

# Antisecretory Factor–Inducing Therapy Improves Patient-Reported Functional Levels in Meniere’s Disease

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**Objectives:** The aim of this study was to evaluate the effectiveness of specially processed cereal (SPC) as a suitable adjunctive treatment for Meniere’s disease.

**Methods:** We performed a randomized double-blinded, placebo-controlled, crossover study in a tertiary referral center of patients who had a diagnosis of Meniere’s disease based on the guidelines of the Committee on Hearing and Equilibrium of the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS). The main outcome measure was the AAO-HNS Functional Level Scale (FLS).

**Results:** Thirty-nine patients completed the study without any reported complications. The mean pretreatment FLS score for the entire study cohort was 3.8 (median, 4; range, 1 to 6). The overall FLS score improved significantly ( $p < 0.001$ ), to 2.8 (median, 3), after SPC treatment. No patients showed worsening on the FLS during SPC or placebo treatment. Of the 39 patients, 23 showed improvement on the FLS, and no change was observed in the remaining 16. The median improvement on the FLS in these 23 patients was 2 points (mean, 1.7; range, 1 to 4). The mean FLS score after placebo cereal treatment was not significantly different from baseline ( $p = 0.452$ ), but was significantly higher than that after SPC treatment (mean, 3.7;  $p < 0.001$ ). The marginal difference observed between the baseline FLS score and the placebo FLS score was due to the fact that 5 patients reported 1-point improvements on the FLS after placebo treatment. Nevertheless, significantly fewer patients improved on placebo than on SPC ( $p < 0.001$ ).

**Conclusions:** Treatment with SPC appears to be well tolerated by most patients (91%) without any complications. More than half (59%) of the study cohort reported subjective improvement in functional level.

**Key Words:** antisecretory factor, cereal, endolymphatic hydrops, Meniere’s disease.

## INTRODUCTION

The myriad of treatments available to patients with Meniere’s disease (MD) and the varying responses to treatment underscore the lack of knowledge about its pathophysiology. It has been hypothesized that the symptoms of MD are secondary to endolymphatic hydrops. Several studies have focused on the function of the endolymphatic duct and sac in the pathogenesis of hydrops, and there is histopathologic evidence that suggests decreased absorption or stimulation of secretion of the endolymph in these tissues.<sup>1</sup>

Antisecretory factor (AF) is a 41 kd protein produced in the brain, gallbladder, lungs, kidneys, and intestine in response to infection. It has been postulated that AF acts as a modulator of water and ion transport by regulating chloride homeostasis and thereby counteracting excessive fluid secretion into the intestinal lumen. Interest in AF was spurred by the need to find a replacement for antimicrobial

growth promoters in pig feed, as these were banned throughout the European Union in 2006 because of concerns about the risk of inducing antibiotic resistance.<sup>2</sup> Antimicrobial growth promoters had been used in animal diets to improve growth performance and prevent the side effects of early weaning such as infectious gastrointestinal and respiratory diseases. Endogenous AF synthesis can be stimulated by dietary modifications in animals and humans. Ingestion of specially processed cereal (SPC) that was optimized for increasing endogenous AF synthesis was shown to significantly increase plasma levels of AF in clinical trials, and the levels remained raised for 4 weeks after termination of the trial.<sup>3</sup> Patients with long-standing symptoms of inflammatory bowel disease who received SPC reported improved clinical symptoms in comparison to a group of patients treated with placebo cereals.<sup>3</sup>

Hanner et al<sup>4</sup> hypothesized that the antisecretory properties of AF could improve symptoms by reduc-

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AAO-HNS FUNCTIONAL LEVEL SCALE<sup>5</sup>

Regarding my current state of overall function, not just during attacks (check the ONE that best applies):

- 1 My dizziness has no effect on my activities at all.
- 2 When I am dizzy I have to stop what I am doing for a while, but it soon passes and I can resume activities. I continue to work, drive, and engage in any activity I choose without restriction. I have not changed any plans or activities to accommodate my dizziness.
- 3 When I am dizzy, I have to stop what I am doing for a while, but it does pass and I can resume activities. I continue to work, drive, and engage in most activities I choose, but I have had to change some plans and make some allowance for my dizziness.
- 4 I am able to work, drive, travel, take care of a family, or engage in most essential activities, but must exert a great deal of effort to do so. I must constantly make adjustments in my activities and budget my energies. I am barely making it.
- 5 I am unable to work, drive, or take care of a family. I am unable to do most of the active things that I used to. Even essential activities must be limited. I am disabled.
- 6 I have been disabled for 1 year or longer and/or I receive compensation (money) because of my dizziness or balance problem.

ing endolymphatic hydrops. In their pilot study of 24 patients who took SPC over a 4-week period, 50% of patients reported improvement in severity of vertigo. That study also demonstrated the presence of immunoreactivity to AF, especially in the crista ampullaris, organ of Corti, Reissner's membrane, and stria vascularis, in rats fed with SPC. Immunoreactivity was negative in control animals. The aim of our present study was to evaluate the effectiveness of SPC as a suitable adjunctive treatment for MD.

## METHODS

*Ethical Considerations.* This study was approved by the Liverpool Local Research Ethics Committee (reference 09/H1016/95). All patients were provided with information about the study and gave full written informed consent.

*Participants.* This was a randomized double-blinded, placebo-controlled crossover study. Suitable patients were initially identified from general otolaryngology, audiology, and skull base clinics at University Hospital Aintree and Southport General Hospital. The patients were then screened by the research team, and those who had a diagnosis of MD with symptoms that persisted despite conventional treatment were eligible for inclusion. The diagnosis of MD was based on the guidelines of the Committee on Hearing and Equilibrium of the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS).<sup>5</sup> Only patients with MD who were exclusively managed medically were eligible for inclusion. Thus, patients who had undergone grommet insertion or chemical or surgical labyrinthectomy were excluded. In addition, those with a known allergy to barley malt products were excluded, as were those with celiac disease. All subsequent assessments and follow-ups were undertaken in the otolaryngology outpatient department at University Hospital Aintree.

*Interventions.* The SPC and the placebo cereal were supplied by Vitaflo International (Liverpool, England). The SPC was manufactured through a

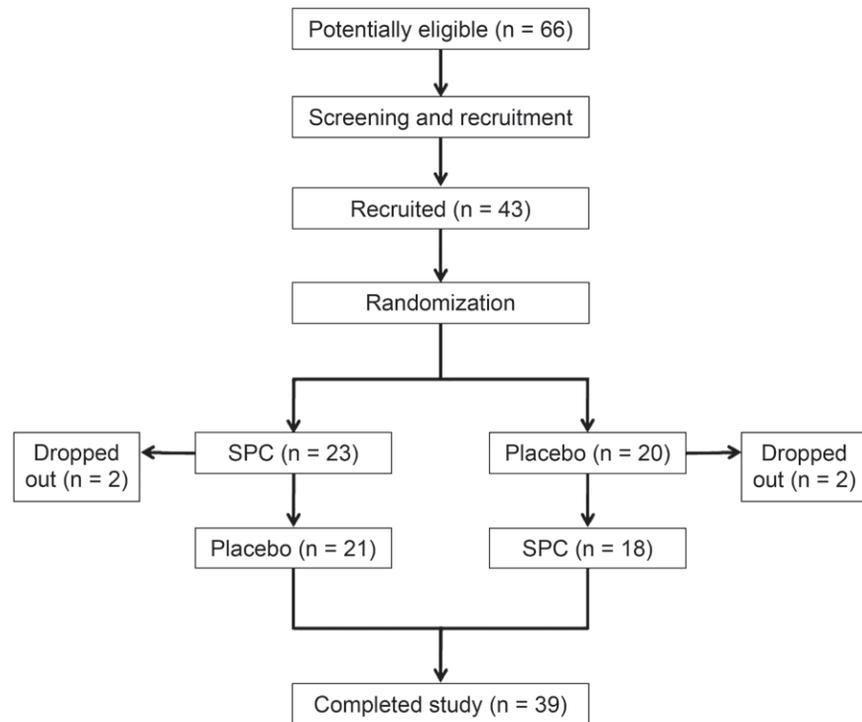
patented hydrothermal process that allows cereal kernels to reach an optimal concentration of specific amino acids and oligosaccharides, capable of inducing endogenous AF secretion.<sup>3</sup> The hydrothermally processed cereals were replaced by ordinary cereals to produce the placebo. The SPC and the placebo cereal appeared identical, and were provided free of charge to the patients, who were given sachets sufficient for a 3-month treatment period at a time. The cereals were consumed together with milk twice daily as a dietary supplement, at a dose of 1 gram per kilogram of body weight per day.

*Outcomes.* We used the Functional Level Scale (FLS) proposed by the AAO-HNS<sup>5</sup> as the primary outcome measure (see Table). A decrease in the FLS value represents a positive effect. The participants completed this questionnaire just before commencement of the trial (baseline) and after each treatment period. As a secondary outcome measure, they were also asked if there were any subjective changes (improved, worse, no change) in hearing, tinnitus, or dizziness at the end of each treatment period compared to baseline. These outcome measures were used throughout the clinical trial. We decided not to include pure tone audiometry, because previous clinical studies on SPC did not show any change in pure tone thresholds.<sup>4,6</sup>

*Sample Size.* Statistical support was provided by the University of Liverpool. According to sample size calculation using paired *t*-tests to obtain a desired accuracy or precision of  $\pm 5\%$  for 0.05 alpha value at 0.75 power at a 95% confidence interval, a study cohort of 30 participants were required to be randomized and complete the trial.

*Randomization.* Randomization of the participants was undertaken at Vitaflo International (by T. Partington). The patients were dispensed either active or placebo cereal according to a computer-generated randomization list. They received either SPC or placebo cereal for an initial 3-month period. Then, after a washout period of 2 weeks, the patients

**Fig 1.** Flowchart of study. SPC — specially processed cereal.



received the other treatment for another 3-month period. No changes were made in the patients' ordinary medication. The participants were reviewed in the otolaryngology outpatient department at the end of each treatment arm.

**Blinding.** Both SPC and placebo cereal were supplied by Vitaflo. The clinicians (including data collectors) and patients were blinded to the assignment of interventions during the clinical trial. The randomization list was only revealed after all participants had completed the study.

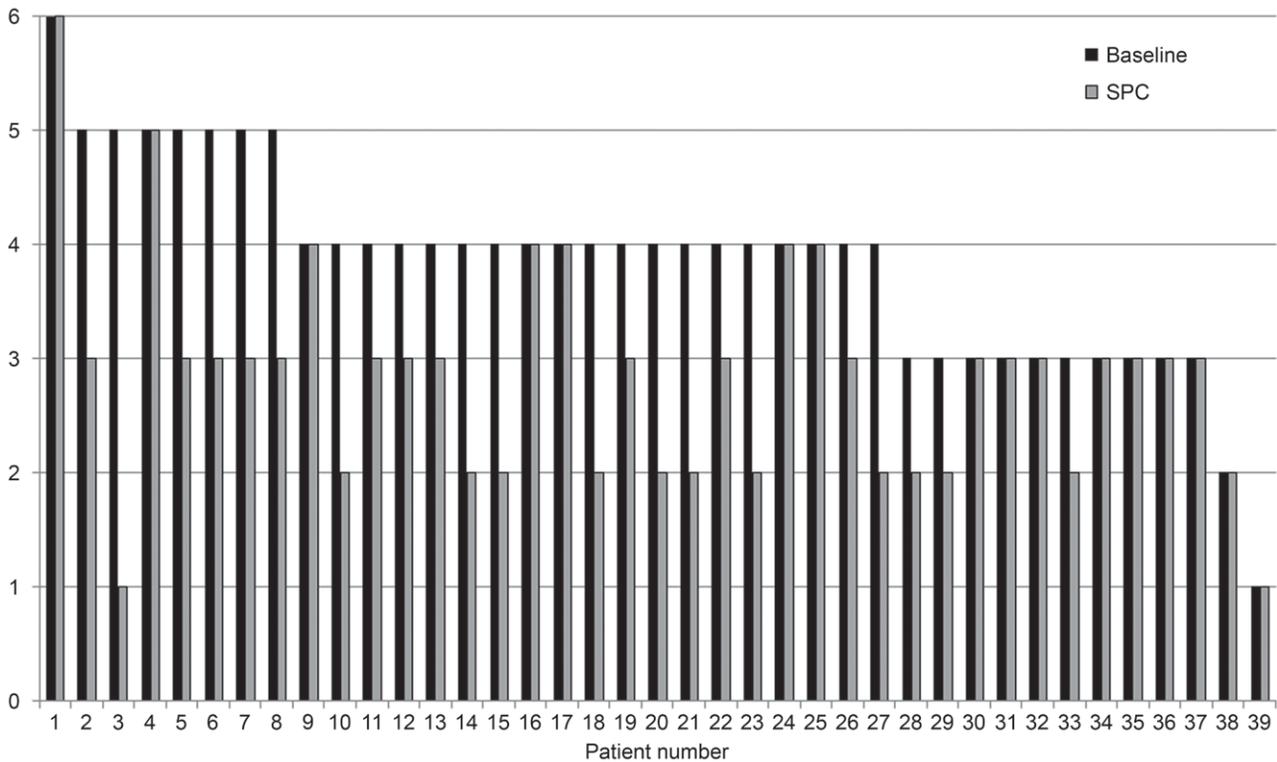
**Statistical Methods.** The mean values of the FLS scores prior to treatment and following every treatment were compared with a Wilcoxon signed-rank test. Fisher's exact test was used to analyze the secondary outcome measure. Statistical analysis was performed with SigmaPlot version 12 (Systat Software, Inc, Chicago, Illinois).

## RESULTS

This clinical trial was undertaken over a 10-month period in 2011. All participants in the study had a definite diagnosis of MD. A total of 66 patients were referred to the research team for assessment for suitability to enter the trial. Of the 23 excluded, 18 declined to participate; the most common reason cited was the inability to adhere to the twice-daily requirement to consume SPC (Fig 1). Of the 43 patients recruited into the trial and subsequently randomized, 4 did not complete the study and stat-

ed difficulty complying with the dietary regimen. The reasons given included unacceptable changes in bowel habits and time constraints. Two patients dropped out during the placebo and SPC treatment periods, respectively. These patients were excluded from the final analysis. The remaining 39 patients (23 female) completed the study without any reported complications. The mean age of the study cohort was 55 years (range, 22 to 80 years).

The mean pretreatment FLS score for the entire study cohort was 3.8 (median, 4; range, 1 to 6; confidence interval [CI], 0.29). The overall FLS score improved significantly ( $p < 0.001$ ), to 2.8 (median, 3; CI, 0.31), after SPC treatment. No patients had worse FLS scores at the end of SPC treatment. Of the 39 patients, 23 reported improvement on the FLS, and no change was observed by the remaining 16 (Fig 2). The median improvement on the FLS in these 23 patients was 2 points (mean, 1.7; range, 1 to 4; CI, 0.31). The mean FLS score (3.7; median, 4; range, 1 to 6; CI, 0.30) after the placebo cereal treatment was not significantly different from baseline ( $p = 0.452$ ), but it was significantly higher than the mean FLS score after SPC treatment ( $p < 0.001$ ). The marginal difference observed between the baseline and placebo FLS scores was due to the fact that 5 patients reported better FLS scores of 1 point each after placebo treatment (Fig 3). Nevertheless, the number of patients who improved on placebo was significantly lower than the number who improved on SPC ( $p < 0.001$ ).



**Fig 2.** Functional Level Scale scores of study cohort after use of specially processed cereal (SPC), compared to baseline.

Only patients who had improved FLS scores reported subjective improvement in their dizziness, hearing loss, or tinnitus. Of these 23 patients, 21 (91%) reported subjective improvement in dizziness during the SPC treatment period. Improvements in tinnitus and hearing were reported in 11 patients (49%) and 7 patients (30%), respectively. These subjective improvements in symptoms were reported in significantly more patients ( $p < 0.05$ ) after SPC treatment than after placebo treatment. No patients reported any improvement in hearing, tinnitus, or dizziness while on the placebo cereal. In fact, 2 patients reported worsening of their symptoms, although their FLS scores were unchanged from baseline.

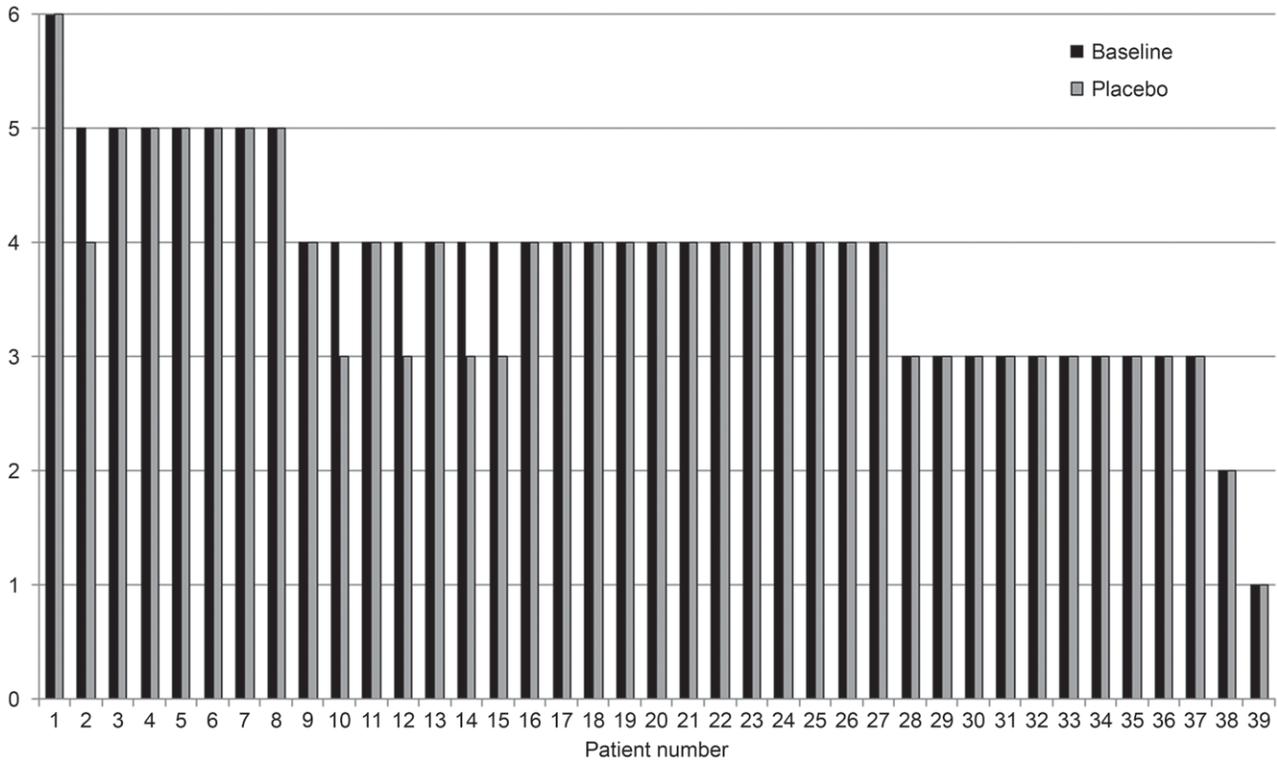
#### DISCUSSION

Meniere's disease is a common presentation to both audiovestibular and otolaryngology clinicians. The MD Society UK estimates a prevalence of up to 1 in 2,000 population. The impact of MD on the quality of life is not insignificant. The average FLS score of the present study cohort indicates that patients experience significant hindrance to normal daily activities. The myriad of treatments available underscores the inability to manage this chronic illness properly.<sup>7</sup> Nevertheless, our study has demonstrated the effectiveness of AF in improving both the functional level and the symptoms in patients with MD, confirming that an AF-inducing diet could be

useful in some MD patients and that AF could be involved in inner ear homeostasis. No patients had worsening of their symptoms with SPC, and there were no reported adverse reactions during the treatment period. Thus, SPC could be recommended to all patients for a trial period as a useful adjunct to the treatment ladder for MD.

Although clinical improvement was not observed universally, 59% of the study cohort reported a positive response to SPC, with an average improvement of 2 FLS points. This is a significant improvement that could result in patients' living a relatively symptom-free and productive lifestyle. The main symptomatic improvement was that of dizziness, followed by those of tinnitus and hearing loss. In a study by Hanner et al,<sup>6</sup> 27 patients were randomized to receive SPC for 3 months. More than half (52%) of the patients reported improvement on the FLS, with an average improvement of 3 FLS points. No changes in the pure tone audiogram average or speech audiometry tests were recorded after SPC treatment.

It was not possible to predict which patients would derive benefit from SPC, and 41% of patients in our study reported no improvement. The response to SPC was variable and was not related to the severity of the symptoms. The reason for this finding remains uncertain, but could be related to the variable bioavailability of AF following ingestion of



**Fig 3.** Functional Level Scale scores of study cohort after use of placebo cereal, compared to baseline.

SPC. Hanner et al<sup>4</sup> demonstrated that although the reduction of vertigo correlated significantly with serum AF activity in patients who reported improvement, serum AF activity was detected in some patients whose symptoms did not respond to SPC. A subsequent clinical trial by the same research group also noted that the response to SPC was variable and was unrelated to the severity of disease.<sup>6</sup>

The pathophysiology of MD remains debatable, and as such, the effect of AF on the disease is hypothetical. Gibson and Arenberg<sup>8</sup> postulated that a narrowed endolymphatic duct becomes obstructed by debris and causes accumulation of endolymph. As a result, an endogenous hormone called saccin is secreted to enhance the production of endolymph within the cochlea in an attempt to clear the obstruction. It is proposed that restoration of longitudinal flow initiates the attacks of vertigo (the “flushing theory”). Antisecretory factor is a potent modulator of water and chloride transport and thus has significant anti-inflammatory properties. It is possible that AF acts antagonistically to saccin to reduce endolymph production.

The notion that a relatively simple change in a food processing method can have a significant positive impact on symptoms is certainly attractive to patients, who are increasingly conscientious consumers of health care. Specially processed cereal does not contain any active compound, since the mode of

action is to stimulate endogenous production of AF, which is a naturally occurring endogenous protein. The fact that it is not a medical drug simplifies its use by, and accessibility to, patients. Nevertheless, it is recognized that consuming cereal flakes may not be to everyone’s preference and that taking SPC twice daily is not a small undertaking. A tenth of the patients recruited into this study dropped out, citing unacceptable changes in bowel habits and difficulty with compliance with the twice-daily regimen. Furthermore, the patients had to be maintained on SPC to derive benefit, as it would appear that the effects of AF were short-lived. All patients who had SPC first reported worsening on the FLS after switching to the placebo cereal.

The alternative to SPC may lie in Salovum egg yolk powder, which contains protein with antisecretory properties in a much higher (500 times) concentration than is found in normal hen eggs.<sup>9</sup> It is made by feeding hens with SPCs capable of inducing production of protein with antisecretory properties in the yolk, from which an egg powder is produced. In view of its apparent antisecretory and anti-inflammatory effects, Salovum egg yolk powder was given to children with diarrhea.<sup>10</sup> After 3 days of treatment, their diarrhea was significantly less frequent and severe than that of a group given placebo powder. It is possible that Salovum eggs or egg yolk powder could be a viable alternative to SPC in

the symptomatic management of MD. Further clinical trials correlating symptoms with serum levels of AF would be required to determine the amount of eggs that would need to be consumed.

#### CONCLUSIONS

Treatment with SPC appears to be well tolerated by most patients (91%) without any complications.

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More than half (59%) of the study cohort reported subjective improvement of MD in both functional level and symptoms of dizziness and tinnitus. The effect of AF may be short-lived, given that patients' symptoms worsened after they stopped using SPC. Antisecretory factor-inducing cereal may be a suitable therapeutic option in the armamentarium for treating MD.