not necessarily mean adherence to diet composition

Can we assume that higher protein diets would now receive recognition as a dietary strategy to combat overweight and obesity? Well, the American Heart Association (AHA), the American College of Cardiology (ACC) and The Obesity Society (TOS) recently published guidelines for the management of overweight and obesity [11]. However, the importance of diet composition was completely dismissed because the panel applied a level for required evidence strikingly different from that used in systematic reviews and meta-analyses such as this one by Clifton et al. [8]. Whereas Clifton et al. include all available long-term trials, the AHA–ACC–TOS group excluded RCTs with a retention rate below 90% for 'completer' analyses, or below 80% for 'intention-to-treat' analyses [11]. The argument is that lower retention is a marker of poor compliance, but is that justified?

"Retention" was used as a marker of quality of a trial, and trials that failed to reach a retention rate of 80–90% were judged as "low quality". The assumption that "high quality", i.e. "high compliance with behavioural adherence and with dietary prescription", can be assessed by the retention rate is questionable [12].

Dietary interventions require participants to consume all meals every day over a period of several months in compliance with one particular diet composition. Retention in weight management trials is mainly determined by outcome success and tolerability, and in RTC's arms with greater weight loss and maintenance typically increase retention rates. Consequently, retention rate should not be used only as an indicator of trial quality, but rather as a primary outcome that provides a measure of the success and acceptability of the diet. However, many other factors influence retention (see Table 1).

Adherence to diet composition should be assessed by biological markers

However, in the few dietary intervention trials accepted by the AHA–ACC–TOS panel for inclusion in the data analysis no critical assessment of diet adherence (for example, measurement of urinary nitrogen excretion among

Table 1 Determinants of retention in dietary intervention trials.

- Weight loss success. Any treatment that produces greater weight loss success causes lower drop-out rate. It also implies that treatments with low efficacy may cause low retention.
- More intensive control, e.g. more frequent visits, phone calls etc., cause fewer drop-outs.
- Very intensive treatment and time consuming study examinations can be too demanding and impact on participants' social relations, and increase risk of drop-out.
- Rewards for completion of trial, e.g. cash. This incentive can theoretically increase retention to close to 100%.
- Unforeseen incidents – increases with duration of trial.
- Individual factors associated with higher retention:
  - Higher age
  - Higher degree of motivation and readiness to change
  - A biologically determined sensitivity to high-protein diets, e.g. the TFAP2B gene (rs987237) [18]
  - Socio-economic and educational background of participants

Adapted from Stocks T et al. [18].