ELEVATED VITAMIN B12 BLOOD LEVELS

Anecdotic but not rare clinical cases lead health care professionals to question the reason for finding high or very high blood levels for cobalamin (vitamin B12). Most cases are considered as having been supplemented, possibly through self-medication or from another practitioner, and very often no practical measure is foreseen.

But very frequently among those patients, careful inquiries demonstrate that no external human intervention may explain the finding. So we have to find some explanation to the increase within the metabolism. The presence of vitamin B12 in human faeces doesn't only correspond to what is left from the absorption in the ileum, but it also reflects the production of significant quantities of cobalamin by the colonic microflora [1].

The fact that intestinal micro-organisms produce significant amounts of vitamins B is fully accepted and has been published by peer-reviewed international medical journals [2, 3]. Intestinal bacterial vitamins B biosynthesis concerns at least vitamin B1 (thiamine) [4], vitamin B2 (riboflavin) [5], vitamin B5 (pantothenic acid) [6], vitamin B8 (biotin) [6-8], vitamin B9 (folic acid) [9, 10],and vitamin B12 (cobalamin) [1]. As a matter of fact, bacteria obtained from dairy and belonging to the genus *Propionibacterium* (also abundant in the human intestinal microflora) are extensively used for the biological production of **cobalamin** [11].

It has been shown, already in 1980, that "at least two groups of organisms in the small bowel, *Pseudomonas* and *Klebsiella sp.*, may synthesize significant amounts of the vitamin [B12]" [1]. Oppositely to all the other B vitamins, **cobalamin** is not absorbed in the jejunum or in the proximal ileum as they are, but only in the terminal ileum from a quite complex absorption process. This makes it very sensitive to diseases affecting specifically, or more frequently, this portion of the digestive tract such as Crohn's disease. We should rather speak about "cobalamins", due to the presence of four different metabolically important forms in the diet: **methylcobalamin**, **hydroxocobalamin**, **cyanocobalamin**, and **deoxyadenosylcobalamin**, mostly bound to proteins in our foods. In <u>first</u>, the cobalamins must be released from their protein complexes through the action of *acid* or *pepsin* in the stomach. In <u>second</u>, they have to bind *R proteins* (secreted in saliva and in gastric juice) which consist in cobalamin-binding glycoproteins. In <u>third</u>, these cobalamin-protein complexes must be degraded by *pancreatic proteases* and the whole process of absorption may be ruined in case of pancreatic insufficiency [12]. In <u>fourth</u>, the free cobalamin combines in the duodenum with another glycoprotein called *intrinsic factor* and secreted by the stomach parietal (oxyntic) cells; this glycoprotein dimerises and each part of the dimer binds one molecule of cobalamin, the complex resisting to digestion [13].

The formation of the cobalamin-intrinsic factor complex appears indispensable for the vitamin to be absorbed in the terminal ileum via an active transport system [12]. In <u>fifth</u>, the brush border membrane of those enterocytes contains a *specific receptor* for the dimeric complex and its importance in the process is shown by a congenital vitamin B12 malabsorption syndrome due to a defect in the receptor. The absorption is hampered by an abnormally low ileum pH, which may occur in some diseases such as the Zollinger-Ellison syndrome.

Now, supposing that all these steps leading to an effective absorption of vitamin B12 function adequately, the presence in significant amounts of bacteria producing cobalamin in the terminal ileum would explain - at least theoretically - a sharp increase in absorption and lead to higher blood levels of this vitamin. If we consider some specific circumstances in the above mentioned study about folate absorption [10], we might find out which mechanisms could lead to an excessive absorption of cobalamine and to an elevation of blood levels.

In this exemplary study for functional medicine, two groups of patients were formed - healthy volunteers and subjects suffering from gastric arthritis - and were studied before and after omeprazole (a proton pump inhibitor, which turns off the gastric acid production) administration [10]. Logically, both patients with atrophic gastritis and receiving omeprazole showed an increased duodenal pH (which stands for less acidity), but also an overgrowth of the small intestinal microflora or small intestinal bacterial overgrowth (SIBO) [10].

In physiological conditions, bacterial growth in the small intestine is limited by the acidic environment due to the presence of hydrochloric acid. The small intestinal environment, normally hostile to the local microflora, enables a "**small intestinal bacterial overgrowth**" (**SIBO**) either in case of atrophic gastritis [14] or in case of drug-induced hypochlorhydria [15], especially among "subjects taking a hydrogen pump blocking agent [such as] omeprazole" [16]. Interestingly, SIBO seems to provide "a unifying framework for understanding **irritable bowel syndrome** (**IBS**) and other functional disorders" [17], among which **fibromyalgia** [17, 18].

We come back once again to the experimentation with labelled folate to give its conclusions as presented in the corresponding abstract: "(1) Mild bacterial overgrowth caused by atrophic gastritis and administration of omeprazole are associated with *de novo* folate synthesis in the lumen of the small intestine; (2) the human host absorbs and uses some of these folates" [10]. Indeed, the unexplained increase of blood levels that we are describing about vitamin B12 may also occur with folic acid. We present a first **case study** concerning a four-year old boy who suffered from diarrhoea and abdominal bloating. Cœliac disease had been dismissed but he showed an increase of specific urinary organic metabolites corresponding to a bacterial overgrowth, typically from *Clostridium*. This child had never been treated with vitamins at the time of his first blood check, though his erythrocytic **folic acid** level was measured at **913**µg/l whereas 257µg/l - 582µg/l represent the lab's normal range for the parameter. Besides, the plasmatic level for **cobalamins** was raised at **1324**ng/l, contrasting with the laboratory's normal range going from 450ng/l up to 1200ng/l. He was treated for intestinal dysbiosis and put on a casein-free diet, improved dramatically… and was not blood tested again!

We present a second **case study** concerning a thirty-year old woman whose blood parameters were monitored for unrelated matters but strikingly presented repetitive high **vitamin B12** levels without any related supplementation neither from the vitamin itself, nor through vitamin B complexes / multivitamin formulas. All the results for vitamin B12 are expressed in pg/ml and the normal range provided by the Belgian laboratory starts from 200pg/ml up to 900pg/ml, even if the lower limit could be considered as too low to be compatible with optimal health. Five first measurements, from February 1999 to April 2000, consistently fluctuated around 2500pg/ml (respectively **2796**pg/ml on 6/2/99, **2355**pg/ml on 19/4/99, **2572**pg/ml on 30/7/99, **2697**pg/ml on 7/3/2000 and **2325**pg/ml on 17/4/00), which is far too much! At that time, the patient's blood had to be monitored in relation with a drug-based anti-epileptic treatment. But the young woman was not complaining about her digestive system, even if she occasionally mentioned some abdominal cramps.

Her digestive problems started during the summer season in 2000, with IBS like symptoms, bloating, diarrhoea and excruciating pain in the belly. She was explored thoroughly and the gastroenterologist suspected initial Crohn's disease due to the presence of mucosal ulcerations in the proximal small intestine. During that period of major clinical deterioration, blood vitamin B12 level increased even further as seen from two measurements performed on 25/08/00 (**3220**pg/ml) and on 28/11/00 (**3221**pg/ml). Then, she refused to take the corticoids prescribed by the specialist and went on a natural treatment based on diet modifications (exclusion of high IgG foods, in her case: dairy products, beef, bananas and black pepper), supplements (according to her biological results in blood and in 24-hour urine), antimicrobial herbs (such as grapefruit seed extracts) and probiotics.

She didn't improve dramatically, but slowly started to complain less within a few weeks, then was feeling slightly better in March 2001 and significantly better when she came back five months later, in August 2001. Very interestingly, vitamin B12 blood levels started to withdraw to **2740**pg/ml on 24/3/01 and then down to **2132**pg/ml on 22/08/01. In fact, the last result provided her lower blood value from the beginning of the study. In September 2001, we then asked the gastroenterologist to perform a new endoscopy, in order to dismiss the diagnosis of Crohn's disease and make sure that we were not harming her by not giving the prescribed drugs. The digestive exploration was then considered as normal, besides some "non specific mucosal inflammation". So the case was much less worrying and it took about seven months before she consulted again, in March 2003. She was symptom-free, finally expressing a much better digestive capacity since she was on this diet, even though she hadn't renewed her supplements for a while. The cramps had disappeared and her blood reading for the vitamin B12 was **1001**pg/ml on 26/3/02, almost back to the normal range. She definitely reached and stayed within the normal range on further checks with **726**pg/ml on 31/08/02, **677**npg/ml on 21/5/03 and finally **516**pg/ml on 15/5/04. The last time we saw her, she was still symptom-free.

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