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Treatment of Obstructive Airway Disease With a Cysteine Donor Protein Supplement*

A Case Report *

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Oxidant/antioxidant imbalance can occur in obstructive airways disease as a result of ongoing inflammation. Glutathione (GSH) plays a major role in pulmonary antioxidant protection. As an alternative or complement to anti-inflammatory therapy, augmenting antioxidant protection could diminish the effects of inflammation. We describe a case of a patient who had obstructive lung disease responsive to corticosteroids, and low whole blood GSH levels. After 1 month of supplementation with a whey-based oral supplement designed to provide GSH precursors, whole blood GSH levels and pulmonary function increased significantly and dramatically. The potential for such supplementation in pulmonary inflammatory conditions deserves further study.

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Key words: glutathione; inflammation; oxidative stress; supplementation

Abbreviations: ELF = epithelial lining fluid; GSH = glutathione; GSH-Px = glutathione peroxidase; PFT = pulmonary function test; ROS = reactive oxygen species

Evidence of oxidant/antioxidant imbalance has been demonstrated in obstructive airway disease.^{1,2} Continued lung inflammation with the mobilization and activa-

tion of neutrophils, macrophages, and eosinophils and their release of free oxygen radicals and other reactive oxygen species (ROS) is a source of oxidative stress. In addition to the direct effects of such ROS on cell membranes, DNA, and proteins, breakdown products act as signals perpetuating the inflammatory cascade. Glutathione (GSH) and the GSH system play a key role in protecting against the effects of ROS.^{3,4} Modulation of the oxidant/antioxidant status in obstructive airway disease, primarily aimed at enhancement of the GSH system, has been limited by difficulties in delivery of an effective substrate.^{2,3,5} We describe the response to an oral, whey-based supplement designed to supply GSH precursors.

CASE REPORT

A 40-year-old woman of North African origin was followed by the pulmonology service at a tertiary care hospital in 1997. Her medical history was significant for Hodgkin's lymphoma, diagnosed 27 years earlier and treated with radiation and chemotherapy. She had a 25-pack-year smoking history and had quit smoking in 1994. In 1995, she received a diagnosis of mild valvular heart disease (aortic and mitral regurgitation). At that time (time 1), pulmonary function tests (PFTs) suggested mild airflow obstruction (Fig 1); bronchodilators were not prescribed. In 1997 (time 2), she was admitted to hospital with a virally induced exacerbation of obstructive lung disease as well as mild heart failure. She improved with diuretics, bronchodilators (salbutamol and ipratropium bromide), and oral prednisone, 20 mg/d. She was discharged taking a tapering course of prednisone.

When seen in follow-up 1 week later (time 3), she had suffered an exacerbation of her respiratory symptoms (shortness of breath, wheeze, chest tightness, and excessive mucus production) coincident with cessation of prednisone. Prednisone was prescribed again.

She returned 2 weeks later (time 4) with significant symptomatic improvement while still taking systemic corticosteroids and regular bronchodilators (salbutamol metered-dose inhaler and ipratropium bromide metered-dose inhaler qid). An attempt was made to discontinue prednisone. When the patient was seen 1 month later (time 5), her symptoms had returned. At that time, review of her history revealed no environmental insult that could account for her deterioration. Additionally, serum IgE was 52 kU/L (laboratory control, 0 to 100 kU/L), and both allergen skin testing and *Aspergillus* precipitins testing were negative. A further course of oral prednisone was prescribed (40 mg/d initially; tapering over 1 month).

Four months later (time 6), the patient returned to clinic independently, having begun taking HMS90 (Immunocal; Immunotec Research Ltd; Vaudreuil, Quebec, Canada), a whey-based protein supplement (10 g bid), 1 month before. She had heard that the product could be helpful in inflammatory conditions, and had started taking the product of her own accord. She reported a remarkable improvement in her respiratory status and had discontinued all inhalers and steroids, and was not taking any other supplements, medications, or over-the-counter therapies. She was asked to discontinue the Immunocal, and within 3 months her symptoms returned. PFTs were performed at this time (time 7). She then restarted Immunocal of her own accord, and 1 month later (time 8), PFTs were again assessed. Additionally, whole blood GSH levels were measured before and 1 month after therapy was reinitiated, using a modification of the method previously described.^{6,7} Again, a remarkable improvement in both symptoms and PFTs was noted (Fig 1). In addition, the total lung capacity increased from 3.91 L at time 7 to 5.00 L at time 8, and the residual volume/total lung capacity ratio fell from 33 to

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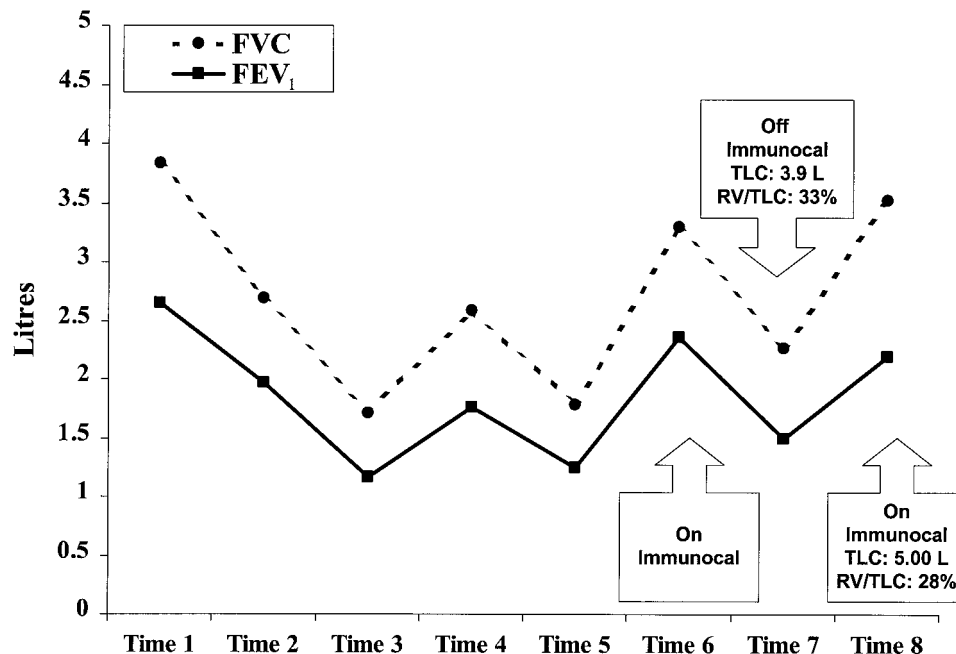


FIGURE 1. Tracking of the pulmonary function values over time. TLC = total lung capacity; RV = residual volume.

28%. Her whole blood GSH levels increased from 235 to 457 $\mu\text{mol/L}$ (laboratory control, $589.2 \pm 112.6 \mu\text{mol/L}$; $n = 10$). It should be further remarked that the last two PFTs performed showed reversibility of the obstructive airway disease (change in FEV₁, 48% at time 7 to 15% at time 8), whereas no prior PFT had shown reversibility. The patient continues to take HMS90 and no other respiratory medications, without return of her symptoms.

DISCUSSION

The patient suffered from a worsening of her previously diagnosed obstructive airway disease. The relative contributions of smoking, asthma, and cancer therapy to her baseline lung disease are unclear, as was the cause of her deterioration. She required multiple courses of systemic steroids to maintain lung function. Symptomatic improvement correlating with pulmonary function coincided with her initiation of HMS90. More significantly, pulmonary function worsened with withdrawal of HMS90 and improved with reintroduction. Her final respiratory status is objectively and subjectively better than at any time in the previous 4 years.

HMS90 is a bovine whey-protein concentrate purified by ultrafiltration and low-temperature pasteurization of milk. The undenatured whey protein is rich in cystine (the oxidized form of cysteine) and γ -glutamylcystine,⁶ which are precursors of GSH synthesis. The tripeptide GSH (glycyl- γ -glutamylcystine) is synthesized in the cell in two steps. The first step, the synthesis of γ -glutamylcystine, is limited by the availability of intracellular cysteine.⁴ As well, γ -glutamylcystine, as a γ -glutamyl amino acid, can easily be transported into the cell where it combines with glycine in the second step of GSH synthesis.⁸ Cells cannot take up extracellular GSH.³

In the patient described, whole blood GSH levels were significantly increased (94%) following regular intake of HMS90. This is much higher than the reported intraindividual variation in whole blood GSH values (7.8 to 15.8%).⁹ In order to avoid any possible influence of the timing of sampling on GSH levels and pulmonary function, the patient was tested between 10:00 AM and 11:00 AM on each visit. Animal studies of GSH metabolism have demonstrated that whole blood GSH is reflective, temporally and quantitatively, of lymphocyte and tissue GSH levels. Although no direct markers of oxidant/antioxidant status or inflammation were measured in the patient described, the observed clinical effect is coincident with augmented GSH levels.

Several specific abnormalities, or inadequacies, of the GSH antioxidant system have been identified in reversible obstructive airway disease. GSH itself is present in high concentrations in the lung epithelial lining fluid (ELF), where it may act to directly reduce ROS.^{10,11} Clinically stable asthmatics have higher ELF GSH than symptomatic asthmatics,⁵ while experimental models of oxidative stress show an increase in ELF GSH with oxidative stress.¹⁰ Upregulation of antioxidant defenses, although not in proportion to oxidative stress, is hypothesized to account for the increased BAL fluid GSH levels observed in both these studies and other pulmonary conditions that are attributed, in part, to excessive oxidative stress.¹⁰ GSH is also a substrate for the enzyme glutathione peroxidase (GSH-Px), which catalyzes the decomposition of a large number of ROSS (including hydrogen and other peroxidases).⁴ Studies have shown decreased peripheral blood GSH-Px activity in asthmatic patients.¹ Finally, it has been recently demonstrated in a murine model that GSH levels

in the antigen presenting cell affect the differentiation of the T-helper cell Th1/Th2 cytokine response.¹²

Improvement in GSH status could result in augmented lung function through several mechanisms. Within lung epithelial cells, augmented GSH may block the activation of nuclear factor κ B by tumor necrosis factor- α ,¹³⁻¹⁵ and so limit the production and release of proinflammatory cytokines. Augmented intracellular GSH may reduce the need to recycle GSH from the lung lining fluid, and thus maintain extracellular levels.¹⁶ Alternatively, increased intracellular GSH levels may lead to extracellular transport to buttress lung lining levels. In the lung lining fluid, augmented GSH may prevent oxidative damage to antiproteases.^{17,18} Improvement in skeletal muscle function due to augmented GSH stores⁷ may also partially account for our results, as the baseline FEV₁/FVC ratio did not change between times 7 and 8 (66% and 62%, respectively).

The ELF GSH pool has been the target of direct administration of nebulized GSH, although success has been limited by GSH-induced bronchospasm.⁵ Trials of systemic N-acetyl cysteine, acting as both a cysteine donor and an ROS scavenger, for the treatment of chronic obstructive airway disease have met with limited success, because of N-acetyl cysteine toxicity and limited clinical effect.^{2,19}

The relationship between whole blood GSH, lung epithelial cell GSH levels, ELF GSH, and peripheral blood GSH-Px activity is poorly defined. There are several possible mechanisms by which GSH could improve obstructive airway disease, either via immunologic modulation or by improving antioxidant defenses. More work needs to be done to further define the specific abnormalities of antioxidant function, as well as the relative contribution of such abnormalities to the pathophysiology observed in obstructive airway disease. Nevertheless, the modulation of GSH and antioxidant defenses in obstructive airway disease (and many other diseases) represents an intriguing potential modality for anti-inflammatory therapy.

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An Unreported Risk in the Use of Home Nasal Continuous Positive Airway Pressure and Home Nasal Ventilation in Children*

Mid-Face Hypoplasia

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We report the case of a 15-year-old boy with obstructive sleep apnea and obesity who was treated since the age of 5 with nasal continuous positive airway pressure. Due to the long-term use of a nasal mask, the child developed a mid-face hypoplasia. Chronic use of a nasal mask for home ventilation in children should always be associated with regular evaluations of maxillo-mandibular growth.

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Key words: apnea; children; complication; craniofacial; growth; nasal continuous positive airway pressure; risk; sleep apnea

Abbreviations: CPAP = continuous positive airway pressure; OSA = obstructive sleep apnea

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