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## Deficiencies in fat-soluble vitamins in long-term somatostatin analogue users

Helle-Brit Fiebrich, Gerrit van den Berg, Ido P Kema, Thera P Links, Jan H Kleibeuker, Andre van Beek, Annemiek Me Walenkamp, Wim J Sluiter, Elisabeth Ge de Vries

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**Deficiencies in fat-soluble vitamins in long-term  
somatostatin analogue users**

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4 **1 Deficiencies in fat-soluble vitamins in long-term somatostatin analogue users**

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7 2  
8  
9 3 **Authors:** Helle-Brit Fiebrich<sup>1</sup>, Gerrit van den Berg<sup>2</sup>, Ido P. Kema<sup>3</sup>, Thera P. Links<sup>2</sup>, Jan H.  
10 4 Kleibeuker<sup>4</sup>, André van Beek<sup>2</sup>, Annemiek M.E. Walenkamp<sup>1</sup>, Wim J. Sluiter<sup>2</sup>, Elisabeth G.E.  
11 5 de Vries<sup>1</sup>

12 6 Departments of <sup>1</sup>Medical Oncology, <sup>2</sup>Endocrinology, <sup>3</sup>Laboratory Medicine,  
13 7 <sup>4</sup>Gastroenterology, University Medical Center Groningen and University of Groningen,  
14 8 Groningen, The Netherlands  
15 9

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28  
29 11 **Corresponding author:**  
30

31  
32 12 E.G.E. de Vries, MD, PhD  
33

34 13 Department of Medical Oncology  
35

36 14 University Medical Center Groningen  
37

38 15 P.O. Box 30001  
39

40 16 9700 RB Groningen  
41

42 17 The Netherlands  
43

44 18 Tel +31-50-3612934  
45

46 19 Fax +31-50-3614862  
47

48 20 E-mail: [e.g.e.de.vries@int.umcg.nl](mailto:e.g.e.de.vries@int.umcg.nl)  
49  
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51 21  
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56 23 analogues  
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3 **1 ABSTRACT**  
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8 **3 Background**  
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10 Somatostatin analogues are administered to control hormone hypersecretion in acromegaly  
11 and carcinoid patients. Somatostatin analogues can increase fat in the stools, which can lead  
12 to loss of fat-soluble vitamins. The effect of long-term somatostatin analogue use on vitamin  
13 levels is unknown.  
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22 **9 Aim**  
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24 To investigate the prevalence of fat-soluble vitamin deficiencies in long-term somatostatin  
25 analogue users.  
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32 **13 Methods**  
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34 All acromegaly and carcinoid patients using somatostatin analogues for  $\geq 18$  months visiting  
35 the UMCG, between December 2008 and April 2009 were eligible. Vitamin levels of fat-  
36 soluble vitamins in blood, clinical and vitamin-dependent laboratory parameters were  
37 collected.  
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47 **19 Results**  
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49 19 acromegaly and 35 carcinoid patients were included. Twelve patients experienced  
50 steatorrhoea, two carcinoid patients experienced night blindness. Forty-two (78%) were  
51 deficient for  $\geq$  one vitamins, 32% (n=17) for multiple. Deficiencies for vitamin A, D, E, K1  
52 and E in erythrocytes occurred in 6%, 28%, 15%, 63% and 58% of the patients. Prevalence of  
53 vitamin D, E and K1 deficiencies were similar in both patients groups. Treatment duration did  
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3 1 not influence vitamin levels. Length of intestinal resection and age correlated negatively with  
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5  
6 2 vitamin A levels.

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10 4 **Conclusions**

11  
12 5 Fat-soluble vitamins deficiencies are frequent during long-term somatostatin analogue  
13  
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15 6 treatment. Therefore, fat-soluble vitamins should be monitored in these patients.

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For Peer Review

## 1 INTRODUCTION

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8 Long-term somatostatin analogue therapy is important to control symptoms of hypersecretion  
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10 of biologically active amines and peptides in diseases such as acromegaly or metastatic  
11  
12 carcinoid tumours. Other indications for long-term use include certain pancreatic islet cell  
13  
14 tumours and the dumping syndrome. Side effects of somatostatin analogue treatment are  
15  
16 usually acceptable and often passing. The most common adverse effects are diarrhoea,  
17  
18 abdominal discomfort and nausea. Gallstones, usually asymptomatic, occur in 10–50% of the  
19  
20 treated patients.<sup>1-3</sup> Steatorrhoea is an adverse effect experienced by up to 29% of patients on  
21  
22 somatostatin analogue treatment.<sup>4</sup> When patients with acromegaly or a carcinoid tumour  
23  
24 cannot be cured by complete surgical tumour resection, they often require long-term  
25  
26 somatostatin analogue treatment for symptom control.  
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32 Two somatostatin analogues are currently available for clinical use. Octreotide is  
33  
34 registered since 1989, and lanreotide in the Netherlands since 1999. With the passing of time,  
35  
36 numerous patients have now received a significantly long-term treatment with these drugs.  
37  
38 Given the fat loss in the stool following somatostatin treatment, this will go together with loss  
39  
40 of fat-soluble vitamins A, D, E and K1 in the stool. A likely risk factor is the duration of  
41  
42 somatostatin analogue treatment. Studies performed thusfar have investigated patients after a  
43  
44 relative short treatment period and may therefore well underestimate the frequency of vitamin  
45  
46 deficiencies during long-term somatostatin analogue treatment. The only evidence pointing  
47  
48 towards an increased risk of a deficiency of fat-soluble vitamins in patients receiving long-  
49  
50 term somatostatin analogue treatment comes from a study in acromegaly patients. In this  
51  
52 study 103 patients were treated for 3-30 months with a mean duration 24 months. They  
53  
54 reported a slight but significant fall of carotene, although values remained in the normal  
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56 range. In addition, one patient in their study developed a prolonged prothrombin time (PT),  
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3 1 which resolved after vitamin K supplementation.<sup>5</sup> Others observed no changes in serum  
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6 2 carotene, vitamin D, or vitamin K in eight acromegaly patients who were on octreotide for  
7  
8 3 four months.<sup>6</sup>  
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10  
11 4 The frequent resection of a part of the small intestine, as performed in midgut  
12  
13 5 carcinoid patients, could be an additional reason for malabsorption. The severity of the  
14  
15 6 malabsorption after an intestinal resection depends on the total of digestive surface area and  
16  
17 7 the portion of small intestine remaining.<sup>7</sup> Carcinoid patients, that have undergone a partial  
18  
19 8 small bowel resection, may therefore be at greater risk to develop vitamin deficiency than  
20  
21 9 carcinoid or acromegaly patients without a bowel resection.  
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24  
25 10 No previous study has systematically investigated long-term somatostatin users and  
26  
27 11 has done so for levels of the complete set of fat-soluble vitamins. Therefore, the extent and  
28  
29 12 severity of fat-soluble vitamin deficiency in patients with acromegaly or a carcinoid tumour  
30  
31 13 are unknown. We hypothesise that deficiencies may be more frequent than currently reported.  
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33 14 This study aims to determine the frequency and severity of fat-soluble vitamin deficiency in  
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35 15 these patients with a treatment duration of at least 18 months.  
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## 42 **METHODS**

### 43 44 45 18 **Patients**

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48 19 Patients eligible for this cross-sectional study visited the UMCG between December  
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50 20 2008 and April 2009 for acromegaly or a metastasised midgut carcinoid tumour and were  
51  
52 21 treated with a somatostatin analogue for more than 18 months. Patient inclusion was limited  
53  
54 22 to the winter months in order to rule out seasonal influences on vitamin levels (especially  
55  
56 23 vitamin D, which levels are lowest during these months due to lack of sunlight-induced  
57  
58 24 vitamin D production) as an explanation for variation of vitamin levels between patients.  
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1 Patients younger than 18 years and those unable to give informed consent were excluded.  
2 Patient charts were checked for diagnosis, reports of previous intestinal resection and length  
3 of resection, dose and length of treatment with somatostatin analogues and possible signs and  
4 symptoms of a deficiency of fat-soluble vitamins. In addition, patients were asked if they took  
5 vitamin supplements, whether they experienced steatorrhoea (defined as loose, greasy stools  
6 that are difficult to flush), had special eating habits and if they had complaints that could be  
7 due to a vitamin deficiency, such as night blindness or an increased propensity for bleeding.  
8 The study was approved by the local medical ethics committee (approved on the 16<sup>th</sup>  
9 December 2008) and all patients gave written informed consent. The study was registered at  
10 the Netherlands (Dutch) trial register (registry), trial code 1730.

## 12 **Biochemical Analysis**

13 To estimate the extent of side effects of somatostatin analogues on the uptake of fat-  
14 soluble vitamins we determined plasma concentrations of the fat-soluble vitamins A (retinol),  
15 D, E, K1 as described earlier.<sup>8-11</sup> Vitamin E was also measured in the membrane of  
16 erythrocytes with an HPLC method, as vitamin E levels in erythrocytes provide a better  
17 measure of long-term vitamin E status than plasma levels.<sup>12, 13</sup> After liquid/liquid extraction  
18 with hexane, using tocol and retinol acetate as internal standards, a 35  $\mu$ L sample was injected  
19 on a Waters Symmetry C18 column (Waters Corporation, Milford, MA) and analysed, using a  
20 ASI-100 autosampler (Dionex, Sunneyvale, CA), a P680 HPLC pump (Dionex, Sunneyvale,  
21 CA) and a Thermo-Finnigan PDA (photodiode array) detector (Thermo Fisher Scientific Inc.,  
22 Waltham, MA). ATLAS Chromatography Data System (Thermo Fisher Scientific Inc.,  
23 Waltham, MA) was used for recording and calculating the results. Lower limits of normal in  
24 plasma were 0.8  $\mu$ mol/L for vitamin A, 50 nmol/L for vitamin D<sup>14</sup>, 19.2  $\mu$ mol/L for vitamin E  
25 and 0.8 nmol/L for vitamin K1. Lower limits of normal for vitamin E in erythrocytes was 4.58



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3 1  $\mu\text{mol per } 10^{13}$  erythrocytes. Reference interval verification, performed in 25 samples of  
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6 2 healthy individuals using the EP Evaluator software package release 8 (Data Innovations Inc.,  
7  
8 3 South Burlington, VT), confirmed that the values used in our center for vitamin A and E were  
9  
10 4 correct.<sup>15</sup>

11  
12  
13 5 To measure effects of a possible fat-soluble vitamin deficiency, vitamin-dependent  
14  
15 6 parameters were included. For vitamin D parathyroid hormone (PTH) was measured, while  
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17 7 for vitamin K1, PT and activated partial thromboplastin time (aPTT) were evaluated.  
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## 21 22 23 9 **Statistical Analysis**

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26 10 Normal values were those determined for healthy controls in our laboratory. In a  
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28 11 sample size of 19 acromegaly patients we can demonstrate a significant difference between  
29  
30 12 vitamin levels if 3 abnormal values are measured (15%). In 35 carcinoid patients it is possible  
31  
32 13 to show a significant difference between vitamin levels if 4 abnormal values are measured  
33  
34 14 (12%).

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36  
37 15 The chi-square test was used to test for differences between patients and normal values  
38  
39 16 and the Mann-Whitney U test to test for differences between groups of carcinoid and  
40  
41 17 acromegaly patients. In a linear univariate regression analysis age, sex, length of treatment,  
42  
43 18 treatment dose, type of somatostatin analogue, presence of steatorrhoea, pancreatic enzyme  
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45 19 supplementation, diagnosis and bowel resection were tested for associations with plasma  
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47 20 vitamin levels. For the analysis, bowel resection was divided into four categories based on the  
48  
49 21 risk of developing malabsorption: no resection, less than 100 cm of bowel resected, between  
50  
51 22 100 and 200cm resected and more than 200 cm resected.<sup>16</sup> Factors with a *P* level < 0.15 were  
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53 23 tested in a multivariate regression analysis, using the reverse stepwise method. Significance  
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55 24 level was .05, two-sided. Statistical tests were performed using the SPSS package version  
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## 2 RESULTS

### 4 Patient Characteristics

5 A total of 56 patients were asked to participate, one carcinoid patient and one  
6 acromegaly patient declined participation. The remaining 54 patients were analyzed, 19  
7 patients with acromegaly and 35 with a carcinoid tumour. Characteristics of these patients are  
8 shown in Table 1.

9 Median length of somatostatin analogue treatment was 48 months (range 18-155), and  
10 did not differ between acromegaly and carcinoid patients ( $P = 0.18$ ). Median dose of  
11 somatostatin analogue was 30 mg per 4 weeks for octreotide and 75 mg per 4 weeks for  
12 lanreotide. Median doses were the same for both patient groups. Of the carcinoid patients 25  
13 had undergone a bowel resection in the past; in 23 less than 100 cm of bowel was resected, in  
14 one between 100 and 200 cm and in one more than 200 cm.

### 16 Symptoms

17 Two carcinoid patients experienced night blindness, which coincided with vitamin A  
18 deficiency. One patient was already referred to an ophthalmologist. Electroretinography  
19 demonstrated abnormalities typical for vitamin A deficiency in both patients. Oral  
20 supplementation of vitamin A resulted in a quick resolution of their symptoms. Twelve  
21 patients ( $n = 4$  acromegaly patients and  $n = 8$  carcinoid patients) complained about  
22 steatorrhea. Twelve carcinoid patients experienced increased stool frequency (range 1-10  
23 times daily), but most had normal stools. An additional five carcinoid patients received  
24 supplementation of pancreatic enzymes for steatorrhea. Despite this supplementation all five

1 patients had abnormal vitamin levels. Four patients (one acromegaly patient and three  
2 carcinoid patients) took non-prescribed vitamin supplements (which included vitamins A, D  
3 and E), but three of these patients did show deficiencies for one ( $n = 2$ ) or two ( $n = 1$ ) of the  
4 fat-soluble vitamins. None of the patients had symptoms of increased bleeding tendency.

## 6 Overall vitamin-deficiencies

7 Abnormally low plasma levels for one or more fat-soluble vitamins were detected in  
8 78% ( $n = 42$ ). A deficiency of multiple vitamins was present in 32% ( $n = 17$ ); in 26% ( $n = 14$ )  
9 of two, in 4% ( $n = 2$ ) of three and in 2% ( $n = 1$ ) of all fat-soluble vitamins. The three patients  
10 with a deficiency of three or four vitamins were all carcinoid patients. When vitamin E levels  
11 in erythrocytes, which reflects long-term vitamin E status, were considered for vitamin E  
12 status instead of plasma vitamin E levels more patients ( $n = 51$ , 91%) had a deficiency.  
13 The most frequently deficient vitamin overall was vitamin K1 ( $n = 34$ , 63%). Low plasma  
14 levels of vitamin A were detected in 6%, of vitamin D in 28%, of vitamin E in 15% and low  
15 levels of vitamin E in erythrocytes in 58% of patients. The number of patients with a  
16 deficiency for vitamin D, E and K1 in plasma and for vitamin E in erythrocytes was  
17 significantly higher compared to what can be expected based on the normal values of our  
18 laboratory ( $P < 0.001$ ). This was not the case for vitamin A ( $P = 0.15$ ).

## 20 Subgroup Analysis

21 In the group of acromegaly patients 74% ( $n = 14$ ) had abnormally low plasma levels  
22 for at least one vitamin and 47% for two vitamins. Based on vitamin E levels in erythrocytes,  
23 89% had abnormally low levels for at least one vitamin. In this group all patients had normal  
24 levels of vitamin A. Vitamin D levels below 50 nmol/L were found in four acromegaly

1 patients (21%). Lowered vitamin E plasma levels were present in three patients (16%), while  
2 vitamin K1 was deficient in 10 patients (53%). Vitamin E levels in erythrocytes were lowered  
3 in 14 (74%).

4 Of the carcinoid patients 80% (n = 28) had abnormally low plasma levels of at least  
5 one fat-soluble vitamin, while 32% had more than one deficiency. When vitamin E levels in  
6 erythrocytes were considered for vitamin E status, 91% had abnormally low levels for at least  
7 one vitamin. Vitamin A deficiency was detected in three patients (9%). Vitamin D levels  
8 below 50 nmol/L were found in 11 patients (31%). Low vitamin E plasma levels were found  
9 in five patients (14%), while vitamin K1 was deficient in 24 patients (69%). Vitamin E in  
10 erythrocytes was low in 15 (43%). Vitamin plasma levels for both patient groups are shown in  
11 Figure 1. Frequency or severity of deficiencies for vitamin D, E and K1 did not differ  
12 significantly between patients with acromegaly or a carcinoid tumour, while vitamin A  
13 deficiency was only seen in carcinoid patients.

#### 15 **Vitamin-dependent parameters**

16 In 60% of patients (n = 9) with vitamin D levels below 50 nmol/L PTH was elevated;  
17 these included 3 acromegaly patients and 6 patients with a carcinoid tumour. Four (12%) out  
18 of 34 patients with low vitamin K1 level, all with a carcinoid tumour, showed a prolonged PT,  
19 one patient also had a prolonged aPTT. This last patient was also on a vitamin K antagonist,  
20 which explains the prolonged PT and aPTT.

#### 22 **Multivariate regression analysis**

23 Neither duration of treatment nor dose of either somatostatin analogue was associated  
24 with the plasma level of the various fat-soluble vitamins or vitamin E in erythrocyte levels.

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3 1 Increased stool frequency was not associated with lower vitamin levels in plasma or  
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6 2 erythrocytes. Resection of a longer portion of small bowel showed an association with lower  
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8 3 plasma vitamin A levels ( $P = 0.004$ ). In addition, higher vitamin A levels were negatively  
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10 4 associated with older age ( $P = 0.03$ ). Plasma levels of vitamin D, E, K or levels of vitamin E  
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12 5 in erythrocytes were not associated with any of the investigated factors.  
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## 18 7 **DISCUSSION**

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23 9 This study shows that 78% of acromegaly and patients with metastasised midgut  
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26 10 carcinoids who received a somatostatin analogue for longer than 18 months have deficiencies  
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28 11 of one or more fat-soluble vitamins.

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30 12 This high level of vitamin deficiency was until now unknown. Two earlier studies  
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33 13 addressing vitamin levels in patients treated with a somatostatin analogue<sup>5,6</sup> found a lowering  
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35 14 of carotene, but values remained in the normal range. The major difference of our study  
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37 15 versus these studies is a median treatment duration which was much longer. Interestingly, we  
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39 16 did not observe in our patients an association between length and dose of somatostatin  
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41 17 analogue treatment with the incidence and severity of vitamin deficiencies. This may indicate  
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43 18 that once a certain threshold in length or dose of treatment is reached, additional length of  
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45 19 treatment or higher doses of somatostatin analogues do not affect incidence and severity of  
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47 20 vitamin deficiencies.  
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51 21 Our study indicates that over the coming years vitamin deficiencies will be seen more  
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53 22 frequently in the increasingly growing group of long-term somatostatin analogue users.  
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55 23 Acromegaly patients precluded from surgical cure can receive long-term somatostatin  
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57 24 analogue treatment.<sup>17</sup> In addition, the life expectancy of patients with a metastasised carcinoid  
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3 1 tumour has improved clearly during the last decades.<sup>18</sup> Consequently, patients receive  
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5 2 somatostatin analogues for extended periods.  
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8 3 The most impressive symptom we observed was night blindness in two patients which  
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10 4 showed a quick resolution of their complaints after vitamin A supplementation. Vitamin K1  
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12 5 was the most frequently observed deficient vitamin in our study. This deficiency resulted only  
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14 6 in few patients in prolonged clotting times. However the plasma values indicate that these  
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16 7 patients should be closely followed, in case of surgery vitamin K1 should be supplemented to  
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18 8 prevent bleeding.  
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22 9 In our study bowel resection also influenced plasma levels of vitamin A, but  
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24 10 interestingly not to plasma levels of the other fat-soluble vitamins. Patients with a less than  
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26 11 200 cm residual bowel after resection run the highest risk to develop vitamin deficiencies.  
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28 12 Both the guidelines of the British Society of Gastroenterology and of the American  
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30 13 Gastroenterology Association Institute mention that fat-soluble vitamins may need to be  
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32 14 supplemented if less than 200 cm of short bowel remains after resection, but do not suggest a  
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34 15 specific screening regimen.<sup>16, 19</sup> Early studies in small numbers of patients who had  
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36 16 undergone resection of varying lengths of intestine showed that resection of more than 100  
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38 17 cm of the terminal ileum leads to insufficient intra-intestinal bile salt concentrations, which  
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40 18 might in turn lead to fat and fat-soluble vitamin malabsorption.<sup>20, 21</sup> However, for patients  
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42 19 with a resection of more than 100 cm no regular monitoring of these vitamins is  
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44 20 recommended by any of the existing guidelines. In our study in only two carcinoid patients  
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46 21 this was the case. In most carcinoid patients only short segments of the small bowel have been  
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48 22 resected.  
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53 23 Current guidelines of various national and international consensus groups for the  
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55 24 treatment of acromegaly or carcinoid tumours do not recommend the assessment of fecal fat  
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57 25 malabsorption in patients treated with a somatostatin analogue.<sup>1, 17, 22-26</sup> Furthermore, only the  
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3 1 guidelines by the European Neuroendocrine Tumour Society (ENETS) and of the Nordic  
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5 2 neuroendocrine tumour group mention that pancreatic enzyme replacement can be given to  
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7 3 alleviate steatorrhoea.<sup>22, 25</sup> Deficiencies of fat-soluble vitamins may be less frequent in  
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9 4 patients, who take pancreatic enzyme supplementation to improve fat uptake and uptake of  
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11 5 fat-soluble vitamins and consequently steatorrhoea. In our population five patients took such  
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13 6 medication. These five patients did however still show deficiencies of the fat-soluble  
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15 7 vitamins.

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20 8 Intestinal perfusion studies in humans have shown that somatostatin analogues  
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22 9 interfere with the absorption of nutrients.<sup>27,28</sup> Administration of somatostatin analogues  
23  
24 10 significantly decreases the duodenal absorption of carbohydrates and triglycerides.<sup>28</sup>  
25  
26 11 Therefore, in addition to their effect on pancreatic enzyme secretion, direct antiabsorptive  
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28 12 effects of somatostatin analogues may also well play a role in explaining vitamin deficiencies  
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30 13 in these patients.

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34 14 Carcinoid patients may have another risk factor for the development of deficiencies of  
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36 15 fat-soluble vitamins, as they frequently experience diarrhoea as part of the carcinoid  
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38 16 syndrome. Transit times in the small bowel and the colon are 2-6 times faster in carcinoid  
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40 17 patients compared to healthy controls.<sup>29</sup> A shorter transit time reduces the time available for  
41  
42 18 the absorption of water and nutrients. Consequently, less fat is absorbed with shorter transit  
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44 19 time.<sup>30</sup> In that case fat-soluble vitamins will also be absorbed less. In our study no association  
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46 20 between increased stool frequency and vitamin deficiency was found.

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50 21 We determined plasma vitamin E as well as vitamin E levels in erythrocytes. Plasma  
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52 22 vitamin E half-life is subject to extensive interindividual variation because of the many  
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54 23 factors that influence the turnover of the various lipoproteins.<sup>31</sup> Vitamin E in erythrocytes, on  
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56 24 the other hand, has a longer half life than vitamin E in plasma and therefore better reflects  
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58 25 long-term vitamin E status.<sup>12, 13</sup> Vitamin E in erythrocytes is located in the cell membrane

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3 1 where it is essential to prevent free radical damage to tissues and specifically to unsaturated  
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5 2 lipids.<sup>32</sup> Vitamin E levels in erythrocytes were deficient in 58% patients illustrating a clear  
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8 3 effect on long-term vitamin E status in these patients while plasma vitamin E levels was only  
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10 4 lowered in 15%, likely due to recent dietary intake.

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13 5         Decreased vitamin levels can also be the consequence of insufficient dietary intake.  
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15 6 We did not perform a detailed dietary history, but none of our patients reported an abnormal  
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17 7 eating behavior. The four patients who reported to take non-prescribed vitamin supplements  
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19 8 did still have vitamin deficiencies. Apparently, over-the-counter available vitamin  
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21 9 supplements do not contain doses high enough to prevent fat-soluble vitamin deficiencies in  
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23 10 these patients.

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27 11         In conclusion, deficiencies of fat-soluble vitamins in patients receiving long-term  
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29 12 somatostatin analogue treatment are more frequent than previously known. Considering the  
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31 13 possible consequences, we recommend routine assessment of fat-soluble vitamin in plasma  
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33 14 and vitamin E in erythrocytes in these patients twice a year, especially in patients with an  
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35 15 intestinal resection, and earlier in case of signs or symptoms. Vitamin supplementation should  
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37 16 be initiated when symptoms are present or to prevent complications, such as a risk of  
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39 17 increased bleeding when surgery is planned (vitamin K deficiency) or osteoporosis in case of  
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41 18 vitamin D deficiency.

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49 20 **Statement of interests:** None declared.  
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**Table 1.** Patient characteristics

	Total group	Acromegaly	Carcinoid tumour	<i>P</i> value
Number of patients	54	19	35	
Sex, male/female (n = 54)	27/27	11/8	16/19	0.40
Age in years, median (range)	60 (31-83)	56 (31-79)	62 (50-83)	0.003
Octreotide/lanreotide (n = 54)	46/8	10/9	34/1	0.000
Dose, median (range)				
Octreotide, mg / 4 weeks		25 (10-30)	30 (4.5-110)	
Lanreotide, mg / 4 weeks		90 (30-120)	60 (60)	
Length of somatostatin analogue treatment, median (range)	48 (18-222)	57 (18-222)	47 (19-155)	0.18
Complaints suggestive of steatorrhoea (n = 54)	12	4	8	0.88
Complaints suggestive of vitamin deficiency (n = 54)	2	0	2	0.46

**FIGURE LEGENDS**

**Figure 1.** Scatter plots showing the range of plasma levels (unless otherwise noted) of the different fat-soluble vitamins per patient. **Panel A.** Vitamin A, **Panel B.** Vitamin D, **Panel C.** Vitamin E, **Panel D.** Vitamin E in erythrocytes **Panel E.** Vitamin K. Horizontal bars represent the median value, dotted lines the lower and upper limits of normal.

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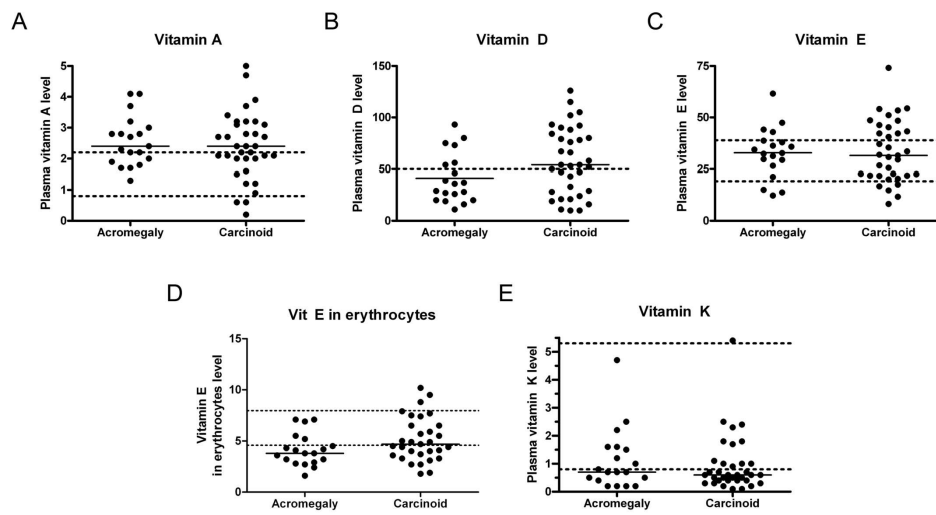


Figure 1. Scatter plots showing the range of plasma levels (unless otherwise noted) of the different fat-soluble vitamins per patient. Panel A. Vitamin A, Panel B. Vitamin D, Panel C. Vitamin E, Panel D. Vitamin E in erythrocytes Panel E. Vitamin K. Horizontal bars represent the median value, dotted lines the lower and upper limits of normal.

96x52mm (600 x 600 DPI)