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# Routine duodenal biopsy to screen for coeliac disease is not effective

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## ABSTRACT

Background: Routine duodenal biopsies during upper gastrointestinal endoscopy (UGE) have been suggested to be useful in detecting coeliac disease (CD). However results from previous studies are not conclusive. The aim of this study is to investigate the diagnostic yield and cost-effectiveness of routine duodenal biopsy during UGE.
Methods: In this retrospective single-centre study, we studied 6442 patients undergoing first-time UGE at the Rijnstate Hospital, Arnhem, the Netherlands, from January 2009 to December 2010. All UGE reports were analysed for indication, duodenal intubation, and endoscopic aspect of duodenal mucosa. Endomysium and tissue transglutaminase antibody titre, when present, were scored as positive or negative. CD was defined as Marsh 3a or higher. Costs of duodenal biopsies and pathology analysis were calculated. Comparisons were done with T-tests for continuous data and Chi-square tests for categorical data.
Results: Forty-one patients had newly diagnosed CD; 34 of these 41 patients had definite indications for biopsy prior to UGE, e.g. positive serology or symptoms. Thus, routine duodenal biopsies identified seven patients as having CD, who otherwise would not have been biopsied. The number needed to biopsy was therefore 577, spending more than € 30,000 per case.
Conclusions: We do not recommend routine duodenal biopsy to screen for coeliac disease because of the high number needed to biopsy as well as high costs.

## KEYWORDS

Coeliac disease, duodenal biopsy, screening

## INTRODUCTION

Coeliac disease (CD) is defined as a permanent intolerance to gluten. In genetically susceptible individuals, the ingestion of gluten initiates a specific T-cell driven immune response that ultimately leads to gluten-sensitive enteropathy, which resolves with elimination of gluten from the diet.[1,2]
Small bowel histopathology according to the Marsh classification, consisting of lymphocytic enteritis, hyperplasia of crypts and atrophy of the villi, remains the gold standard in the diagnosis of CD, at least in adults.[3,4] The diagnosis may be supported and for that matter in the future even (partially) replaced by testing for the presence of coeliac-specific autoantibodies (endomysium and tissue transglutaminase) and immunogenetic markers (HLA DQ 2 and/or 8).[5] This strategy is already accepted in recent paediatric guidelines.[6]
Large screening studies in Western countries, based on serological markers, indicate that up to 1 in 100 people are affected.[7,8] Beginning in Europe and expanding throughout the world, studies systematically show great discrepancies between screening prevalence and actual prevalence of the disease.[9] Already in the 1990s, the concept of the coeliac iceberg was introduced, referring to the large majority of CD patients that remain unrecognised 'underneath the surface'.[10-12] Due to improved knowledge, scientific research and education of healthcare workers, the awareness for diagnosing CD has improved. Coeliac disease is now a more common disease throughout the world.[7,8] Incidence rates have been rising since, but still the largest part of the iceberg remains to be brought to the surface.
Although the burden of asymptomatic CD is rather unknown, population screening has even been suggested.[13,14] As CD may present with a diffuse spectrum of (mild) symptoms, it has been suggested that routine duodenal biopsies taken at upper gastrointestinal

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endoscopy (UGE) for various, non-specific indications such as iron deficiency anaemia, dyspepsia, (upper) abdominal symptoms and in patients who are known to have any other autoimmune disease, may help to identify un-recognised CD patients. Several studies have addressed this issue, but conclusions run both ways, claiming routine biopsies as either useful[15-18] or not effective.[19,20]

To our knowledge no studies have evaluated the cost-effectiveness of this procedure.

In the endoscopic detection of CD a variety of features are described: reduced or absent folds, scalloping of folds, mosaic pattern of the mucosa and mucosal fissures or cracks.[21-24] However, the sensitivity for detecting villous atrophy during standard UGE on endoscopic interpretation alone is poor (59%), in part because partial villous atrophy may elude visual detection.[25]

The aim of this study is to investigate the diagnostic yield and cost-effectiveness of routine duodenal biopsy during UGE in the identification of CD.

## METHODS

### Study design and patient population

In this retrospective single-centre study, we studied all patients undergoing UGE at the Rijnstate Hospital, Arnhem, the Netherlands, from January 2009 to December 2010. All endoscopies were performed by one of seven gastroenterology staff members or three gastroenterology residents. The majority of the procedures were performed with, at the time of the investigation, the latest selection of endoscopes on the market (GIF-Q180, GIF-H180 endoscopes on CV-180 Excera II processors Olympus Medical Systems Corp, Tokyo, Japan). The GIF-H180 endoscope gives the opportunity of real-time high-definition images. Depending on the indication, some endoscopies were performed with intervention-type endoscopes such as the GIF-1TQ160 endoscope on a CV-160 Excera processor (Olympus Medical Systems Corp, Tokyo, Japan). The Rijnstate Hospital has a long interest in CD research and for most endoscopists routine duodenal biopsies are the standard of care at first UGE. Approval of the medical ethics committee was therefore not necessary. All patient identifiers were coded and could not be traced back to the patient.

### Data collection

All UGE study reports from the endoscopy database, Endobase (Olympus Medical Systems Corp, Tokyo, Japan), containing full report text, age and sex, in the study period were entered into the research database. Second, the pathology reports from duodenal biopsies, when present, were retrieved from the pathology database and matched with the UGE study reports. Then, the endomysium and tissue transglutaminase antibody titres, when present, were retrieved from the laboratory database and matched with the data in the research database. For patients with signs of villous atrophy in pathology specimens or CD-specific antibodies, as well as for patients either with clinical suspicion for CD or in follow-up, haemoglobin levels in the period surrounding biopsy, ± 3 months, were retrieved from the laboratory database.

Only one study report per patient was taken into analysis. This was either the first investigation, or the first investigation with a report of duodenal biopsy during the study period.

### Data analysis

All UGE reports were analysed for indication, duodenal intubation, and endoscopic aspect of duodenal mucosa.

Next, all duodenal biopsy pathology reports were analysed for mentioning any signs of villous atrophy. CD was defined as Marsh 3a or higher. All endomysium and tissue transglutaminase antibody titres, when present, were scored as positive or negative. Anaemia was diagnosed when decreased haemoglobin levels were found, according to local reference values. Costs of duodenal biopsies and pathology analysis were calculated as if they were actually billed.

Comparisons were done with T-tests for continuous data and Chi-square tests for categorical data. Statistical analyses were performed using SPSS 20 for Mac (SPSS inc, Chicago, Illinois, USA)

## RESULTS

During the study period 8350 UGE were performed in 6442 patients; 4085 patients had duodenal biopsies analysed at our pathology lab (*figure 1*).

**Figure 1.** *Upper gastrointestinal endoscopies (UGE) during study period 2009-2010*

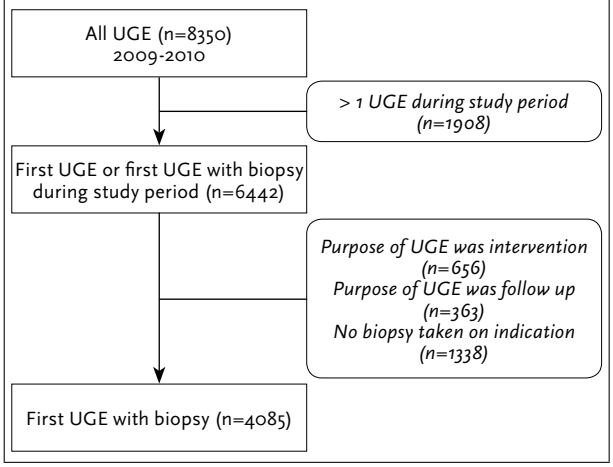

**Table 1.** *Patient characteristics and indications of UGE**

| | Biopsy (n=4085) | | No biopsy (n=2357) | | P |
|---|---|---|---|---|---|
| Characteristic | Mean | SD | Mean | SD | |
| Age | 54.6 | 18.5 | 62.4 | 17.4 | <0.001 |
| | | | | | |
| Sex | N | % | N | % | |
| Male | 1705 | 41.7 | 1244 | 52.8 | |
| Female | 2380 | 58.3 | 1113 | 47.2 | |
| | | | | | |
| Indication | N | % | N | % | |
| Anaemia | 454 | 11.1 | 158 | 6.7 | <0.001 |
| Diarrhoea | 225 | 5.5 | 36 | 1.5 | <0.001 |
| Weight loss | 244 | 6.0 | 54 | 2.3 | <0.001 |
| Dyspepsia | 1421 | 34.8 | 358 | 15.2 | <0.001 |
| Clinical suspicion of coeliac disease | 133 | 3.3 | 6 | 0.3 | <0.001 |
| Coeliac disease follow-up | 81 | 2.0 | 6 | 0.3 | <0.001 |
| Lactose intolerance | 2 | 0.04 | 2 | 0.1 | 0.577 |
| Other | 1605 | 39.3 | 831 | 35.3 | 0.001 |
| Intervention endoscopy | 109 | 2.7 | 656 | 27.8 | <0.001 |
| Follow-up endoscopy | 0 | | 363 | 15.4 | <0.001 |

***More than one indication possible. Comparison is based on T-tests for continuous variables and Chi-square tests for categorical variables. UGE = upper gastrointestinal endoscopy.**

**Table 2.** *Diagnosis of coeliac disease (number of UGE, n=4085)**

| Indication | UGE with biopsy | CD n (%) |
|---|---|---|
| Anaemia | 454 | 0 |
| Diarrhoea | 225 | 3 (1.3) |
| Weight loss | 244 | 2 (0.82) |
| Dyspepsia | 1421 | 2 (0.14) |
| Clinical suspicion of coeliac disease | 133 | 31 (23.3) |
| Coeliac follow-up | 82 | 10 (12.2) |
| Lactose intolerance | 2 | 0 |
| Other | 1605 | 3 (0.19)<br>2 heartburn<br>1 dysphagia |

***More than one indication possible, the diagnosis of coeliac disease has only been attributed to one indication.**

**Table 3.** *The diagnostic yield of coeliac disease (CD) specific serology* (number of patients, n=4085)*

| | |
|---|---|
| **Serology*** | |
| Positive | 61 |
| CD follow-up | 19 |
| Suspected CD | 42 |
| | |
| Villous atrophy in patients with suspected CD and positive serology | |
| Marsh 3A or higher | 35 |
| Marsh 2 | 2 |
| Marsh 0 | 5 |

***Tissue transglutaminase and/or endomysium antibodies.**

**Table 4.** *Characteristics of new coeliac disease (CD) patients (n=41)*

| Characteristic | | SD |
|---|---|---|
| Age* | 37.9 | 27.6 |
| | | |
| Sex | | |
| Male | 14 | |
| Female | 27 | |
| | | |
| Indication | n | % |
| Anaemia (no other signs of CD) | 0 | 0 |
| Diarrhoea (no other signs of CD) | 3 | 7.3 |
| Weight loss | 2 | 4.9 |
| Dyspepsia | 2 | 4.9 |
| Clinical suspicion of coeliac disease i.e. positive serology† or typical symptoms‡ | 31 | 75.6 |
| Heartburn | 2 | 4.9 |
| Dysphagia | 1 | 2.4 |
| Total | 41 | 100 |
| | | |
| Serology* | | |
| Positive | 35 | 85.4 |
| Negative | 3 | 7.3 |
| No serology | 3 | 7.3 |
| Total | 41 | 100 |
| **Anaemia at diagnosis§** | 11 | 26.8 |

***Age in years. †Tissue transglutaminase and/or endomysium antibodies. ‡Diarrhoea, steatorrhoea, abdominal complaints, weight loss etc. §Anaemia according to age and sex adjusted levels.**

The patient characteristics and indications for UGE are summarised in *table 1*. Pathology results revealed histological abnormalities graded as Marsh 3a or higher, i.e. compatible with CD, in 51 patients: this is 1.25% of all UGE with duodenal biopsy. Forty-one patients (1.00%) were 'newly' diagnosed, ten patients were in follow-up. The number of diagnoses of CD per indication are summarised in *table 2*. CD-specific serology was positive in 61 patients, 42 patients without prior history of CD and 19 patients in follow-up for CD. Out of 41 newly diagnosed CD patients, 26 had positive serology prior to the endoscopy. Thirty-five out of 42 had duodenal biopsy specimens revealing Marsh 3a or higher and thus 7/42 patients with CD antibodies had no CD-related enteropathy (*table 3*). CD-specific serology was positive in 35 of 41 newly diagnosed CD patients, 3 out of 41 had no serology tests performed, 3 were seronegative (*table 4*). Anaemia was present in 11 out of 41 newly diagnosed CD patients (*table 4*) and 6 out of 10 known CD patients with follow-up biopsy still graded as Marsh 3a or higher, of which one patient was diagnosed with enteropathy associated T-cell lymphoma.

Endoscopic abnormalities of the duodenal mucosa were seen in a total of 305 patients. CD-specific abnormalities, i.e. indicators of atrophy, were seen in 96 patients. The endoscopic abnormalities observed during UGE and their predictive values are summarised in *table 5*.

**Table 5.** *Abnormalities of the duodenal mucosa and the predictive value for coeliac disease (CD)* (number of patients, n=4085)*

| | Frequency of endoscopic abnormality N | Incidence of CD in patients with endoscopic abnormality n(%) |
|---|---|---|
| Absent folds | 10 | 7 (70.0) |
| Reduced folds | 31 | 16 (51.6) |
| Mosaic pattern | 20 | 2 (10.0) |
| Crackles or fissures | 8 | 6 (75.0) |
| Scalloping | 21 | 0 |
| Abnormal appearance of villi | 90 | 1 (1.1) |
| Vascular [lesions] | 31 | 0 |
| Other non-specific abnormalities | 209 | 0 |

***More than one abnormality possible.**

**Table 6.** *Cost analysis and number needed to biopsy on UGE per indication (number of patients, n=4085)*

| Indication | NNTB | Costs/diagnosis* |
|---|---|---|
| Anaemia (no other signs of CD) | Unlimited | Unlimited |
| Diarrhoea (no other signs of CD) | 75 | €4719.75 |
| Weight loss | 122 | €7677.46 |
| Dyspepsia | 710.5 | €44,711.77 |
| Clinical suspicion of coeliac disease i.e. positive serology or symptom complex | 4.3 | €269.99 |
| Other | 535 | €33,667.55 |

***Only standard pathology analysis charges and biopsy costs of €62.93 calculated. In case of abnormalities additional costs may be charged. UGE = upper gastrointestinal endoscopy; NNTB = number needed to biopsy; CD= coeliac disease.**

No complications due to duodenal biopsies occurred during the study period, according to the complication records.

The costs of performing routine duodenal biopsies, on first endoscopy, in our setting largely depend on the need for biopsies of other tissue(s) during the same procedure. Pathology labs can only bill one specific analysis per application. The costs, categorised per indication and calculated as if no other biopsies were taken, are shown in *table 6*. In our setting, as described before, the additional costs were negligible as over 99% of patients with duodenal biopsies had other tissue(s) (gastric antrum and/or corpus) biopsied as well.

## DISCUSSION

Over the last decades several studies have addressed the efficacy of routine duodenal biopsy during UGE in different subgroups, populations and in different indications with contradicting outcomes.[10-13] Furthermore, to our knowledge none of these studies addressed the cost-effectiveness of this procedure.

We retrospectively studied the outcome of routine duodenal biopsy during UGE in a large Dutch hospital with a long history of specific interest in CD research. Out of 6442 endoscopies performed in patients, 4085 had duodenal biopsies taken during UGE. The remaining 2357 patients had no biopsy because of intervention, another explanation for the symptoms or follow-up.

CD was newly diagnosed in 41 out of 4085 patients (1.00%). However, 26 of the 41 newly diagnosed patients had positive serology before UGE, 5 patients had typical symptoms for CD and 3 patients had diarrhoea, all definite indications for biopsy. Thus, routine duodenal biopsies identified 7 patients to have CD, who otherwise would not have been biopsied. This implicates that over 577 patients needed to be biopsied in order to find one CD patient. Compared with previously published studies the incidence of newly diagnosed CD in this study is slightly lower.[10-13] A possible explanation for this can be a higher prevalence of detected CD and a lower prevalence of non-detected CD in our study population. This might be explained by the hospitals specific interest and thus higher prevalence of detected CD (data not published) and could possibly lead to a shift towards lesser symptomatology in the population of non-detected individuals with CD. Another explanation for the lower incidence compared with other studies is the pathology diagnosis of CD, in this study defined as Marsh 3a or higher. Other studies diagnosed less progressed lesions as CD, where in another study the criteria of diagnosis were not specified.[16,18,20]

The predictive value of CD-specific serology (endomysium and tissue transglutaminase antibodies) found in this study is lower than described in the literature.[26-28] The tissue transglutaminase antibodies test used in our hospital is manufactured by Phadia AB, Uppsala, Sweden, and commercially available. All patients with positive serology and negative biopsies had on average over six biopsy samples. Anti-tissue transglutaminase antibody levels were on average only five times the upper limit of normal, a possible explanation for false positivity.

Endoscopic abnormalities of duodenal mucosa more or less specific for the diagnosis of CD can be a guide towards diagnosis, though the sensitivity remains insufficient to rely on. An earlier study reported a sensitivity of 59% for the detection of villous atrophy during standard endoscopy.[25] Endoscopic features for detecting villous atrophy had predictive values between 51-75% in our study, except for the mosaic pattern of the mucosa with a value of 10%.

Payments for specific procedures, in this case duodenal biopsy, can vary per country, region and even insurance company. Local settings and payment agreements, as well as the prevalence of the disease in the hospital's target population, can also attribute to the cost-effectiveness or ineffectiveness. We tried to estimate the 'fictive' costs of routine duodenal biopsies, as if all pathology analyses had actually been billed, in our setting which is largely comparable to other larger hospitals in the Netherlands. The large majority of CD patients will be identified by taking biopsies on indications as positive serology, anaemia, chronic diarrhoea, family history and other autoimmune diseases and endoscopic features that correlate with CD. For the remaining small group, taking biopsies in over 577 individuals and spending more than € 30,000 to identify one patient, seems at least disputable. Besides CD, other diagnoses such as Crohn's disease, Giardiasis and Whipple's disease can arise from duodenal biopsies. However, these conditions, due to their symptomatology and in the case of Crohn's disease endoscopic features, were not found in the group of patients without specific symptomatology. The question is when a diagnosis of CD will be cost-effective. Except for two North American studies that cannot simply be extrapolated to our setting, to our knowledge no literature is available on this topic.[29,30] Furthermore the benefit of being diagnosed on both quality of life and general health needs to be taken into consideration.

Therefore we conclude that, although duodenal biopsies seem a safe screening tool, random biopsies cannot be propagated in general during UGE.

## REFERENCES

1. Rostom A, Murray JA, Kagnoff MF. American Gastroenterological Association (AGA) Institute technical review on the diagnosis and management of celiac disease. Gastroenterology. 2006;131:1981-2002.
2. Green PH, Cellier C. Celiac disease. New Engl J Med. 2007;357:1731-43.
3. Marsh MN. Gluten, major histocompatibility complex, and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue'). Gastroenterology. 1992;102:330-54.
4. Wahab PJ, Meijer JW, Goerres MS, Mulder CJ. Coeliac disease: changing views on gluten-sensitive enteropathy. Scand J Gastroenterol. 2002(Suppl. 236):60-5.
5. Wolters VM, van de Nadort C, Gerritsen SA, et al. Is gluten challenge really necessary for the diagnosis of coeliac disease in children younger than age 2 years? J Pediatr Gastroenterol Nutr. 2009;48:566-70.
6. Husby S, Koletzko S, Korponay-Szabo IR, al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. J Pediatr Gastroenterol Nutr. 2012;54:136-60.
7. Fasano A, Berti I, Gerarduzzi T, et al. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. Arch Int Med. 2003;163:286-92.
8. Catassi C. The world map of celiac disease. Acta Gastroenterol Latinoam. 2005;35:37-55.
9. Schweizer JJ, von Blomberg BM, Bueno-de Mesquita HB, Mearin ML. Coeliac disease in The Netherlands. Scand J Gastroenterol. 2004;39:359-64.
10. Admou B, Essaadouni L, Krati K, et al. Atypical celiac disease: from recognizing to managing. Gastroenterol Res Pract. 2012;2012:637187.
11. Kamin DS, Furuta GT. The iceberg cometh: establishing the prevalence of celiac disease in the United States and Finland. Gastroenterology. 2004;126:359-61; discussion 61.
12. Csizmadia CG, Mearin ML, von Blomberg BM, Brand R, Verloove-Vanhorick SP. An iceberg of childhood coeliac disease in the Netherlands. Lancet. 1999;353:813-4.
13. Evans KE, Hadjivassiliou M, Sanders DS. Is it time to screen for adult coeliac disease? Eur J Gastroenterol Hepatol. 2011;23:833-8.
14. Katz KD, Rashtak S, Lahr BD, et al. Screening for celiac disease in a North American population: sequential serology and gastrointestinal symptoms. Am J Gastroenterol. 2011;106:1333-9.
15. Ackerman Z, Eliakim R, Stalnikowicz R, Rachmilewitz D. Role of small bowel biopsy in the endoscopic evaluation of adults with iron deficiency anemia. Am J Gastroenterol. 1996;91:2099-102.
16. Mandal AK, Mehdi I, Munshi SK, Lo TC. Value of routine duodenal biopsy in diagnosing coeliac disease in patients with iron deficiency anaemia. Postgrad Med J. 2004;80:475-7.
17. Riestra S, Dominguez F, Fernandez-Ruiz E, et al. Usefulness of duodenal biopsy during routine upper gastrointestinal endoscopy for diagnosis of celiac disease. World J Gastroenterol. 2006;12:5028-32.
18. Emami MH, Karimi S, Kouhestani S. Is routine duodenal biopsy necessary for the detection of celiac disease in patients presenting with iron deficiency anemia? Int J Prev Med. 2012;3:273-7.
19. Tischendorf JJ, Wopp K, Streetz KL, et al. [The value of duodenal biopsy within routine upper endoscopy: a prospective study in 1000 patients]. Zeitschrift fur Gastroenterologie. 2008;46:771-5. Epub 2008/09/02. Die Wertigkeit der tiefen Duodenalbiopsie im Rahmen der Routineendoskopie: Eine prospektive Studie mit 1000 Patienten.
20. Abbass R, Hopkins M, Dufour DR, et al. Celiac disease in an urban VA population with iron deficiency: the case against routine duodenal biopsy. Dig Dis Sci. 2011;56:2037-41.
21. Brocchi E, Corazza GR, Caletti G, Treggiari EA, Barbara L, Gasbarrini G. Endoscopic demonstration of loss of duodenal folds in the diagnosis of celiac disease. New Engl J Med. 1988;319:741-4.
22. Jabbari M, Wild G, Goresky CA, et al. Scalloped valvulae conniventes: an endoscopic marker of celiac sprue. Gastroenterology. 1988;95:1518-22.
23. Olds G, McLoughlin R, O'Morian C, Sivak MV, Jr. Celiac disease for the endoscopist. Gastrointest Endoscopy. 2002;56:407-15.
24. Dickey W. Endoscopic markers for celiac disease. Nature clinical practice Gastroenterol Hepatol. 2006;3:546-51.
25. Oxentenko AS, Grisolano SW, Murray JA, Burgart LJ, Dierkhising RA, Alexander JA. The insensitivity of endoscopic markers in celiac disease. Am J Gastroenterol. 2002;97:933-8.
26. Hill PG, Holmes GK. Coeliac disease: a biopsy is not always necessary for diagnosis. Aliment Pharmacol Ther. 2008;27:572-7.
27. Lewis NR, Scott BB. Systematic review: the use of serology to exclude or diagnose coeliac disease (a comparison of the endomysial and tissue transglutaminase antibody tests). Aliment Pharmacol Ther. 2006;24:47-54.
28. Toftedal P, Nielsen C, Madsen JT, Titlestad K, Husby S, Lillevang ST. Positive predictive value of serological diagnostic measures in celiac disease. Clin Chem Lab Med. FESCC. 2010;48:685-91.
29. Green PH, Neugut AI, Naiyer AJ, Edwards ZC, Gabinelle S, Chinburapa V. Economic benefits of increased diagnosis of celiac disease in a national managed care population in the United States. J Insur Med. 2008;40:218-28.
30. Lorig KR, Ritter PL, Laurent DD, Plant K. Internet-based chronic disease self-management: a randomized trial. Med Care. 2006;44[11]:964-71.