

Serum 25-hydroxyvitamin D levels are lower in chronic rhinosinusitis with nasal polyposis and are correlated with disease severity in Taiwanese patients

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ABSTRACT

Background: Vitamin D deficiency is reported to be associated with increased incidence of allergic airway diseases and is correlated with the severity of asthma. This study was designed to determine if serum Vitamin D level is lower in chronic rhinosinusitis with nasal polyposis (CRSwNP) patients and if low serum Vitamin D level is correlated with the severity of CRSwNP.

Methods: New CRSwNP patients undergoing elective endoscopic sinus surgery were recruited. Patients with malignancies or asthma were excluded. Twenty chronic rhinosinusitis without nasal polyposis (CRSsNP) patients were used as control. Demographic characteristic information was collected. The severity of CRSwNP was assessed with the Lund-Mackay (LM) score and polyp grading system. Vitamin D status was assessed by measuring circulating 25-hydroxyvitamin D (25OHD) by using commercial chemiluminescence immunoassay. Data were stratified by factors known to affect serum 25OHD, including sex, race, and body mass index.

Results: Serum 25OHD levels (ng/mL $\pm$ SD) were significantly lower in patients with CRSwNP (21.4 ± 5.7) than in those with CRSsNP (28.8 ± 6.2 ; $p < 0.001$). The incidences of vitamin D deficiency (<20 ng/mL) in CRSwNP and CRSsNP patients were 45.5 and 6.3%; however, the incidences of vitamin D insufficiency (20–30 ng/mL) in these patients were 50.0 and 62.5%, respectively. A significantly negative relationship was found between serum 25OHD level and polyp grade ($r = -0.63$; $p = 0.001$), indicating lower serum 25OHD was associated with higher polyp grade. Serum 25OHD was inversely related to both LM score and total IgE level as well; however, statistical significance was not found.

Conclusion: A significantly lower vitamin D level was found in a group of Taiwanese CRSwNP patients, which revealed an association with greater nasal polyp size. Serum vitamin D levels could be added to the routine workup of patients suffering from CRS and these data could be used to potentially help determine the disease severity.

(Am J Rhinol Allergy 27, e162–e165, 2013; doi: 10.2500/ajra.2013.27.3948)

In addition to its traditional role in the endocrine system, many effects of vitamin D occur outside the feedback-controlled osseous endocrine loop and are independent from serum calcium, phosphorus, or parathyroid hormone levels. This discovery, together with the realization that essentially every tissue and cell in the body had vitamin D receptors,¹ has prompted new interest in the vitamin D system and its previously unrecognized actions. There had been more studies indicating that vitamin D deficiency is associated with non-skeletal conditions such as cancer, autoimmune diseases, cardiovascular diseases, and allergic disorders, *e.g.*, asthma.^{1,2} The relationship between vitamin D and asthma has been the subject of many studies in the past 10 years. Several epidemiological studies have suggested that vitamin D deficiency is associated with an increased incidence of asthma and allergy symptoms.^{3–7} Vitamin D deficiency correlates with decreased lung function in child^{7,8} and adult Chinese⁹ asthma patients. A study by Searing *et al.*¹⁰ even established a significant association between lower vitamin D levels and poor asthma control.

Chronic rhinosinusitis with nasal polyposis (CRSwNP) is a common and costly health problem. However, its exact mechanism of pathogenesis is still unclear. The histological appearance of nasal polyposis is characterized by inflammatory cell infiltration, modifications of epithelial cell differentiation, and tissue remodeling that includes basement membrane thickening, gland modifications, extracellular matrix accumulation, and edema. CRSwNP shows both characteristic inflammatory features and histopathological findings which also occur in asthma. This fact inspired us to hypothesize that serum vitamin D levels might be associated with CRSwNP. We have therefore investigated the association of serum vitamin D level and disease severity of CRSwNP.

SUBJECTS AND METHODS

Patients

The study was approved by the Institutional Review Board of Kaohsiung Medical University Hospital (KMUH-IRB-990427) and written informed consent was obtained from each subject before study. Based on the definition in European Position Paper on Rhinosinusitis and Nasal Polyps 2007,¹¹ patients with latest diagnosis of CRSwNP undergoing elective endoscopic sinus surgery at our hospital were recruited. Patients with malignancies or asthma were excluded from the study. Through clinical and radiographic examination that revealed inflammatory sinus disease without frank nasal polyp, patients were diagnosed with chronic rhinosinusitis without nasal polyposis (CRSsNP) and then collected as study controls. Demographic characteristic information of the patients enrolled was collected. The severity of CRSwNP was assessed with the Lund-Mackay (LM) score¹² and the severity of nasal polyp (grades 1–4) was assessed with the nasal polyp grading system described by Lund and Mackay.¹³ All of the scorings were performed by an experienced otolaryngologist who participated in the study. The status of allergy was assessed with the Phadiatop test (Pharmacia & Upjohn, Inc.,

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Funded in part by the National Science Council (NSC100–2314-B-037-045) and in part by Kaohsiung Medical University Hospital (KMUH-OR36)

The authors have no conflicts of interest to declare pertaining to this article

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Table 1 Demographic data of study patients

	CRSwNP	CRSsNP	<i>p</i> Value
Sex			
Male	14	10	
Female	8	6	0.945
Age (mean; yr)	45.63	54.06	0.132
BMI (mean)	26.03	26.21	0.818
Vitamin D level (ng/mL)	21.4	28.8	<0.001*

**p* < 0.05, reach statistical significance.

BMI = body mass index; CRSwNP = chronic rhinosinusitis with nasal polyposis; CRSsNP = chronic rhinosinusitis without nasal polyposis.

Peapack, NJ) in this study. Phadiatop is a commercially available qualitative serologic test used for screening of allergic sensitization, which can be used as a valid alternative to the skin-prick test to diagnose atopy.^{14,15} All patients were asked to stop any anti-inflammatory medications, including antibiotics and topical steroids, for at least 2 weeks before admission. Data were stratified by factors known to affect serum 25-hydroxyvitamin D (25OHD), including sex, race, and body mass index.¹⁶ Latitude, duration of sunshine, and season affect the skin's ability to produce vitamin D. Because all participants are Taiwanese living in Kaohsiung, Southern Taiwan, and immediate surrounding areas (latitude 23° N), this homogeneous population has relatively fewer unmeasured or uncontrolled (residual) confounding factors by ethnicity (*i.e.*, skin color) and other variables, such as duration of sunshine.

Vitamin D Measurement

Vitamin D status is best assessed by measuring circulating 25OHD, which is the main circulating vitamin D metabolite with the most potent biological effect. Serum 25OHD was measured by using commercial chemiluminescence immunoassay (DiaSorin-Liaison, Inc., Stillwater, MN). The limitation of detection was 4 ng/mL. Vitamin D deficiency was defined as ≤ 20 ng/mL and insufficiency was defined as ≤ 30 ng/mL.^{1,17} Samples analyzed in these studies were collected at latitude of 23° N in spring and summer of 2012 to minimize the impact of seasonal variation in vitamin D level.

Statistics

Statistical analyses were performed with SPSS software, Version 12.0 (SPSS, Inc., Chicago, IL). The differences of serum vitamin D level between each group were statistically analyzed using one-way analysis of variance and chi-square tests as appropriate. Multiple logistic regressions were also used to adjust the simultaneous effects of confounding variables such as age, sex, body mass index, and allergic status on the vitamin D level between patient groups. To assess the association between serum vitamin D levels and severity of disease, a Pearson's correlation analysis was used. Statistical significance was reported at *p* < 0.05.

RESULTS

Twenty-five patients with the latest diagnosis of CRSwNP who were scheduled for elective endoscopic sinus surgery during April to September of 2012 at our hospital were recruited. Furthermore, 20 patients were diagnosed with CRSsNP and then collected as study controls. None of the study subjects reported major disabling diseases on enrollment.

Demographic data of the study population were presented in Table 1. There were no significant differences between groups regarding age, sex, or body mass index. The preliminary results of the study revealed serum 25OHD levels (ng/mL $\pm$ SD) were significantly lower in CRSwNP patients (21.4 $\pm$ 5.7) than in CRSsNP patients (28.8 $\pm$ 6.2;

Table 2 Distribution of serum vitamin D status in each group by percentage

	CRSwNP	CRSsNP
Vitamin D status		
Normal (>30 ng/mL)	4.5%	31.2%
Insufficiency (20–30 ng/mL)	50%	62.5%
Deficiency (<20 ng/mL)	45.5%	6.3%

CRSwNP = chronic rhinosinusitis with nasal polyposis; CRSsNP = chronic rhinosinusitis without nasal polyposis.

Polyp Grade

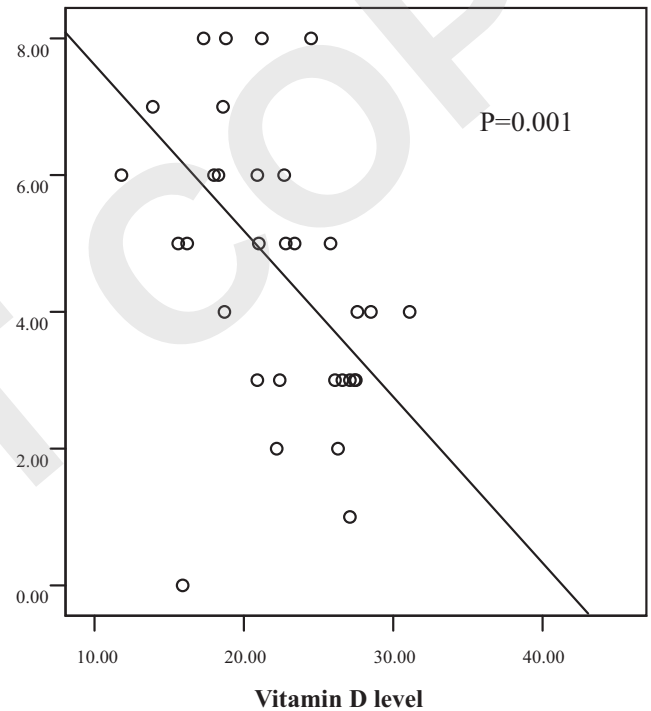


Figure 1. Relationship between serum 25-hydroxyvitamin D (25OHD) level (x-axis) and polyp grade (y-axis).

p < 0.001). After adjusting the model for age, sex, body mass index, and allergic status, the odds ratio still remained significant. The incidences of vitamin D deficiency (<20 ng/mL) versus insufficiency (20–30 ng/mL) in CRSwNP and CRSsNP patients were 45.5% versus 50% and 6.3% versus 62.5%, respectively. These results are detailed in Table 2. Only 31.2% of CRSsNP patients were in the normal range, which was comparable with the results of the general population seen in the National Health and Nutrition Examination Survey during 2005–2008 in Taiwan. Furthermore, a negative relationship was found between serum 25OHD level and polyp grade (*r* = −0.63; *p* = 0.001; Fig. 1), indicating that lower serum 25OHD was associated with higher polyp grade. Serum 25OHD was inversely related to LM score (Fig. 2) and total IgE level (Fig. 3) as well but without statistical significance.

DISCUSSION

This study is the first to investigate the correlation of serum 25OHD level and the severity of CRSwNP. In this study, we show that serum 25OHD levels in patients with CRSwNP were significantly lower than those in patients with CRSsNP. Serum 25OHD level was significantly

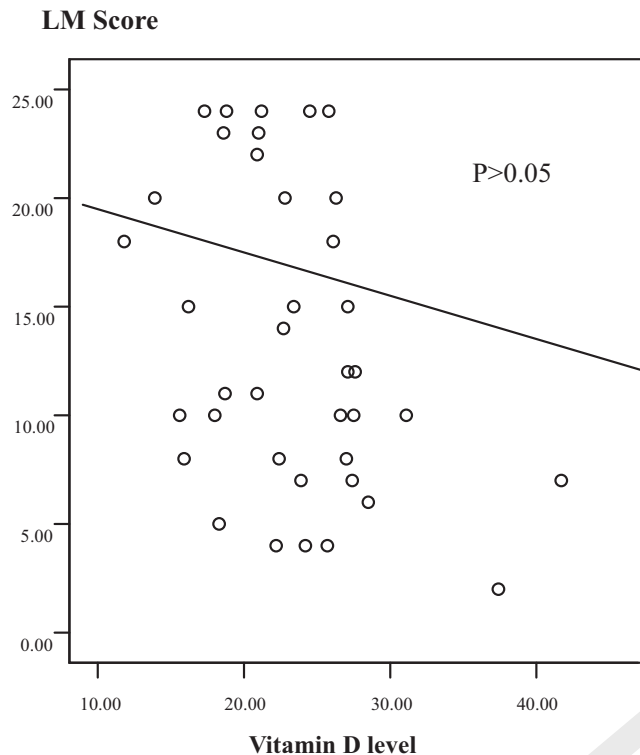


Figure 2. Relationship between serum 25-hydroxyvitamin D (25OHD) level (x-axis) and Lund-Mackay (LM) score (y-axis).

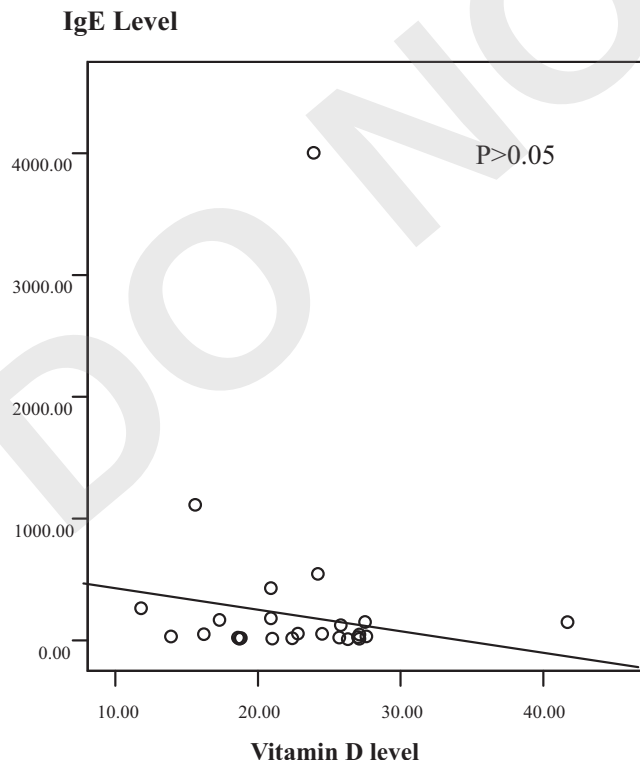


Figure 3. Relationship between serum 25-hydroxyvitamin D (25OHD) level (x-axis) and IgE level (y-axis).

and inversely related to polyp grade. However, the correlation of serum 25OHD level to LM score did not reach statistical significance.

Vitamin D is also known to have a number of immunologic effects, including those on T cells, dendritic cells, and macrophages.^{18,19} CRSwNP is characterized by severe mucosal inflammation, and thus vitamin D deficiency might lead to an increase in inflammation, as seen in CRSwNP. Indeed, administration of vitamin D to subjects with steroid-resistant asthma has been reported to enhance subsequent steroid responsiveness, a finding with implications for CRS, a disease in which steroids are an important therapy.²⁰

The pathogenesis of CRSwNP is still unknown. However, there is evidence that chronic inflammation, often similar to that seen in allergic rhinitis and asthma, is a histopathological finding in these patients. Recent evidence supports a role of vitamin D in these two diseases. Nutritional studies point to a possible inverse association between a mother's vitamin D intake during pregnancy and her child wheezing^{6,21,22} and/or rhinitis and asthma at 5 years old,²³ suggesting that *in utero* exposure of vitamin D might play a role in the development of the immune system. Another population database study also showed that the prevalence of allergic rhinitis was associated with serum 25OHD level. Given the fact that CRSwNP is associated with atopy and asthma and has similar inflammatory cellular profiles, these studies might give us a hint about the role of vitamin D in chronic sinus disease.

However, there exists a paucity of literature with regard to the role of Vitamin D in the pathophysiology of CRSwNP. A recent epidemiological study had shown that there was a positive correlation of sinus infection with low Vitamin D.² Pinto *et al.*²⁴ explored the relationship of vitamin D levels in African American patients with CRS when compared with age and sex-matched controls, finding that vitamin D levels were significantly lower in the African American CRS patients. A recent study by Mulligan *et al.* indicated that lower vitamin D levels were noted in patients with CRSwNP and allergic fungal rhinosinusitis; however, no significant difference in vitamin D level was found between CRSwNP patients and its controls.²⁵ Vitamin D receptor and vitamin D metabolic enzymes have been found in many cells. To evaluate if vitamin D reduces fibroblast proliferation in the tissues sliced from nasal polyps of CRSwNP patients, a Polish study showed a significantly dose-dependent decrease in fibroblast proliferation when tissue samples were treated with various doses of calcitriol and tacalcitol.²⁶ Rostkowska *et al.*²⁷ also indicated that calcitriol and tacalcitol inhibited the synthesis of the proinflammatory cytokines IL-6 and IL-8 in fibroblast cultures. In the study by Mulligan *et al.*,²⁵ an inverse relationship between serum vitamin D levels and the levels of dendritic cells was found in CRSwNP patients. The same relationship between serum vitamin D levels and plasma levels of prostaglandin E₂ and granulocyte monocyte colony-stimulating factor were also found. All of these evidenced the immune regulatory function of vitamin D for CRSwNP patients and thus led to the idea that vitamin D might act as an anti-inflammatory agent for CRSwNP patients. In this study, we showed that serum 25OHD levels in CRSwNP patients were significantly lower than those in CRSsNP patients. Serum 25OHD level was significantly and inversely related to the size of nasal polyposis. We postulated that low vitamin D level might fail to reduce the level of cytokines released by inflammatory cells and fibroblasts. This might lead to the results of perpetuation of chronic inflammatory sinus diseases and supported vitamin D in the pathogenesis and degree of severity of nasal polyposis.

Our study has several limitations. First, a small sample size might jeopardize its significance. Future work may extrapolate these data to a larger patient set, ideally through a prospective study to clarify the association of serum vitamin D and severity of CRSwNP. Second, its cross-sectional design precludes the ability to discern temporal association. It is possible that patients with severe CRSwNP might reduce their outdoor activities, which leads to reduced sun exposure. However, given that these participants are all patients with the latest diagnosis of CRSwNP, it likely has a negligible effect on our result.

Third, we did not have detailed information on the socioeconomic status and lifestyle of the participants. Because all participants are Taiwanese living in Kaohsiung, a southern city in Taiwan (latitude 23° N), this homogeneous population likely has relatively fewer unmeasured or uncontrolled (residual) confounding factors by ethnicity (e.g., skin color) and other variables, such as duration of sunshine. Finally, we did not collect information on the use of daily vitamin D supplements.

In conclusion, a significantly lower vitamin D level was found in a group of Taiwanese CRSwNP patients, which revealed an association with greater nasal polyp size. Serum vitamin D levels could be added to the routine workup of patients suffering from CRS and these data could be used to potentially help determine the disease severity.

REFERENCES

- Holick MF. Vitamin D deficiency. *N Engl J Med* 357:266–281, 2007.
- Frieri M, and Valluri A. Vitamin D deficiency as a risk factor for allergic disorders and immune mechanisms. *Allergy Asthma Proc* 32:438–444, 2011.
- Hyppönen E, Sovio U, Wjst M, et al. Infant vitamin d supplementation and allergic conditions in adulthood: Northern Finland birth cohort 1966. *Ann N Y Acad Sci* 1037:84–95, 2004.
- Weiss ST, and Litonjua AA. Childhood asthma is a fat-soluble vitamin deficiency disease. *Clin Exp Allergy* 38:385–387, 2008.
- Freishtat RJ, Iqbal SF, Pillai DK, et al. High prevalence of vitamin D deficiency among inner-city African American youth with asthma in Washington, DC. *J Pediatr* 156:948–952, 2010.
- Camargo CA Jr, Rifas-Shiman SL, Litonjua AA, et al. Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 y of age. *Am J Clin Nutr* 85:788–795, 2007.
- Brehm JM, Celedón JC, Soto-Quiros ME, et al. Serum vitamin D levels and markers of severity of childhood asthma in Costa Rica. *Am J Respir Crit Care Med* 179:765–771, 2009.
- Gupta A, Sjoukes A, Richards D, et al. Relationship between serum vitamin D, disease severity, and airway remodeling in children with asthma. *Am J Respir Crit Care Med* 184:1342–1349, 2011.
- Li F, Peng M, Jiang L, et al. Vitamin D deficiency is associated with decreased lung function in Chinese adults with asthma. *Respiration* 81:469–475, 2011.
- Searing DA, Zhang Y, Murphy JR, et al. Decreased serum vitamin D levels in children with asthma are associated with increased corticosteroid use. *J Allergy Clin Immunol* 125:995–1000, 2010.
- Fokkens W, Lund V, and Mullol J. EP3OS 2007: European position paper on rhinosinusitis and nasal polyps 2007. A summary for otorhinolaryngologists. *Rhinology* 45:97–101, 2007.
- Lund VJ, and Kennedy DW. Staging for rhinosinusitis. *Otolaryngol Head Neck Surg* 117:S35–S40, 1997.
- Lund VJ, and Mackay IS. Staging in rhinosinusitis. *Rhinology* 31:183–184, 1993.
- Garcia-Marcos L, Sanchez-Solis M, Martinez-Torres AE, et al. Phadiatop compared to skin-prick test as a tool for diagnosing atopy in epidemiological studies in schoolchildren. *Pediatr Allergy Immunol* 18:240–244, 2007.
- Vidal C, Gude F, Boquete O, et al. Evaluation of the phadiatop test in the diagnosis of allergic sensitization in a general adult population. *J Investig Allergol Clin Immunol* 15:124–130, 2005.
- Nesby-O'Dell S, Scanlon KS, Cogswell ME, et al. Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: Third National Health and Nutrition Examination Survey, 1988–1994. *Am J Clin Nutr* 76:187–192, 2002.
- Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 96:1911–1930, 2011.
- Wintergerst ES, Maggini S, and Hornig DH. Contribution of selected vitamins and trace elements to immune function. *Ann Nutr Metab* 51:301–323, 2007.
- Sigmundsdottir H, Pan J, Debes GF, et al. DCs metabolize sunlight-induced vitamin D3 to “program” T cell attraction to the epidermal chemokine CCL27. *Nat Immunol* 8:285–293, 2007.
- Xystrakis E, Kusumakar S, Boswell S, et al. Reversing the defective induction of IL-10-secreting regulatory T cells in glucocorticoid-resistant asthma patients. *J Clin Invest* 116:146–155, 2006.
- Miyake Y, Sasaki S, Tanaka K, and Hirota Y. Dairy food, calcium and vitamin D intake in pregnancy, and wheeze and eczema in infants. *Eur Respir J* 35:1228–1234, 2010.
- Devereux G, Litonjua AA, Turner SW, et al. Maternal vitamin D intake during pregnancy and early childhood wheezing. *Am J Clin Nutr* 85:853–859, 2007.
- Erkkola M, Kaila M, Nwaru BI, et al. Maternal vitamin D intake during pregnancy is inversely associated with asthma and allergic rhinitis in 5-year-old children. *Clin Exp Allergy* 39:875–882, 2009.
- Pinto JM, Schneider J, Perez R, et al. Serum 25-hydroxyvitamin D levels are lower in urban African American subjects with chronic rhinosinusitis. *J Allergy Clin Immunol* 122:415–417, 2008.
- Mulligan JK, Bleier BS, O'Connell B, et al. Vitamin D3 correlates inversely with systemic dendritic cell numbers and bone erosion in chronic rhinosinusitis with nasal polyps and allergic fungal rhinosinusitis. *Clin Exp Immunol* 164:312–320, 2011.
- Rostkowska-Nadolska B, Fraczek M, Gawron W, and Latocha M. Influence of vitamin D(3) analogues in combination with budesonide R on proliferation of nasal polyp fibroblasts. *Acta Biochim Pol* 56:235–242, 2009.
- Rostkowska-Nadolska B, Sliupkas-Dyrda E, Potyka J, et al. Vitamin D derivatives: Calcitriol and tacalcitol inhibits interleukin-6 and interleukin-8 expression in human nasal polyp fibroblast cultures. *Adv Med Sci* 55:86–92, 2010.

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