Growth Effects of the Warner Protocol for Children with Down Syndrome

Robert J. Thiel, Ph.D., N.M.D.[1]

Abstract

Children with Down syndrome tend to be short. There is no known effective medical intervention to address height for these children. Since 1986, Dr. F. Jack Warner has specialized in seeing people with Down syndrome. Warner uses an unconventional protocol which includes interventions such as nutrition (HAP Caps, flaxseed oil, N, N-dimethylglycine), physical therapy, ophthalmology, and conventional medicine. Warner claims his interventions can help make children with Down syndrome more like non-Down's children. The purpose of this investigation was to determine if the Warner protocol could improve growth for children with Down syndrome.

Method: This investigation used a pretest-posttest, natural control group design. An independent investigation of a random sample of Warner's records was performed. Height and weight data, based on age, were compared against growth grids for Down's children for two visits to the Warner House: the initial measurement and the final measurement.

Results: An analysis of the sample suggests that the combined interventions appear to significantly improve height ($p < .001$) for children with Down syndrome. The average (mean) height percentile grew from 63.4 to 76.0 (gender was not a significant factor). Although weight percentile went from 52.2 to 56.2 ($p = .209$), there was a significant difference in gender with the male percentile increasing from 45.2 to 53.7 ($P = .035$), while female percentile decreased from 60.9 to 59.3 ($p = .755$).

Conclusion: Nutrition is the most likely intervention to be credited for improving height. A prospective study to test this position should be performed.

1. 1248 E. Grand Avenue, Suite C, Arroyo Grande, CA 93420

Introduction

Trisomy 21, more commonly referred to as Down syndrome, is a genetic disorder which is present in approximately 1 out of every 700 live births. Although there is a consensus that Down syndrome is caused by total or partial triplication of the 21st chromosome, the underlying causes that interfere with normal chromosomal duplication are a matter of some dispute.[1] While there is no recognized effective medical intervention for trisomy 21, there are treatments for complications such as cardiovascular disorders, hypothyroidism, and infections.[2] Although some physicians and a few scientists are now recommending a variety of nutritional interventions as part of a treatment program for those with trisomy disorders, the prevalent medical opinion appears to be that nutrition is ineffective.[3,4]

One of the well documented characteristics of Down syndrome is impaired growth. Down's patients tend to be short .[5] At age 18 the median average female with Down Syndrome grows to approximately 4'9 1/2", whereas the average male grows to approximately 5' 1/2".[6]

Since 1986, Dr. F. Jack Warner (MD) has specialized in seeing non-institutionalized patients with trisomy 21. He is associated with the Warner House, a non-profit organization for the study and treatment of trisomy disorders. The Warner House uses a multi-disciplinary approach with interventions including nutrition, medicine, physical therapy, and opthamology. Dr. Warner has seen thousands of patients who suffer from trisomy disorders, but because many of these patients are seen only at traveling clinics, follow-up records do not exist on all the patients. All Warner House patients, or their legal guardians, sign a consent form allowing data to be included in published reports.

Although Dr. Warner has presented oral and written information on these interventions to a variety of organizations which deal with trisomy disorders [i.e. 7,8], he has not published any peer-review articles in recent years. This has been a basis for criticism of Dr. Warner's work: "There have been no structured studies of the effects of 'HAP CAPS'. Warner claims that records on 4,200 'patients' who have received 'HAP CAPS' are kept, yet admits that no attempt has been made to analyze them in any systematic way. Neither have these records been made available for others to analyze."[4] This investigation is intended to determine if the Warner interventions might have any efficacy on growth and to determine if further research would be warranted.

Materials

The nutritional interventions used by Warner House are a combination of a multiple vitamin/mineral formula called "HAP Caps" (HAP stands for Health and Progress), plus flaxseed oil (1-3 teaspoons normally recommended), N,N-dimethylglycine (an amino acid derivative, with 30-500 mg normally recommended), and sometimes other nutritional substances. Each HAP Caps capsule contains beta carotene 2000 I.U., vitamin B_1 6.25 mg, vitamin B_2 6.25 mg, vitamin B_3 6.25 mg, calcium pantothenate 25 mg, vitamin B_6 6.25 mg, vitamin B_{12} 1.25 mcg, vitamin C 100 mg, vitamin D_3 33 I.U., biotin 25 mcg, vitamin E 33 I.U., choline 50 mg, folic acid 50 mcg, inositol 5 mg, PABA 75 mcg, cobalt 5 mcg, iron 5 mg, manganese 125 mcg, copper 40 mcg, molybdenum 75 mcg, selenium 7.5 mcg, zinc 2.5 mg, organic iodine (from kelp) 18.75 mcg, rutin (a bioflavonoid) 25 mcg, quercitin (a bioflavonoid) 6 mg, liver extract (bovine) 6.25 mg, betaine hydrochloride 1.8 mg, ox bile 3.6 mg, pancreatin (supplies enzymes) 2.8 mg, co-enzyme Q_{10} 8 mg, and the amino acids glutamine 75 mg, taurine 4 mg, and tyrosine 55 mg—the number of capsules recommended varies by patient weight[8] and normally ranges from 2-12 per day (approximately 1 HAP Cap per 10 lbs.). HAP Caps have a similar composition to the 'U' series nutrients that Dr. Turkel pioneered decades previously (which Turkel safely used for many children with Down syndrome).[3] The Warner House recommends physical therapy for all trisomy patients. It also advises that all with trisomy 21 disorders avoid cow's milk products. Ophthamological interventions, interventions for infections, thyroid medications, and other conventional medical interventions are recommended when indicated.

Method

At Warner House, height and weight data is initially recorded from a medical scale (containing a height attachment) by a trained nurse; follow-up data is normally provided by the same nurse or sometimes is provided by the parents. This specific investigation used a pretest-posttest, natural control group design. Height and weight data (in Warner files), based on age, were compared against growth grids for Down's children[6] for two visits to the Warner House: the initial measurement and the final measurement (the last measurement in the files). "Because of the short stature and abnormal growth pattern in children with Down syndrome, it is preferable to use the growth grids developed specifically for this disorder to evaluate the child's stature".[6] Those grids are based on actual non-institutionalized children with Down syndrome, thus serve as a natural control group for this investigation.

Warner made all of his non-archived files available. Files were randomly selected using a random number table. Files were accepted if they had initial and final age, combined with an initial and final measurement of height and/or weight. Files for patients with ages above 16.0 were excluded. Of the selected files, 84 met the criteria for age and height and 90 met the criteria for age and weight. Approximately

1,500 non-archived records were estimated to be available which met these criteria.

This investigation was pre-approved by an independent review board.

Results

84 of the records selected contained before-and-after height and age information as shown in Table 1. (below)

The total data was analyzed utilizing a paired T-test. With a 95% confidence level the mean difference of improvement is 6.3% to 18.9%; T-value 3.99; p-value <.001. Gender differences were not statistically significant. The average (mean) age at the initial appointment was 2.2 years (range 1 week to 10.2 years) whereas the average age at the final appointment was 5.3 years (range 6 months to 16.0 years).

90 of the records selected contained before-and-after weight and age information as shown in Table 2. (below)

The total data was analyzed utilizing a paired T-test. With a 95% confidence level the mean difference of improvement is -2.3% to 10.3%; T-value 1.27; p-value =.209. In contrast to height data, gender differences in weight appeared to be significant—the males significantly increased (p=.035), whereas the females slightly decreased (though the decrease was not statistically significant, p=75.5). The average (mean) age at the initial appointment was 2.3 years (range 1 week to 10.5 years) whereas the average age at the final appointment was 5.3 years (range 6 months to 16.0 years).

Discussion

The advocacy of an interdisciplinary approach for Down syndrome patients predates Dr. Warner's involvement.[9] The fact that children undergoing the Warner protocol showed significant improvement in height using age-adjusted Down's grids seems to suggest that interventions such as those used by Warner are helpful when begun at an early age. Of various measures, "the measure of growth and body composition in the child, is the most ob-

Table 1. Height.

Gender	N	Attribute	Initial Mean as Percentile on Down's Grid	Final Mean as Percentile on Down's Grid
Female	36	Height	63.1%	73.6%
Male	48	Height	63.6%	77.8%
Total	84	Height	63.4%	76.0%

Table 2. Weight.

Gender	N	Attribute	Initial Mean as Percentile on Down's Grid	Final Mean as Percentile on Down's Grid
Female	40	Weight	60.9%	59.3%
Male	50	Weight	45.2%	53.7%
Total	90	Weight	52.2%	56.2%

jective indicator of that child's nutritional status".[10]

It is of interest to note that the height percentile of the average child in this study began at 63.4. If normal growth patterns were to be expected to occur, from a statistical point of view, the height for these children should have tended downwards (towards the 50th percentile). Instead, these children grew. As the upper border on growth (100.0-63.4) was smaller than the lower border on growth (63.4-0.0), this makes the results of this investigation of even greater interest. While this investigation does not prove that growth of children with Down syndrome will always improve under the Warner protocol, it does show that most of those who followed it for at least some period did grow beyond what would normally have been expected.

The weight results were somewhat unusual. The average female weight percentile dropped from 60.9 to 59.3 (statistically insignificant), while the average male weight percentile increased from 45.2 to 53.7 (statistically significant). While Warner's records do not contain any body mass index calculations, since the growth in height exceeded the growth (or reduction in the case of the female subjects) in weight, it is reasonable to conclude that the average BMI probably reduced. The initial mean age for males (2.1 years) and females (2.5 years) was fairly close as was the final mean age for males (5.1 years) and females (5.6 years), thus weight changes are not explained simply by age differences between the sexes.

The use of nutrition for persons with Down syndrome has been repeatedly challenged[4,11,12] yet there is evidence in the literature that supports that portions of the interventions provided by the Warner House may have some affect on those with trisomy 21. Even some mainstream researchers have recommended vitamin and mineral supplementation for those with Down syndrome,[13,14] but they have not apparently involved growth data. There have been some reports of height and weight based upon diet [i.e. 15], for Down children, however, and some ongoing research involving growth hormone (GH) .[16]

It has been speculated that thyroid abnormalities may increase the risk of developing dementia[17] (Down patients often develop an Alzheimer's like dementia as they age[2]). Down syndrome patients have increased incident of thyroid disorders, [1,18,19] thus thyroid medications, as recommended by the Warner House, would be expected to have at least some symptomatic improvement[20] (though this investigation did not measure symptomatic improvement). Other researchers have concluded that thyroid medications, when confirmed by testing, do help reduce problems faced by those Down syndrome patients[21] and even that "It would seem evident that Down syndrome individuals with hypothyroid disease benefit significantly from thyroid replacement therapy".[22] The primary thyroid hormone (T1) is composed of iodine and tyrosine[23] and since some Down syndrome patients appear to have difficulties converting phenylalanine into tyrosine,[24] it appears logical that supplemental tyrosine may help these patients. Warner's protocol does include iodine which has been shown to be helpful for some thyroid problems[25] and the amino acid tyrosine.

Warner's protocol also includes the mineral zinc. Down syndrome patients often have below normal plasma levels of zinc.[26,27] Supplementation with zinc has been shown to increase DNA synthesis in Down patients with low zinc levels,[28] Since one study found that zinc reduced TSH by 34% for hypothyroid Down syndrome patients,[29] it is possible that the supplemental zinc may also positively affect some Down patients.[30] It has been speculated that zinc deficiency may be a cause of subclinical hypothyroidism in Down syndrome children.[29] Low iodine levels, as well as low zinc levels, can sometimes be associated

with short stature.[25,31] A study involving supplemental zinc for stunted infants concluded that it can increase growth rate to that of non-stunted infants.[32] In addition, it has been found that children with Down syndrome become deficient in a zinc-containing insulin-like growth factor type 1 (IGF-1) after one year of age.[33] Not only has supplementation with zinc been shown to increase IGF-1, one study found that zinc supplementation increased growth in 15 of 22 children with Down syndrome.[33]

Triplication of the 21st chromosome causes metabolic disturbances which lead to an accumulation of various metabolic precursors and a deficiency of certain end products—this is one of the basic reasons why nutritional interventions make scientific sense for persons with Down syndrome.[3] Superoxide dismutase and alpha and beta-interferon levels are elevated[2,34] (interestingly people who live past 100 appear to have lower levels of superoxide dismutase than the general elderly population[35]). It is of interest to note that even though zinc is a constituent in cytoplasmic superoxide dismutase, zinc supplementation has been found to reduce superoxide dismutase levels in non-Down syndrome female subjects;[36] it has been hypothesized that supplemental vitamin E may reduce superoxide dismutase-generated oxidative damage in Down syndrome patients.[37] Levels of alanine, cysteine, isoleucine, lysine, phenylalanine, and threonine seem to be elevated, yet tyrosine, folate, manganese, iron, thiamin, vitamin B_{12}, vitamin C, vitamin E, and selenium levels appear to depressed (additional nutrients have also been implicated).[3,24,26,38,39] Some minerals, such as calcium and magnesium, seem to be higher in non-Down patients in some areas of the body, yet lower in others areas.[3,24] Selenium itself affects thyroid metabolism,[40] it is possible that supplementing with it may have some benefit. Long-chain omega-6 polyunsaturated fatty acid concentrations appear to be higher in Down syndrome patients.[41] Down syndrome patients have an additional copy of the gene that codes for cystathione synthase, which greater increases production of that enzyme and results in lower levels of homocysteine than others have, as well as lower incidence of atherosclerosis.[42] Folate metabolism affects homocysteine production and supplementation with folate is being investigated to see if it may help normalize height in infants with Down syndrome;[43] supplementation with a combination of nutritional antioxidants to help normalize height is also being investigated.[43] It has been speculated that the alteration of the conjunctival epithelium in patients with Down syndrome may be due to altered metabolism of vitamin A;[44] a study involving young, non-Down children found that supplemental vitamin A improved the linear growth of children with very low serum retinol levels.[45] Disorders of vitamin D metabolism have also been speculated for Down patients,[3,46] and since vitamin D does affect bone development, it does play a role in height.[47]

Down patients are more susceptible to certain ophthalmological problems than the general public (most notably strabismus) which leads to distortion of vision.[48] Early ophthamological interventions, such as provided by Warner House, could be expected to lead to improved vision. It does not seem likely, though, that this would affect height or weight.

Physical therapy, such as recommended by Warner House, could be expected to improve muscle tone, which this study did not assess. Some reports suggest that physical therapy could have some effects on appearance and intelligence of those with Down syndrome, especially when used as part of a multidisciplinary approach,[49-50] but no controlled studies on height have been found.

It should be noted that Warner is not the only health professional involved with trisomy 21 to advocate an interdisciplinary

approach, with the resultant combined protocols, to best benefit Down patients. Others, while not necessarily advocating nutrition, feel that an interdisciplinary approach is likely to be of the most benefit to Down patients.[51]

Conclusion

Although this investigation was preliminary, it appears that there is some efficacy in the Warner protocol regarding height. As the Warner protocol combines nutrition with physical therapy, medicine, and ophthalmology, it is not possible to statistically segregate the impact of any one of those interventions. It is possible that all of the interventions may work synergistically to improve height or that one or more interventions on its own has the most (or the entire) effect. There is at least some supporting evidence in the literature for nutrition being able to influence growth. A prospective study would be needed in order to assess the possible impact of any single intervention. This investigator believes that the data in this paper favorably support the need for such a study.

Acknowledgements

The investigator wishes to thank Steve Rein, Ph.D., Statistics Department, California Polytechnic State University, San Luis Obispo for his assistance in this project.

References

1. Cotran RS, Kumar V, Collins T. *Pathologic Basis of Disease*, 6th ed. WB Saunders, Phil., 1999
2. Kissane JM. *Anderson's Pathology*, 9th ed. CV Mosby Co., St. Louis, 1990.
3. Turkel H, Nusbaum I. *Medical Treatment of Down Syndrome and Genetic Diseases*, 4th ed. Ubiotica, Southfield (MI), 1985.
4. Sacks BI, Buckley RF. Multi-nutrient formulas and other substances as therapies for Down syndrome: an overview. *Down Syndrome News and Update*, 1998;1(2):70-83.
5. Toldeo C, Alembik Y, Aguirre JA, Stoll C. Growth curves of children with Down syndrome. *Ann Genet*, 1999; 42(2):81-90; 6.
6. Van Dyke DC, Lang DJ, Heide F, van Duyne S, Soucek MJ, editors. Standardized anthropometric techniques. In *Clinical Perspectives in the Management of Down Syndrome.* Springer-Verlag, NY, 1990: 230-237.
7. Warner FJ, Stephens C. Metabolic supplementation for correction of raging free radicals in trisomy 21. *Presentation at the International Down's Conference.* Madrid, Spain, 1997.
8. Warner FJ. *A Quiet Population Demands Good Health.* Warner House, Fullerton (CA), 1993
9. Connolly B, Russell F. Interdisciplinary early intervention program. *Phys Ther*, 1976; 56(2): 155-158.
10. Baer MT, Waldron J, Gumm H, Van Dyke DC, Chang, H. Nutrition assessment of the child with Down syndrome. In Clinical Perspectives in the Management of Down Syndrome. Springer-Verlag, NY, 1990: 107-125.
11. Dwyer J. Fertile fields for fads and frauds: questionable nutritional therapies. *NY State J Med*, 1993: 105-108.
12. Pruess JB, Fewell RR, Bennett FC. Vitamin therapy and children with Down syndrome: a review of research. *Except Child*, 1989; 55(4): 336-341.
13. Luke A, Sutton M, Schoeller DA, Roizen NJ. Nutrient intake and obesity in prepubescent children with Down syndrome. *J Am Diet Assoc*, 1996; 96(12): 1262-126.7
14. Reading CM. Down's syndrome: nutritional interventions. *Nutr Health*, 1984; 3(1-2):91-111
15. Hopman E, Csizmada CG, Bastiani WF, Engels QM, de Graaf EA, le Cessie S, Mearin ML. Eating habits of young children with Down syndrome in The Netherlands: adequate nutrient intakes but delayed introduction of solid food. *J Am Diet Assoc*, 1998; 98(7):790-794
16. Lantos JD. Growth hormone therapy for Prader-Willi and Down syndromes: a post-modern medical dilemma. *Growth Horm*, IGF Res 2000 Apr;10 Suppl B:S93-94
17. Murray M, Pizzorno J. Alzheimer's disease. In *Encyclopedia of Natural Medicine.* Prima Publishing, Rocklin (CA), 1991:128-135
18. Prasher VP. Down syndrome and thyroid disorders: a review. *Downs Syndr Res Pract*, 1999; 6(1):25-42
19. Karlsson B, Gustafsson J, Hedov G, Ivarson SA, Anneren G. Thyroid dysfunction in Down's syndrome: relation to age and thyroid antibody. *Arch Dis Childhood*, 1998; 79: 242-245.
20. Murray L, Kelly GL, editors. *Physician's Desk Reference*, 55th ed. Medical Economics, Montvale (NJ), 2001
21. Abassi V, Coleman M. A preventative medicine report on Down's syndrome and hypothy-

roidism. *Down's Syndr*, 1984; 7(2):1-2
22. Van Dyke DC, Van Dyke S, Lowe O, Heide F. Alternative and controversial therapies. In *Clinical Perspectives in the Management of Down Syndrome.* Springer-Verlag, NY, 1990:208-216
23. Guyton AC, Hall JE. *Textbook of Medical Physiology*, 9th ed. WB Saunders, Phil.,1996
24. Werbach MR. *Textbook of Nutritional Medicine.* Third Line Press, Tarzana (CA), 1999
25. Hetzel BS, Clugston GA. Iodine. In *Modern Nutrition in Health and Disease*, 9th ed. Williams & Wilkins, Balt.,1999:253-264
26. Hamilton K. Down syndrome: selenium supplementation and trace elements. *Clinical Pearls Currents*, 1994; 4(3):46
27. Sherman AR. Zinc, copper and iron nutriture and immunity. *J Nutr*,1992;122:604-609
28. Stabile A, Pesaresi MA, Stabile AM, Pastore M, Sopo SM, Ricca R, Segni G. Immunodeficiency and plasma zinc levels in children with Down's syndrome: a long-term follow-up of oral zinc supplementation.*Clin Immunolog Immunopath*, 1991;58:207:216
29. Bucci I, Napolitano G, Guiliani C, Lio S, Minnucci A, DiGracomo F, Calabrese G. Zinc sulfate supplementation improves thyroid function in hypozincemic Down children. *Biol Trace Elem Res*, 1999;67(3):257-268
30. Chandra RK, McBean LD. Zinc and immunity. *Nutr*, 1994;10(1):79-80
31. King JC, Keen CL: Zinc. In *Modern Nutrition in Health and Disease*, 9th ed. Williams & Wilkins, Balt.,1999:223-239
32. Umeta M, West CE, Haider J, Deurenberg P, Hautuast JG: Zinc supplementation and stunted infants in Ethiopia: A randomized controlled trial. *Lancet*, 2000;355:2021-2026
33. Napolitano G, Palka G, Grimaldi S, Giuliani C, Laglia G, Calabreese G, Satta MA, Neri G, Monaco F: Growth delay in Down's syndrome and zinc supplementation. *Amer J Med Genetics*, 1990; Supp 7: 63.
34. Teksen F, Sayli BS, Aydin A, Sayal A, Isimir A: Antioxidant metabolism in Down syndrome. *Biol Trace Elem Res*, 1998;63(2):123-127
35. Anderson HR: Lower activity of superoxide dismutase and high activity of glutathione reductase in erythrocytes from centenarians. *Age Aging*, 1998; 27: 643-648.
36. Abdallah SM, Samman S: The effect of increasing dietary zinc on the activity of superoxide dismutase and zinc concentrations in healthy female subjects. *Eur J Clin Nutr*, 1993;47:327-332
37. Sylvester PE: Ageing in the mentally retarded. In *Scientific Studies in Mental Retardation*. MacMillian, London, 1984:259-277
38. Anneren G, Magnusson CG, Nordvall SL: Increase in serum concentrations of IgG2 and IgG4 by selenium supplementation in children with Down's syndrome. *Arch Dis Children*, 1990; 65: 1353-1355.
39. Heggarty HJ, Ball R, Smith M, Henderson MJ: Amino acid profile in Down's syndrome. *Arch Dis Childhood*, 1996; 74: 377-349.
40. Kralik A, Eder K, Kirchgessner M: Influence of zinc and selenium deficiency on parameters related to thyroid metabolism. *Hormone Metabol Res*, 1996; 28: 223-226.
41. Pastor, MC, Sierra C, Dolade M, Navarro E, Brandi N, Cabre E, Mira A, Seres A: Status of erythrocytes of Down's syndrome patients. *Clin Chem*, 1998; 44(5): 924-929.
42. Scott J, Weir D: Homocysteine and cardiovascular disease. *Qtrly J Med*, 1996;89:561-563
43. Elliot P: Proposed randomized, controlled trial of the effects of antioxidants and folinic acid supplementation on the mental development, growth, and health of children with Down syndrome. *Down Syndrome Medical Interest Group Meeting*, San Diego, July 8, 2001
44. Filippello M, Cascone G, Zagami A, Scimone G: Impression cytology in Down's syndrome. *Br J Opthalmol*, 1997; 81(8): 683-685.
45. Hadi H, Stoltzfus RJ, Dibley MJ, Moulton LH, West KP, Kjolhede CL, Sadjimin T: Vitamin A supplementation selectively improves the linear growth of Indonesian preschool children: results from a randomized controlled trial. *Am J Clin Nutr*, 2000; 71: 507-513.
46. Center J, Beange H, McElduff A: People with mental retardation have an increased prevalence of osteoporosis. *Am J Ment Retard*, 1998; 103(1): 19-28
47. Holick MF. Vitamin D: In *Modern Nutrition in Health and Disease*, 9th ed. Williams & Wilkins, Balt.,1999:329-345
48. Fierson WM: Opthalmological aspects. In *Clinical Perspectives in the Management of Down Syndrome.* Springer-Verlag, NY, 1990:27-54
49. Gibson D, Harris A: Aggregated early intervention effects for Down's syndrome persons: patterning and longevity of benefits. *J Ment Defic Res*, 1988; 32(Pt 1): 1-17.
50. Limborck GJ, Fisher-Brandies H, Avalle C: Castillo-Morales' orofacial therapy: treatment of 67 children with Down's syndrome. *Dev Med Child Neurol*, 1991;33(4):296-303.
51. Van Dyke DC, Heide F: Interdisciplinary approaches. In *Clinical Perspectives in the Management of Down Syndrome.* Springer-Verlag, NY, 1990:167-170.