

# ON THE ROLE OF DEPLETIVE TESTS: A REVIEW ANALYSIS

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Ménière's disease (MD) is an inner ear disorder of unknown cause that is characterized by fluctuating hearing loss, tinnitus, aural fullness, and episodic rotatory vertigo. The MD course is quite variable, and its etiology is largely unclear. The MD pathological feature is considered to be endolymphatic hydrops.<sup>1</sup> On the ground that MD could be the aural counterpart of glaucoma, being both associated with increased fluid pressure, Klockhoff and Lindblom in 1966<sup>2</sup> have proposed to test the possibility of reducing the intralabyrinthine pressure via an osmotic dehydration produced by glycerol, so that the glycerol test is largely used as non-invasive diagnostic procedure. The standard glycerol test consists of a per-orally administration of a single dose of glycerol (1.5 g/Kg body weight) on an empty stomach and to compare on pure-tone audiograms the threshold levels obtained before administration with that after one, two and three hours. The criteria of their study were a significant threshold improvement since one hour after glycerol intake with a maximum auditory improvement after two to three hours; an average auditory gain of 17 dB in the range 125-8000 Hz; an improvement in speech perception characterized by increase of speech intelligibility from 60% to 86%, and an improvement of loudness from 70 to 55 dB. According to these criteria they were able to define positivity of the test in the early, fluctuating stages of the disease and a negative one in the advanced stages.

Other investigators have reported on different timings for the analysis of a depletion test, such as a 27% of positivity after one hour and 74% after two hours,<sup>3</sup> or maximum effect after three hours,<sup>4</sup> whilst later on Klockhoff confirmed the previous experience of the maximum auditory improvement after two hours.<sup>5</sup>

Regarding the frequency range affected by the depletion test, Klockhoff and Lindblom identified it at the low frequencies; Snyder at 1000 Hz while decreasing toward the high frequencies;<sup>3</sup> and Swanson<sup>6</sup> confirmed the maximum effect at low frequencies with a relative decrease towards the high frequencies.

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From the above factors it may be possible to summarize as favorable indicators the low-tone hearing loss;<sup>2</sup> the 25-40 dB minimum hearing loss required in the range between 250-4000 Hz;<sup>3</sup> and the absence of any ack near the performance of the test.<sup>7</sup>

Recent investigations have reported that the homeostasis of endolymph is normally maintained without significant volume flow, leading to a local transport of ions with a water equilibrating system<sup>8</sup> owing to the osmotic gradient. New mechanisms for possible actions of glycerol may then be resumed in passive and active mechanisms. By passive mechanism, glycerol not only increases the osmotic pressure of the fluid in which is dissolved, *i.e.*, blood, but also the plasma osmolarity in cochlear capillaries of the stria vascularis, inducing endolymphatic diffusions into blood circulation and reducing pressure in hydropic labyrinth. By active mechanism glycerol would activate the ionic pump, increasing in the endolymphatic sac the secretion of the glycoproteins that would favor the endolymph absorption.

In clinical practice, the term *glycerol test* can be regarded as an 'umbrella term' for describing the effects that follow the administration of several different osmotic and diuretic drugs in reducing the hearing threshold.<sup>9</sup> For instance for the urea, which metabolizes to only a very small extent with a slow penetration into the inner ear, when orally administered at the dose of 25g/body weight, diluted in 100-200 ml of fruit juice, it has been reported 60% of positivity in MD patients.<sup>10</sup> When using for depletive test ethanol or mannitol, positive results were observed only occasionally, since mannitol induces a smaller rise in serum osmolality than glycerol due to less and slower penetration than glycerol, with vascular effects mostly consisting in vasodilatation.<sup>11</sup> Regarding Isosorbide, its effects have been described to last till four hours after oral administration, with 50% of positivity in MD.<sup>12</sup> Acetalazolamide, an inhibitor of carbonic anhydrase, influencing various cellular processes<sup>13</sup> and by reducing the degree of the experimentally endolymphatic hydrops.<sup>14</sup> An impletive effect has also been described for this drug when administered intravenously.<sup>15</sup> Furosemide has been shown to induce its potent natriuretic action on the saccule, as shown by a caloric test 40 minutes after its administration by the improvement of vestibular evoked myogenic potential (VEMP) amplitude.<sup>16</sup>

Nowadays, the interest for glycerol (or depletive tests) is focused on objectivating audiological and vestibular correlates with sensitivity and specificity on test models. It has become clear that the best method to correlate the functional early hearing and vestibular improvement after drug administration glycerol will be to associate to the subjective pure tone and speech audiometry assessment also more objective correlates. In this regard, in the recent years among these latter have been proposed electrocochleography (EcochG), otoacoustic emissions and distortion products (DPOAE), vestibular evoked myogenic potential (VEMP) and MRI.

Coats *et al.* found a highly significant relationship between an enlarged Summating Potential (SP) and a positive glycerol test.<sup>17</sup> Fukuoka has compared gadolinium contrast-enhanced MRI, glycerol test, and the EcochG SP/AP ratio, showing hydrops positivity in 88-90% at the MRI, 55% at the glycerol test and 60% at EcochG.<sup>18</sup>

When pure-tone audiometry and distortion products and otoacoustic emissions were compared before and one, two and three hours after glycerol intake, a prevailing positivity of audiometric findings was found.<sup>19</sup>

The comparison of pure tone audiometry with VEMPs before and two hours after glycerol intake has also shown that to an improvement of the auditory threshold of 50% corresponded a significant amplitude increase of VEMP p1-n1 in 39,3%.<sup>20</sup>

In the last years, Basel has proposed a new method to evaluate in the pure tone audiometry the threshold shift during the glycerol test, for obtaining a greater sensitivity.<sup>9</sup> Instead of considering all the frequencies' shift, he introduced the Aggregate Thresholds Shift concept (ATS), *i.e.*, the individual evaluation the pure tone audiometry results: at 125 Hz; at 500-1000-3000 Hz; and at 4000-6000 Hz, noticing that the greatest positive effect was localized in the low-middle range. According to these criteria, the false positive rate would be 4,5% for a 30-40 dB shift and only 0.8% for a 50 dB shift.

## Conclusions

The use of a standard glycerol test still has a value in the diagnostic of MD since it can be helpful for assessing the stage of the disease and, eventually, the most appropriate initial medical treatment. However, in order to increase its sensitivity and specificity it would be mandatory to also use objective tests other than the simple subjective pure-tone or speech audiometry. The routine use, for example, of MRI will in this regard contribute to definitely exclude all the other conventional tests used for the diagnostic process in case of MD.

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