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Short Communication

A Trap of RCT in Low Protein Dietary Therapy. Revaluation of Pro-Post Study for Dietary Intervention

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Evaluation of RCT in diet therapy

The current trend of clinical research in the medical world, which highly evaluates "evidence-based medicine" only with the RCT methodology, is expected to be seriously reconsidered by those involved. What is important is the scientific truth and the patient's life, and it is essential in dietary therapy for CKD.

Since the report of Volhard [1]. Germany (1918) over 100 years ago, numerous publications have examined the clinical effects of a strict low-protein diet in patients with chronic renal failure (CKD) or uremia. In particular, the Giordano [2]. Giovannetti [3] diet, which appeared in the 1960s, combined with the development of starch products, quietly spread this diet worldwide. This is because the theoretical background and techniques of the two significant skeletons of a low-protein diet, the sufficient energy intake, and consideration of amino acid scores have been solidified for a correct low-protein diet. A low-protein diet is effective in suppressing increases in urea nitrogen, K, and P levels, as well as acidosis. It has been recognized for prolonging life prognosis and delaying the introduction of dialysis therapy.

However, since Rosman., *et al*. [4]. in 1989 reported on a multicenter, prospective, randomized controlled trial (RCT) study, the focus of all outcomes is limited to delaying the rate of progression. As for its delayed effect, many of the results were "no effect" or "difficult to judge effectiveness", and only a few reports were clearly evaluated as "effective". In particular, the MDRD (Modification of diet in renal disease) trial conducted in the United States denied its effects [5]. Since then, interest in the results of low-protein diets has rapidly declined internationally.

The research technique of RCT is highly reliable as a means of clinical research, and the level of evidence is extremely high. Researchers are required to have a modest way of thinking that obediently follows the fact that the research technique of RCT is almost impossible with diet therapy. The lack of adequate discussion of inappropriate research methods and the fact that RCTs have led to unsubstantial conclusions is a significant factor in the chaos that has plunged this field into turmoil.

It is presumed that, in diet therapy, large-scale prospective studies are far cruder and more inaccurate than single-center retrospective studies. Where is the truth in clinical research? Can an RCT be crude? If it is an RCT, is it evidence, even if it is inaccurate?

Naturally, only RCT is a valued technique. If the methodologies and rigor of testing are maintained, the results will be reliable, and discussions and conclusions will be smooth.

I cannot help but strongly distrust today's clinical research of dietary therapy, which is highly evaluated as "evidence-based medicine" with only the RCT methodology. What counts is scientific truth and the patient's life. Why has such a mistake persisted unquestioned?

Dietary therapy is characterized by its invisible and inaccessible aspects. What is difficult to grasp as a phenomenon here is not the "therapeutic effect" phenomenon but the "treatment act itself."

In addition, in most medical settings, it is common to avoid seeing, hearing, and doing things because of this inability to comprehend. In addition, there is a reality that this escape act itself is difficult to see. Therefore, even if they are not doing what they should be, they are unaware of it.

Diet therapy is difficult to grasp the actual situation

What exactly does it mean that the diet is invisible and cannot be grasped by hand?

Diet therapy differs from other treatments in that it is not a therapeutic action performed by the medical side but a treatment performed by the patient. In other words, it is unique in that it is

a treatment that implements everything from one to ten of diet therapy, including menu planning, food purchase, food weighing, cooking, eating, recording, calculation, and reporting. Moreover, as a general rule, all these acts are treatments performed at home, entirely out of the reach of doctors and nutritionists.

In addition, we must recognize that the action as a treatment is invisible. Therefore, diet therapy is a part of everyday life, so not only doctors and nutritionists who are outsiders, but even the people themselves cannot see it.

In this way, discussing diet therapy becomes an empty theory unless we can accurately hold and confirm hidden or difficult-to-understand behaviors. In clinical evaluations and studies of dietary treatment, there is an unreasonable attempt to argue that this inaction is valid, and it is a severe source of research problems.

In the medical field, there is a strong perception that diet therapy is a supplementary treatment, and the sense of responsibility of medical personnel is relatively weak.

Dietary therapy, a peculiar medical practice that is buried in life, has a vast range of backgrounds and frameworks that we cannot ignore in a complex and profound way. It is difficult to see the truth (evidence) in medicine and research that escapes into the world of biological and natural scientific life phenomena only and is carried out only on the surface of the situation.

This is because the reality captured by modern science is mechanistically and dynamically selected and arranged and is limited to facts that can only be prove through abstraction.

Is the RCTs in diet therapy that have been carried out to date a convenient escape to natural science for researchers? As a result, RCTs have likely led to a loss of evidence, at least in diet studies.

Ideal control cannot be set:

In RCTs, it is an essential condition to place controls. However, in diets, feeding a placebo diet is not possible. Even if we randomly select the test and control groups, accurate randomization would not be possible. Also, as long as there is no placebo, there will be room for researchers' arbitrariness to work. There is a possibility that this is a prospective study, so there should be a risk of bias even higher than in retrospective studies.

Dr. Ideura [6] reported a traumatic experience. When the study was started by dividing the control group and the low-protein diet group into groups at random according to the regulations, only two months after the start of the study, all of the control group (6 people) switched to the low-protein diet group. I have doubts about whether the control group never transitioned to the low-protein diet group, what kind of response was made in the event of a transition, and a sense of distrust towards the researchers involved in the research so far.

After the RCT was applied, the results of the low-protein diet were often negative or uncertain about its effects. It is presumed that there was an error in the technique, the precision was loose, and the test setting amount exceeded the guided amount. In the Northern Italian Multi-Center Trial, the set instruction amount was 0.6g/kg BW/day from the beginning and became 0.846g/kg BW/day, which is 39.8% excess at the end [7]. In the case of the MDRD study, the low protein diet group (LPD) set the recommended dose of 0.58 g/kg BW/day, and the actual intake was 0.72 g/kg BW/day [8].

Problems of diet therapy technique required for researchers

Dietary therapy, especially a low-protein diet, requires long-term guidance and training, often months, until the patient understands the theoretical background and the techniques are solid. At the end of repeated instruction through trial and error, they finally acquire the level of technology that can withstand research. It is unbelievable that such a process was followed in the research process of RCTs. The reality that treatment begins on the day the actual drug is taken and symptoms appear after that day, as in a drug trial, is impossible with diet therapy.

The two essential factors for implementing a low-protein diet are adequate energy intake and a sufficiently high amino acid score for protein intake. However, when examining this point in the most influential MDRD study, the average energy intake of subjects was about 25kal/kg BW/day in the end, despite the initially required energy intake of 35kal/kg BW/day. This is low energy, and malnutrition is inevitable if practiced under these conditions.

Researchers should be familiar with dietary theory and techniques before conducting the study. On top of that, the patient must be rigorously educated, which is the premise of clinical research.

Compared to pharmacotherapy, in the case of diet therapy, it is only possible to carry out proper research if the nutritionist and doctor in charge are highly proficient in both diet therapy and nutritional guidance. The data collected is unreliable, and inexperienced researchers can only rely on data from a 24-hour urine collection.

In the case of dietary treatment, the ability to collect accurate data can only be obtained through the skill of the investigator.

So, almost all RCTs failed due to difficulty keeping the programmed amount of protein and energy source intake throughout the study period. RCTs involve many subjects and few observations. Individual difference is significant if we consider the individual gut-kidney axis and other intrabody metabolic networks. Taste preferences and receptivity to dietary advice are also influenced by personality.

Pre-and post-assessment design

Among many clinical intervention designs, pretest-posttest designs are the preferred method to compare participant groups and measure the degree of change occurring due to treatments or interventions. Cost, easiness of practice, and comprehensiveness are other benefits of pre-post tests for most practitioners [9].

So, we recommend a pre-and post-assessment design for a more straightforward and practical method under the solution-oriented strategy. Well-designed case studies such as observational epidemiology are often helpful in judging the effects of treatment by the bird's eye.

In the CKD study for improving negative feedback of the gut-kidney axis is essential. In that occasion, uremic dysbiosis and leaky gut are repaired first, and 24 h urine urinary protein, urinary urea, nitrogen, and β2- microglobulin, NAG, and urinary liver-type fatty acid-binding protein (L-FABP)/Cre and urinary NGAL/Cre for glomerular and tubular damages were also improved. The Maroni formula could calculate to estimate oral protein intake.

We can assess nutritional status by vitamins B1,2,12, folic acid, magnesium, copper, zinc, and TSAT. We also measured hemoglobin A1c, glycated albumin, triglyceride (mg/dL), LDL cholesterol (mg/dL), and HDL cholesterol (mg/dL) as metabolic parameters. Carnitine deficiency is checked by decreasing serum free carnitine level and increasing acylcarnitine/free carnitine ratio. Also, phosphorus, intact PTH, blood counts, electrolytes, liver enzymes, and uric acid were measured. All these markers are available in what is going inside the individual body during dietary therapy.

The patient participated in dietary therapy

A pack of low protein fermented genmai (LPFG) contained 240 kcal, but the protein content was only 0.2-0.3 g. One hundred and fifty g of white rice contains 3.8g of protein. So, we take 11.4 g of protein in three meals a day. When the patient eats three LPFG packages a day, they ingested 720 kcal and 0.9 g of protein. A LPFG pack contains 2 mg of potassium and 77 mg of phosphorus, and no detectable NaCl. The protein content of LPFG is less than 1/10 that of white rice, so we can expect a 10 g protein reduction by replacing staple foods with LPFG packages. It decreases 0.2g/kg protein when the body weight is 50 kg. We allow patients to eat preferred side dishes without solid limitations. So the patients could continue their dietary therapy by themselves [10].

The main weakness of the pre-and post-test design is that it cannot detect other possible causes of positive or negative results among the participants. Specific biomarkers give us insight.

Conflict of Interest

The author has not any COI to declare.

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