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High Vitamin B12 Level

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Vitamin B12/cobalamin functions as an important co-enzyme in the human body and is essential for purine and pyrimidine synthesis. Vitamin B12 deficiency is a very well recognized clinical entity but the conditions leading to elevated levels of vitamin B12 are generally not; hence the purpose of this article is to discuss such etiologies. Understanding the mechanisms will necessitate a brief review of vitamin B12 metabolism, presented below.

Under normal physiological conditions, dietary cobalamin binds to haptocorrin (HC) in saliva to be transported to the duodenum where free cobalamin is released. The free cobalamin in the duodenum binds to intrinsic factor (IF) forming a complex which is taken up by the intestinal mucosa to be ultimately released into the circulation. The majority of cobalamin in circulation is bound to haptocorrin (HC) and only a small portion (5-20%) is bound to transcobalamin (TC II). The plasma half -life (t ½) of TC II is short, only 40min-5hrs, whereas it is a long, 6-9 days for HC. When transcobalamin passes through enterohepatic circulation it is taken up by the liver for storage and is later released into bile.

Bound protein/form	Transcobalamin (TCII)	Haptocorrin (HC)
Plasma t ½	40min-5hrs	6-9 days
Site of synthesis	Liver, intestine, endothelium	Salivary glands, gastric mucosa

The reference range for vitamin B12 levels is 200-900 pg/mL (picograms per milliliter) and elevated cobalamin levels can be seen in various malignancies including hematological conditions like myeloproliferative disorders, renal and liver disorders.

Hematological etiologies	Myeloproliferative conditions -Chronic Myeloid Leukemia (CML), Polycythemia Vera (PV), Hypereosinophilic syndromes (HES), Chronic myelomonocytic leukemia (CMML) Myelofibrosis Acute Promyelocytic leukemia (APL)- less commonly other types of Acute myeloid leukemia (AML)
Malignancy	Solid tumors like Hepatocellular carcinoma (HCC), Breast ca, Renal cell ca, Colon ca, Gastric ca & any cancer with liver metastases
Hepatic etiologies	Hepatitis, Cirrhosis, Hepatocellular carcinoma
Others	Chronic kidney disease, Cystic Fibrosis (due to liver injury) & Iatrogenic - VitB12 administration

Mechanisms of elevated vitamin B12 levels in the above conditions include:

1. Excess Haptocorrin production

Markedly elevated B12 levels (up to 10x!) are often seen with myeloproliferative disorders as listed in the table above. The expanded myeloid cell population in myeloproliferative conditions is thought to be leading to an increase in HC level thereby causing elevated B12 levels. Elevated B12 levels are also more commonly seen in Acute Promyelocytic leukemia (APL) than other types of Acute myeloid leukemia (AML).

2. Release from hepatocytes and reduced uptake

In cases of acute hepatitis, cirrhosis, HCC or metastatic disease of the liver, pathogenesis is thought to be related to both hepatocyte cell injury causing the release of stored vitamin B12 into the circulation along with decreased ability of the damaged hepatocytes to take up the circulating vitamin B12.

3. Excess of transport proteins—both transcobalamin and haptocorrin (TCII and HC)

In several solid tumors as listed above, excess transport levels were thought to be the culprit for elevated B12 levels. The excess transport proteins were both as a result of exogenous production by the tumor directly or by the indirect effects of tumor through stimulation of leukocytes to produce TCII and HC.

As per this overview, we conclude that a thorough medical investigation is necessary for patients with elevated B12 levels including a careful history & physical exam, basic labs including CBC with manual differential count, review of peripheral smear and CMP to carefully look at liver function as well as further work up as guided by these initial steps.

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