Gli integratori di Ferro e Vitamine: Orientarsi tra le Proposte

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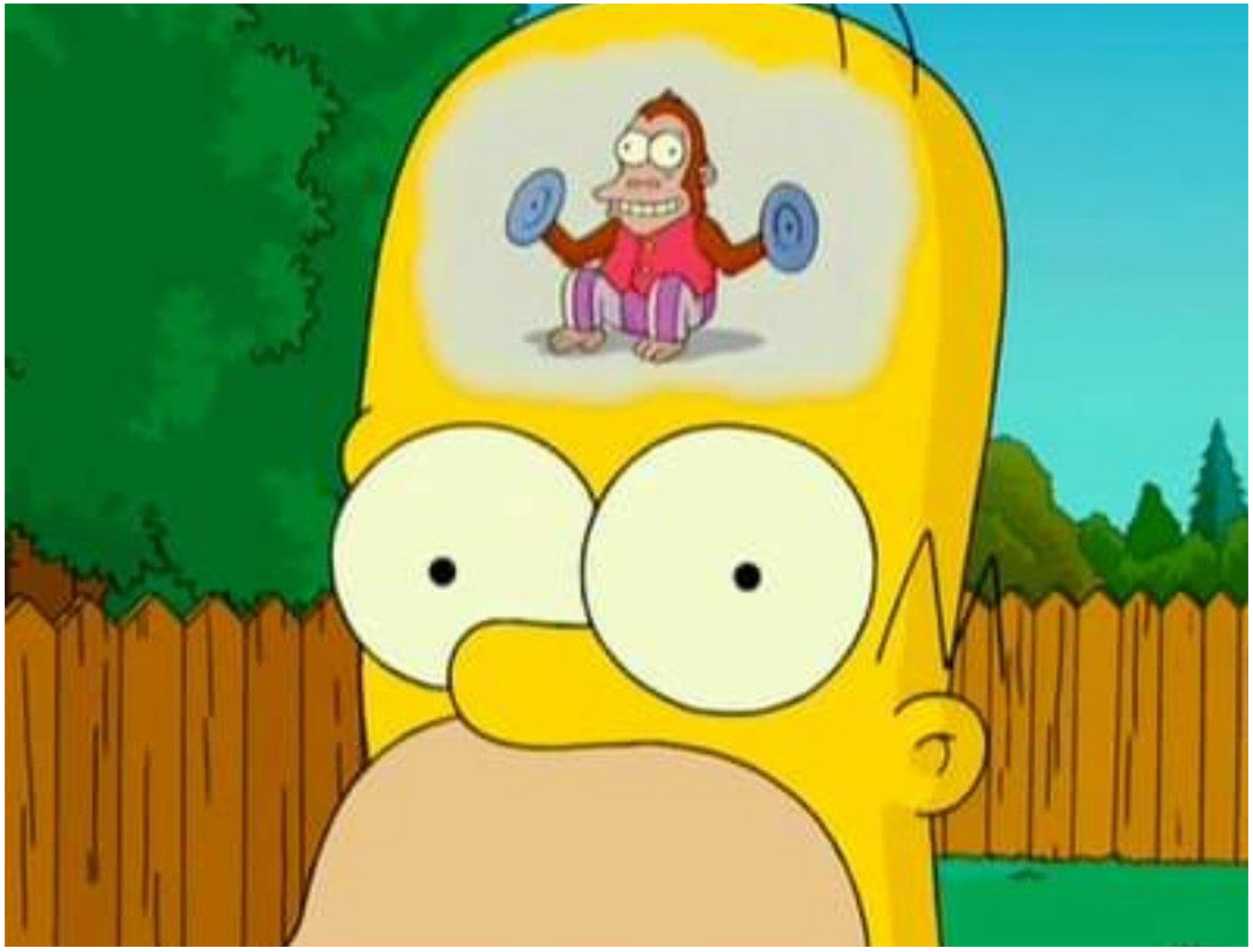

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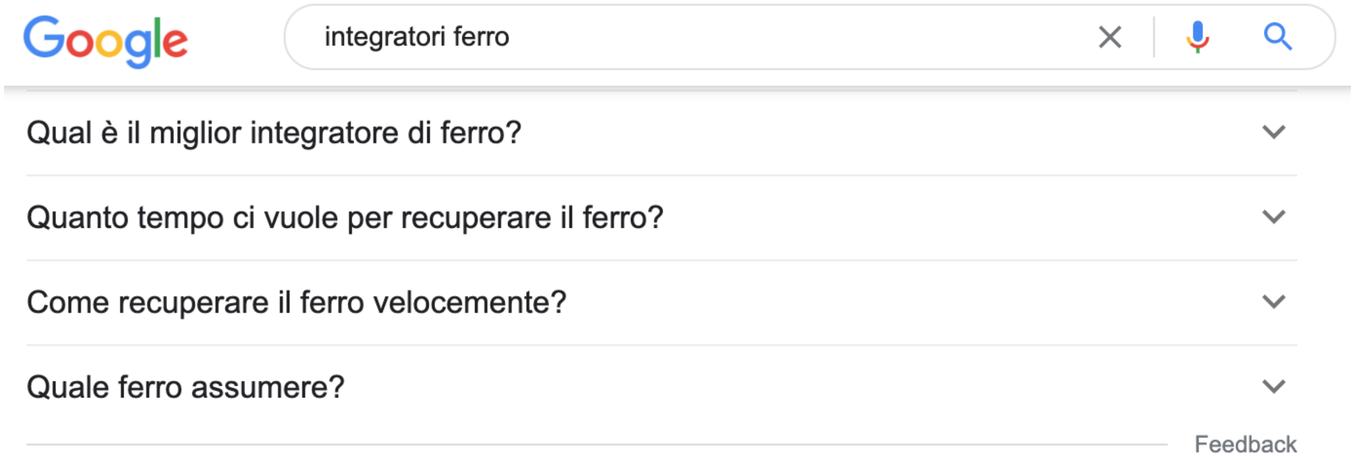

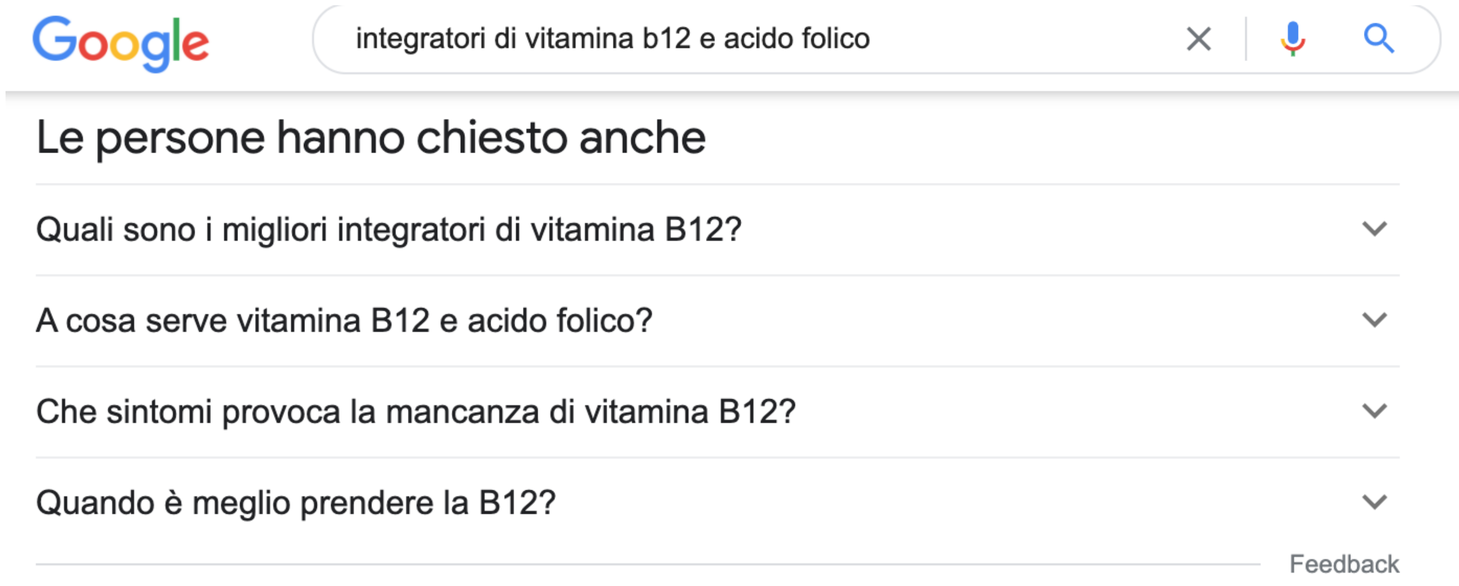

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Integratori di Ferro

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iron formulations

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Page 1 of 288

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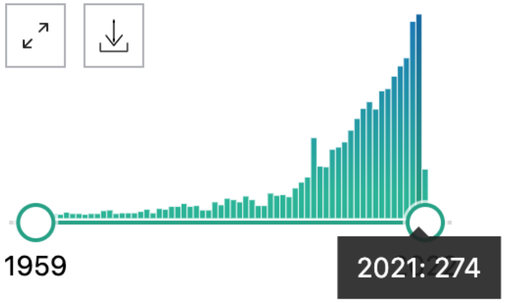

TEXT AVAILABILITY

1

Cite

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Iron deficiency.

Pasricha SR, Tye-Din J, Muckenthaler MU, Swinkels DW.

Lancet. 2021 Jan 16;397(10270):233-248. doi: 10.1016/S0140-6736(20)32594-0. Epub 2020 Dec 4.

PMID: 33285139 Review.

Oral **iron** therapy is the first line of treatment in most cases. Hepcidin upregulation by oral **iron** supplementation limits the absorption efficiency of high-dose oral **iron** supplementation, and of oral **iron** during inflammation. Modern parenteral **iron** ...

Back

Deficit di ferro: Epidemiologia

- Prima causa di malnutrizione nel mondo (dato WHO)

- Colpisce circa 2 miliardi di individui (25% popolazione mondiali)

- Maggiore prevalenza nei paesi in via di sviluppo

- Maggiore prevalenza fra le donne

- Fattori di rischio per incremento mortalità e morbilità

- **SINTOMI**: anemia microcitica, fatica, letargia, cefalea, pallore, difficoltà a concentrarsi, vertigini, acufeni

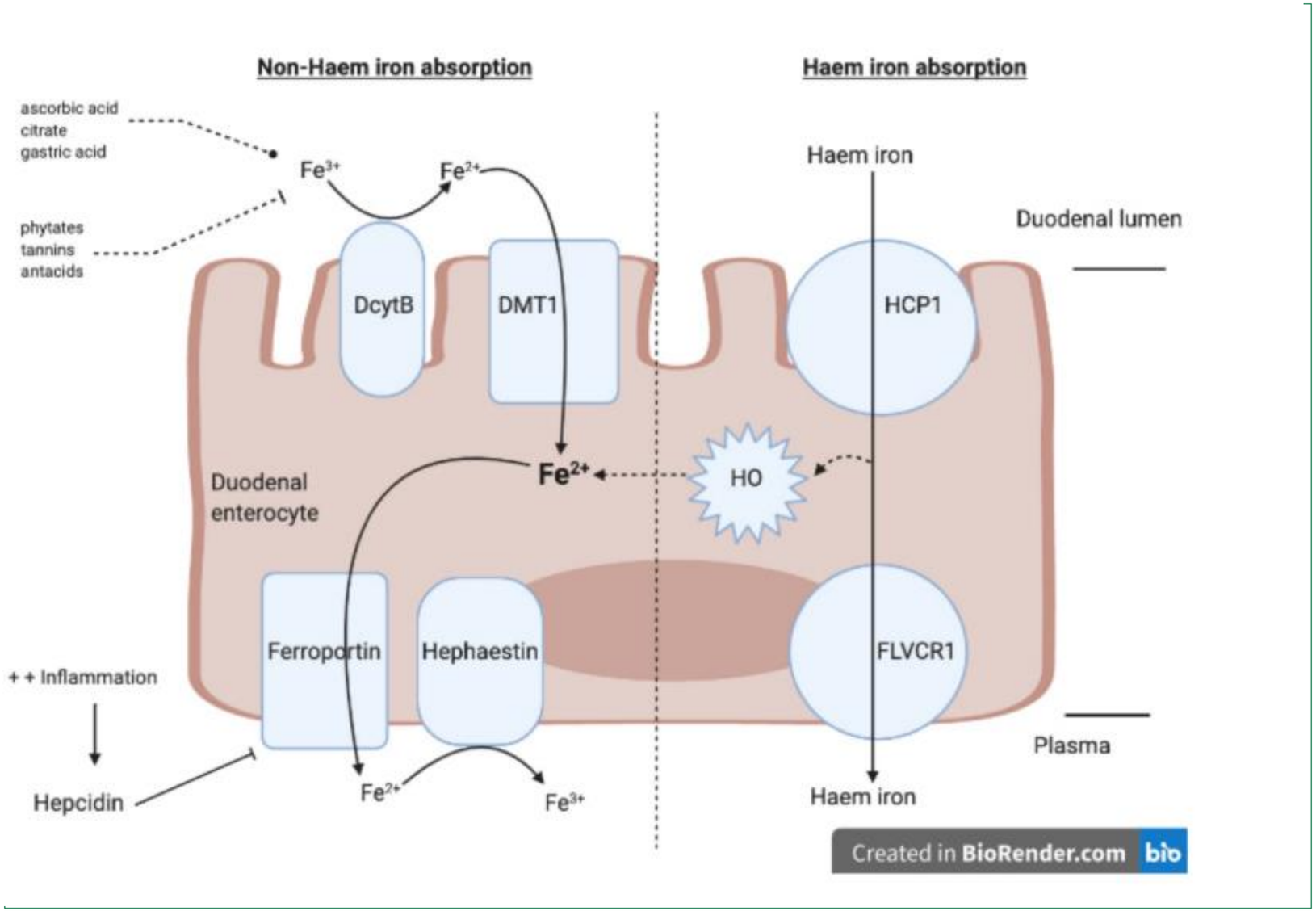
Pasricha SR, Lancet 2021

Assorbimento del ferro: Fisiopatologia

EPCIDINA:

-Risente delle concentrazioni di ferro, stati infiammatori, ipossia

- regola passaggio di ferro nel plasma a livello intestinale
e nei depositi



Pasricha SR, Lancet 2021

Deficit di ferro : Cause

Blood loss

- Intestinal blood loss
  - Oesophageal
    - Varices
    - Carcinoma
    - Ulceration
    - Reflux oesophagitis
  - Gastric*
    - Gastric cancer and gastric p
    - Gastric ulcers*
    - Use of aspirin and other no inflammatory drugs*
    - Angiodysplasia, telangiecta vascular ectasia (watermel
  - Small bowel
    - Hookworm (*Ancylostoma d americanus*)*
    - Inflammatory bowel diseas
    - Duodenal ulcers

Inadequate iron uptake

- Inadequate nutritional iron intake
  - Inadequate dietary iron content
    - Low haem iron content (eg, from a vegetarian or vegan diet)
    - Food insecurity or low dietary diversity* (eg, resulting from poverty, especially in low-income countries)
    - Low iron content complementary diet* (eg, prolonged breastfeeding, or milk preference)
- Inadequate nutritional iron absorption
  - Concomitant consumption of inhibitors of iron absorption (eg, calcium or tea)
  - Inadequate stomach acidification
    - Atrophic gastritis
    - Use of antacids or proton pump inhibitors*
    - *Helicobacter pylori* infection
    - Procedures after gastric bypass
  - Intestinal mucosal dysfunction (eg, coeliac disease* or inflammatory bowel disease)
  - Obesity
  - Inappropriately increased hepcidin concentrations preventing iron absorption (eg, during chronic inflammation or iron-refractory iron deficiency anaemia caused by *TMPRSS6* mutations)

polyps
ctasia, and Meckel's

d gastrointestinal bleeding
nfants younger than

ease*
e aortic stenosis, acquired
ndrome, angiodysplasia,
mia)
in Peutz-Jeghers syndrome

telangiectasia

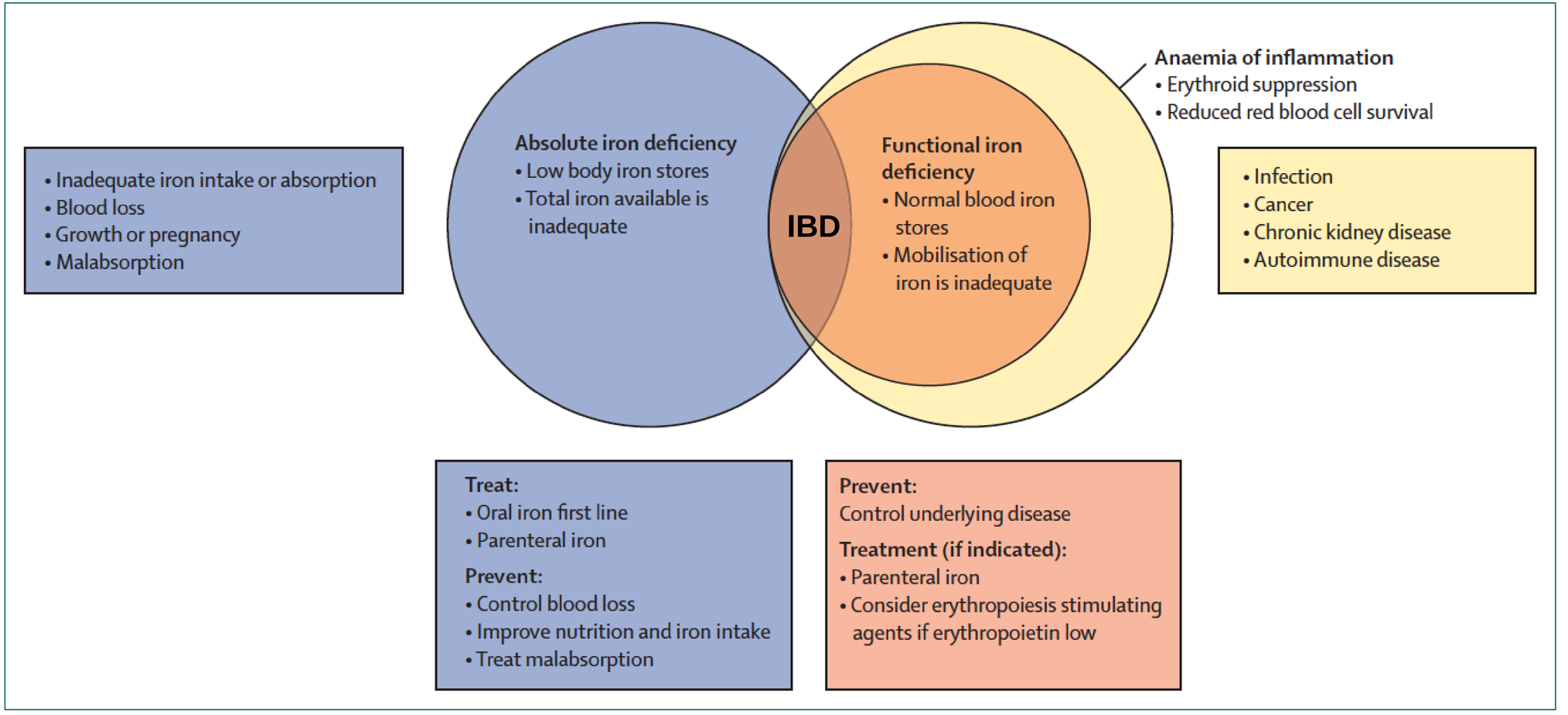
ausal women and girls)*
orders (von Willebrand
hilia A or B, and platelet

e tract cancers

istosoma haematobium)

Pasricha SR, Lancet 2021

Deficit di ferro : Cause



Pasricha SR, Lancet 2021

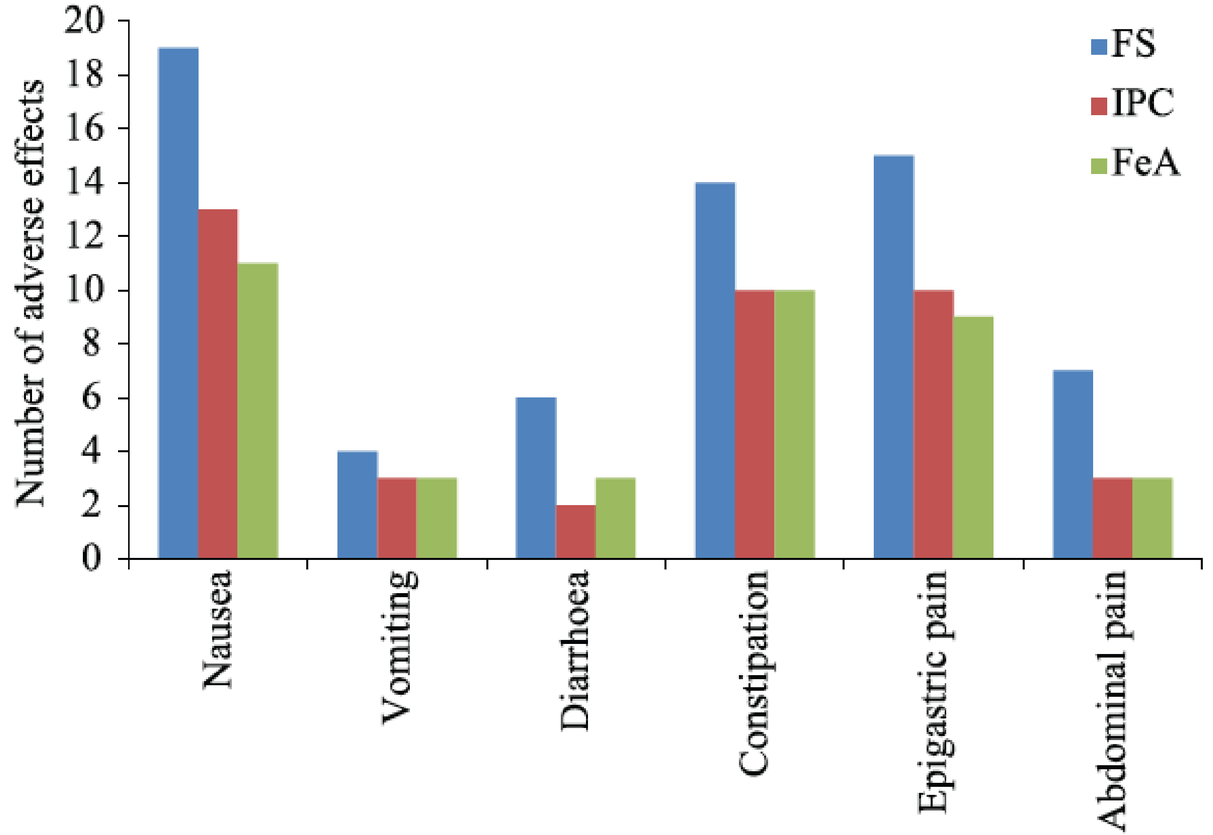
Deficit di ferro : Formulazioni per OS

Iron supplement	Comments
Bivalent	
Ferrous fumarate (Fe^{2+})	
Ferrous gluconate (Fe^{2+})	More adverse effects if not in a prolonged-release formulation
Ferrous sulphate (Fe^{2+})	
Ferrous glycine sulphate (Fe^{2+})	
Trivalent	Poorer absorption
Iron protein succinylate (Fe^{3+})	More expensive
Iron polymaltose complex (Fe^{3+})	A greater number of intakes

Effetti avversi: nausea, vomito, dispepsia (dose-dipendenti)
stipsi e diarrea

Santiago P, The Scientific World Journal 2012

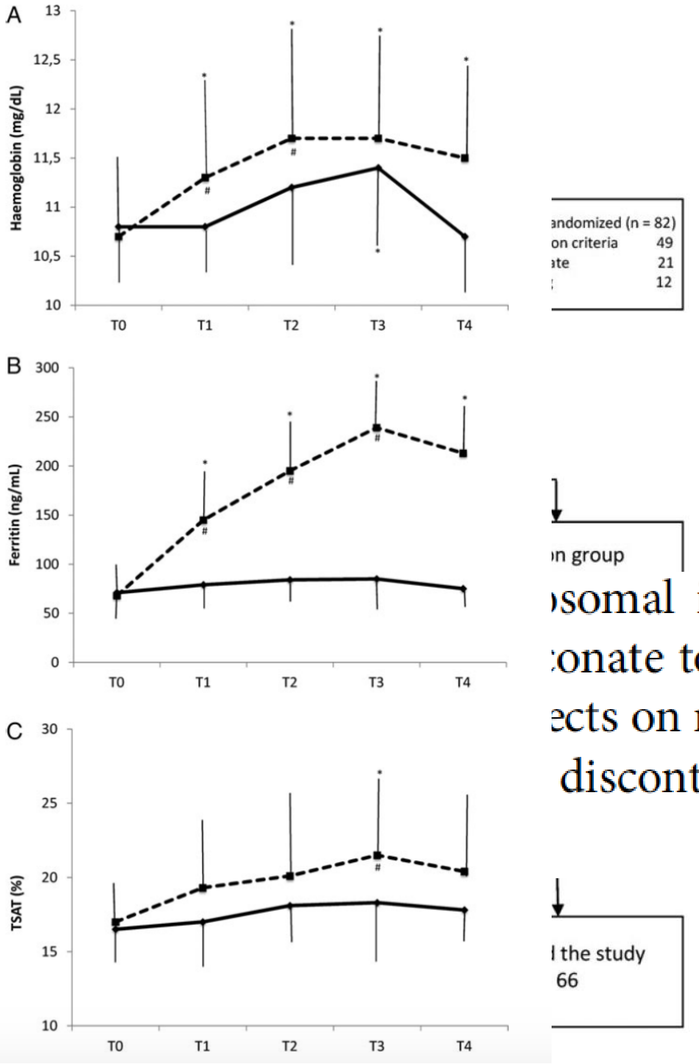
Comparison of efficacy & safety of iron polymaltose complex & ferrous ascorbate with ferrous sulphate in pregnant women with iron-deficiency anaemia



Chavan S et al.
Indian J Med Res 154, July 2021

Effect of oral liposomal iron versus intravenous iron for treatment of iron deficiency anaemia in CKD patients: a randomized trial

	Gr T0	T3
Hb (g/dL)	10.	.1* 11.7 ± 1.0*
eGFR (mL/min)	25.	2.9 27.9 ± 7.8
Ferritin (ng/mL)	71.	.2* 238.5 ± 49.7*
TSAT (%)	16.	.6 21.5 ± 5.2*
PTH (pg/mL)	11(	-118) 104 (34–120)
hsCRP (mg/L)	1.2	-1.5) 1.0 (0.8–1.9)



ndomized (n = 82)
on criteria 49
ıte 21
12

IV iron group

n group

Conclusions. Ou
safe and efficacio
anaemia in ND-C
of iron stores and
are lower.

osomal iron is a
onate to correct
ects on repletion
discontinuation

Completed the study
n = 33

l the study
66

Pisani A et al.
Nephrol Dial Transplant (2014) 0: 1–8

Ferric Maltol: A New Oral Iron Formulation for the Treatment of Iron Deficiency in Adults

Conclusion: FM is a relatively safe, effective oral iron therapy that may be better tolerated than other oral iron formulations. FM may be an effective alternative to IV iron in patients with IBD.

Nuova formulazione di ferro trivalente confronta con ferro bivalente e ferro ev.

3 diverse popolazioni

Study	Treatment group (n)			
AEGIS I and 2[5]		Primary end point: change in Hb concentration from baseline to week 12		
		Baseline Hb (g/dL) Mean (SD)	Week 12 Hb (g/dL) Mean (SD)	Improvement in Hb (g/dL), mean (SE)
OLE[6]				
		Baseline Hb (g/dL), mean (SD)	Week 64 Hb (g/dL), mean (SD)	Improvement in Hb (g/dL), mean (SD)
	Continued[a] (n = 50)	11 (1.03)	13.95 (1.26)	3.07 (1.46)
	Switch[b] (n = 47)	11.1 (0.85)	13.33 (1.46)	2.19 (1.61)
AEGIS-CKD[24]		Primary end point: change in Hb concentration from baseline to week 16		
		Baseline Hb (g/dL), mean (SD)	Change in Hb from baseline to week 16 (g/dL), LSM (SE)	Between-group difference in change in Hb from baseline to week 16
	FM 30 mg bid (n = 111)	10.06 (0.77)	0.5 (0.12)	0.52 (0.21; 95% CI: 0.10-0.93; $P = 0.0149$)
	Placebo bid (n = 56)	10.03 (0.82)	−0.02 (0.16)	
AEGIS-H2H[25-27]		Primary end point: responder rate at week 12		
		Responder rate,[c] n (%)	Difference in RR[d] (%)	Risk difference (95% CI)
	FM 30 mg bid (PP; n = 86)	64 (74)	9	−0.1 (−0.2 to 0.0), $P_{noninf} = 0.017$
	IV FCM (PP; n = 93)	77 (83)		

Khoury et al.
Annals of Pharmacotherapy 2020

Integratori di Ferro: IBD

	Oral Iron	IV Iron
Choice of administration	Mild IDA (Hb > 100 g/L) Quiescent IBD	Severe anaemia (Hb < 100 g/L) Intolerant to oral iron Moderate to severe IBD activity
Pros	Greater availability Ease of administration Low cost	Bypasses GI tract absorption Less side effects
Cons	Side effects with poor patient tolerance Discontinuation in 20% Increases IBD activity Disrupts microbiome	Low bioavailability Inconvenience of IV application Greater cost Risk of hypersensitivity reaction *

Khoury et al.
Annals of Pharmacotherapy 2020

Integratori di Ferro: messaggi chiave

-**Target terapia:** normalizzazione del livello di emoglobina e del volume eritrocitario e il ripristino delle riserve di ferro nei depositi, oltre che di rimuovere e correggere la causa scatenante

-**Formulazione**: OMS suggerisce ferro bivalente (ferroso), ma scelta in base alla tollerabilità individuale

-**Dose:** da 100 a 200 mg di ferro/die in una o due dosi, preferibilmente a stomaco vuoto

-**Durata:** prolungata 4-6 mesi,

-**Modalità di assunzione (prevenire effetti avversi)**: dosaggi più bassi e aumentarli in 4-5 giorni, frazionare il dosaggio giornaliero e/o assumere il ferro ai pasti, anche se ciò determina una riduzione dell'assorbimento

Integratori di Vitamine: Vitamina B12

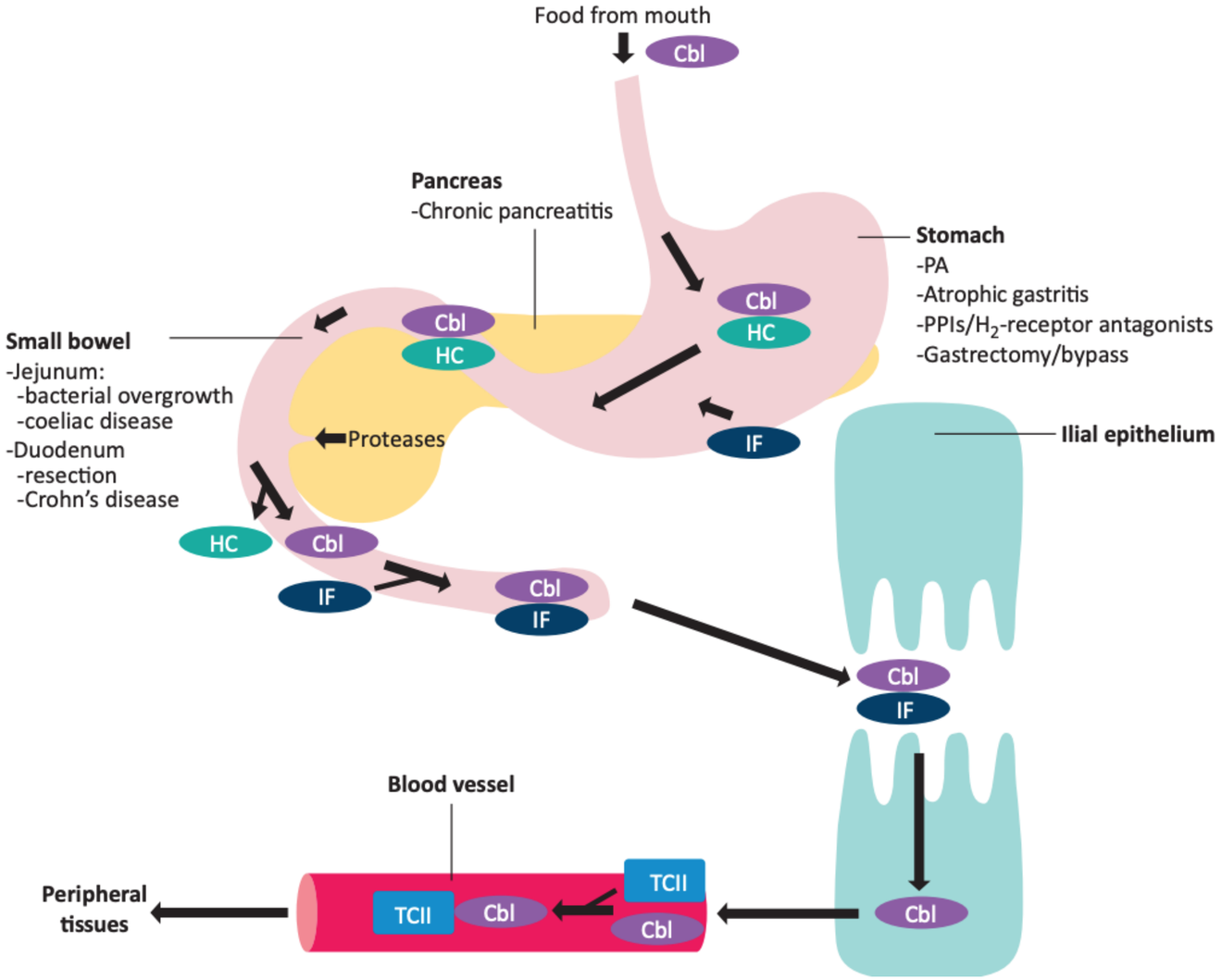
- Tra i deficit vitaminici più frequenti

- Negli USA prevalenza varia con età:
-3% tra i 20-39 anni
- 4% tra i 40 e 59 anni
-6% sopra i 60 anni

- Sintomi: anemia macrocitica, deficit neurologici fino a deterioramento cognitivo

Shipton MJ et al.
Clinical Medicine 2015 Vol 15, No 2: 145–50

Integratori di Vitamine: Vitamina B12



ASSORBIMENTO VITAMINA B12:

- **Acidità gastrica + protesi**
- **Legamente con il fattore intrinseco (IF) prodotto dalle cellule Parietali**

Shipton MJ et al. Clinical Medicine 2015 Vol 15, No 2: 145–50

Deficit Vitamina B12: Cause

Table 1. Causes of low vitamin B_{12} levels.

Cause	Examples
Low vitamin B_{12} intake	Vegetarianism, chronic alcoholism and older people
Autoimmune	Pernicious anaemia and Sjögren's syndrome
Food-bound cobalamin malabsorption	Atrophic gastritis, chronic gastritis and *Helicobacter pylori*-associated gastritis
Surgery	Post-gastrectomy and ileal resection
Malabsorption	Small intestinal bacterial overgrowth, chronic pancreatic exocrine insufficiency, Crohn's disease, coeliac disease and achlorhydria
Obstetric/gynaecological	Oral contraceptive, hormone replacement therapy and pregnancy
Genetic	Transcobalamin II deficiency
Drugs	Metformin, proton pump inhibitors and histamine H_2-receptor antagonists

Shipton MJ et al.
Clinical Medicine 2015 Vol 15, No 2: 145–50

Outcomes	IM vitamin B_{12}	
Serum vitamin B_{12} levels Normal value: > 300 pg/mL (> 221 pmol/L) Follow-up: 90 days and 4 months	See comment	rticipants) used 1000 µg/day oral or IM vit- tal dose 15 mg): MD was -11.7 pg/mL (95% 1) (Bolaman 2003). rticipants) used 2000 µg/day vitamin B_{12} 40 mg) or 1000 µg/day IM vitamin B_{12} (to- g): MD was 680 pg/mL (95% CI 392.7 to our of oral vitamin B_{12} (Kuzminski 1998). rticipants) (using 1000 µg/day oral or IM (total dose 90 mg and 15 mg, oral and IM) reported that 27/30 in the IM vitamin B_{12} and 20/30 in the oral vitamin B_{12} group ieved normalisation of serum vitamin B_{12},) pg/mL (Saraswathy 2012).
Clinical signs and symptoms	Not reported	
Adverse events Follow-up: 90 days and 3 months	See comment	eported no treatment-related adverse he oral and IM vitamin B_{12} groups. 2 reported that 2/30 participants al vitamin B_{12} group left the trial early events.
Health-related quality of life	Not reported	

AUTHORS' CONCLUSIONS

Implications for practice

Questions about the use of oral or intramuscular (IM) vitamin B_{12} have been debated by doctors for nearly 50 years, and a conclusive answer is still lacking. Low-quality evidence indicates that an oral dose of 1000 µg/day vitamin B_{12} works similarly to IM vitamin B_{12} in restoring serum B_{12} levels and acquiring haematological responses in people who are vitamin B_{12} deficient. An oral dose of 2000 µg/day vitamin B_{12} might be more effective than IM vitamin B_{12} .

Adverse events were rare, and low-quality evidence indicates that oral vitamin B_{12} costs less than IM vitamin B_{12} injections. No trial reported on clinical signs and symptoms of vitamin B_{12} deficiency,

Future trials should be performed in primary care settings on participants without considering gender, ethnicity, age, and region. It is important for future research to include participants with poor absorption of oral vitamin B_{12}, such as those with pernicious anaemia, gastrointestinal disease or resection. Considering that the diagnosis and treatment of vitamin B_{12} deficiency is related to the metabolism of vitamin B_{12}, more research should be conducted focusing on the absorption, distribution, metabolism, and excretion processes of vitamin B_{12}.

Wang H et al.
Cochrane Database of Systematic Reviews 2018

Comparison of sublingual vs. intramuscular administration of vitamin B12 for the treatment of patients with vitamin B12 deficiency

Merav Jacobson Bensky[1] · Irit Ayalon-Dangur[2] · Roi Ayalon-Dangur[3] · Eviatar Naamany[4] · Anat Gafter-Gvili[4,5] · Gideon Koren[4,6] · Shachaf Shiber[4,7]

In conclusions, to the best of our knowledge, this is the largest study demonstrating that therapy with SL preparations of VB12 is sufficient and even superior to IM route. It overcomes the challenges of IM injections and should become first line option for patients with VB12d. All other studies which investigated the efficacy of SL VB12 treatment were small and included only tens of subjects. Our study was the first to investigate the pharmacological behavior of SL VB12 on thousands of subjects from different etiologies. The results of this study provide important information for the primary physician who needs to decide the type of administration route in cases of VB12d, even in cases where the etiology is unknown.

Table 3 There are several methods t … 300 ng/L (… vitamin B12 (VB12) prepar… present study was to compar… a retrospective analysis of da… for all patients older than 18… was the change in levels of… supplements. Of them, 830 (… ± SD difference between sV… group vs. IM injection group… an increase of sVB12 level… documents therapy with SL … of IM injections and should … al (SL), and intranasal … acking. The aim of the … g B12 levels. This was … S). Data were recorded … 17. The main outcome … nts treated with VB12 … h SL tablets. The mean … cantly higher in the SL … the odds ratio (OR) for … s the largest study that … ercomes the challenges … e sVB12 levels <

Base line s…				p value
(range 211…				$p < 0.001$
After treat…				$p < 0.001$
Δ betweer…				$p < 0.001$
Δ betweer…				$p < 0.001$
Δ betweer…				$p < 0.001$
Δ between leukocyte levels before ar…			0.12 ± 1.47	$p = 0.11$
Δ between platelets levels before and after treatment		0.16 ± 40.5	− 1.3 ± 39.42	− 0.97 ± 39.8	$p = 0.35$

Bensky et al.
Drug Deliv. and Transl. Res 2019

Grazie per l’attenzione!!!