ÇOCUK SAĞLIĞI VE HASTALIKLARI ARAŞTIRMALARINDA GÜNCEL METODOLOJİK YAKLAŞIMLAR

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Çocuk Sağlığı ve Hastalıkları Araştırmalarında Güncel Metodolojik Yaklaşımlar

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İçindekiler


BÖLÜM 1

Çocuklarda Obezite ile İlişkili Metabolik Sendrom

Ümit Alper Özcan[1]

Giriş

Obezite ve metabolik sendromun görülme sıklığı son yıllarda dünya genelinde artış göstermektedir, bu durum erişkin döneminde artmış sağlık sorunlarına yol açmaktadır, bu yüzden obezite ve metabolik sendrom bir halk sağlığı sorunu haline gelmiştir. Obeziteyle birlikte görülebilen metabolik sendromun diyabet mellitus ve kardiyovasküler hastalık riskini arttırdığı görüldüğünden çocukluk döneminde önlenmesi değerlidir. Bu bölümde obezite ile ilişkili metabolik sendromun tanımı, patofizyolojisi, klinik bulguları ve tanısı, yönetimi ve tedavisi üzerinde durulacaktır.

Tanımlar

Metabolik sendrom yağ, karbonhidrat ve protein metabolizmasındaki bozuluklar ile karakterize metabolik hastalıklar kümesidir (1); temel olarak santral obezite, dislipidemi, hipertansiyon ve insülin direncinden oluşur. Erişkin metabolik senrdom tanımlarının çocuk ve adölesanlara doğrudan uygulanamaması; büyüme, vücut kompozisyonu, yağ dağılımı ve insülin duyarlılığındaki yaşa bağlı değişimlerden kaynaklanmaktadır (2). Bu nedenle çocuklarda metabolik sendrom için bel çevresi, kan basıncı, lipidler ve glukozu içeren, çoğunlukla persentillere dayalı farklı tanımlar geliştirilmiştir. Cook, Weiss, de Ferranti ve IDF gibi yaklaşımlar, kullanılan antropometrik ölçütler ve eşik değerler açısından önemli farklılıklar göstermekte ve prevalansı etkilemektedir. IDF, yaş gruplarına göre sınıflandırma ve persentil temelli bel çevresi kullanımıyla klinikte en yaygın kullanılan tanımı sunmaktadır. Bununla birlikte, yaş, cinsiyet ve bölgesel yaşam tarzı farklılıkları nedeniyle çocuklarda metabolik sendrom için halen evrensel olarak kabul edilmiş tek bir tanım bulunmamaktadır (3).

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Tablo 1. IDF kriterleri (2007)

	10-16 yaş	≥16 yaş
Tanım kriterleri	Santral yağlanma + aşağıdakilerden 2 kriter	Santral obezite + aşağıdakilerden 2 kriter
Bel çevresi	≥90. persentil (ırk ve etnik kökene göre)	Avrupa'da erkekler>94 cm kızlar>80 cm
Kan basıncı	Sistolik kan basıncı ≥130 mmHg; Diyastolik kan basıncı ≥85 mmHg	Sistolik kan basıncı ≥130 mmHg; Diyastolik kan basıncı ≥85 mmHg
Trigliserid (mg/dl)	≥150	≥150
HDL (mg/dl)	<40	<40 erkekler; <50 kızlar
Glukoz	Açlık kan şekeri≥100 mg/dl veya bilinen Tip 2 DM	Açlık kan şekeri≥100 mg/dl veya önceden Tip 2 DM

6-10 yaş arası tanı konulamamakta.

Kaynak: Zhang ve ark, 2025

Epidemiyoloji

Standardize tanım olmaması nedeniyle kesin prevelansı belirlemek zordur. Bildirilen prevalans oranları %6 ile %39 arasında değişmekte olup; bu farklılık tanı kriterleri, yaş, cinsiyet, vücut kitle indeksi, sosyoekonomik durum, sedanter yaşam tarzı ve etnik kökene bağlıdır (4).

Patofizyoloji

Metabolik sendromun patofizyolojisi tam olarak aydınlatılmamış olmakla birlikte, genetik ve epigenetik faktörler ile çevresel etmenler, beslenme alışkanlıkları ve yaşam tarzının etkileşimi hastalığın gelişiminde rol oynamakta (5); özellikle pediatrik popülasyonda obeziteye bağlı insülin direnci temel patojenik mekanizma olarak kabul edilmektedir (4).

İnsülin direnci, obez çocuk ve ergenlerde yüksek prevalansa sahip olup metabolik sendromun gelişiminde temel patofizyolojik mekanizmadır. Serbest yağ asidi artışı, inflamasyon ve adiposit disfonksiyonu; hiperglisemi, dislipidemi, hipertansiyon ve ateroskleroz riskini artıran metabolik bozukluklara yol açmaktadır (4).

Obezite, özellikle viseral yağlanma, çocuk ve yetişkinlerde insülin direncinin temel nedenidir; artmış serbest yağ asitleri, adipokin dengesizliği ve ektopik yağ birikimi insülin sinyalizasyonunu bozarak dislipidemi, hipertansiyon ve glukoz metabolizması bozukluklarına yol açmaktadır. Obeziteye eşlik eden subklinik kronik inflamasyon (IL-6, TNF-α, CRP artışı) insülin fonksiyonunu bozar, endotelyal disfonksiyon ve erken ateroskleroz gelişimini tetikler (6). Bununla birlikte genetik, etnik ve sosyoekonomik farklılıklar hastalık gelişimini

etkilemekte olup, tedavide yaşam tarzı değişikliklerini merkeze alan bütüncül yaklaşımlar ön planda tutulmaktadır.

Tablo 2. Risk faktörleri

DEMOGRAFİK FAKTÖRLER	• Cinsiyet farklılıkları • Ailede obezite öyküsü
PRENATAL & ERKEN YAŞAM DÖNEMİ FAKTÖRLERİ	• Gestasyonel diyabet • Düşük doğum ağrılığı
OBEZİTE İLE İLİŞKİLİ FAKTÖRLER	• Erken ve uzun süreli obezite • Polikistik over sendromu • Çölyak hastalığı • Tip 1 diyabet • Tiroid disfonksiyonu
BESLENME İLE İLGİLİ FAKTÖRLER	• Düzensiz öğünler • Sağlıksız diyet • B vitamini takviyesi
YAŞAM TARZI & DAVRANIŞSAL FAKTÖRLER	• Aşırı ekran süresi • Sedanter yaşam tarzı • Yetersiz uyku (<6.5 saat gecelik)
METABOLİK FİZYOLOJİK FAKTÖRLER	• Bozulmuş apolipoprotein düzeyleri • İnsülin direnci, glukoz intoleransı • Sistemik inflamasyon • Çevresel kirleticiler

Kaynak: Anton-Păduraru ve ark., 2025

Yönetim ve Tedavi

Obezite, insülin direnci ve son olarak metabolik sendromun ortaya çıkması enerji alımı ve tüketimi arasındaki dengesizlikle olur. Bu yüzden tedavideki birincil amaç enerji alımını azaltıp, tüketimi yani fiziksel aktivitenin arttırılmasıdır. Pediatrik hastaları özellikle adölesanları sağlıksız yaşam tarzlarını değiştirmeye teşvik etmek zordur, ancak doğru psikolojik destek ile bu mümkündür (3).

Dünya Sağlık Örgütü, Amerikan Pediatri Akademisi diyet değişikliklerinin temelinde sebze ve meyve tüketiminin arttırılması, şeker ve doymuş yağ asitlerinin tüketiminin azaltılması vardır (9). Dengeli beslenmenin sağlanabilmesi için; protein, yağ ve karbonhidratların yaşa uygun oranlarda tüketilmesi, besin çeşitliliğinin olması ve posa içerikleri yüksek gıdalar ile beslenmenin gerçekleşmesi gerekir. Posa içerikleri yüksek gıdalar insülin

duyarlılığını arttırarak etki gösterir. Akdeniz diyeti glukoz ve lipid profili üzerine olumlu etkilere sahiptir. Şekerli içecek tüketimi azaltılmalı, basit karbonhidratların tüketimi kısıtlanmalı, doymamış yağ asitlerinin beslenmedeki yeri arttırılmalıdır.

Düzenli egzersiz yapan hastaların insülin duyarlılığı, kan basıncı ve lipid profili üzerinde olumlu etkiler gerçekleşir. Etkili egzersiz programlarının en az 12 hafta sürmesi, haftada en az 3 gün ve günde 60 dakika üzerinde yapılması önerilir (8).

Yaşam tarzı değişiklikleri ile düzelmeyen ağır olgularda farmakolojik tedavi ve cerrahi yöntemler gündeme gelebilir. Statinler, GLP-1 analogları ve metformin tedavi seçenekleri arasındadır. Morbid obez hastalar için bariatrik cerrahi en etkili yöntemdir (3).

Tedavi stratejisini belirlerken hastaya özel olarak temelde yaşam tarzı değişiklikleri, gerekirse farmakolojik tedavi ve cerrahi yaklaşım tercih edilmelidir.

Önleme Stratejileri

Metabolik sendromun önlenmesi ve yönetiminde yaşam tarzı değişikliklerini merkeze alan bütüncül yaklaşımlar temel önem taşımaktadır. Metabolik sendrom için genetik yatkınlık dışında birçok risk faktörü değiştirilebilir nitelikte olup, özellikle gebelik öncesi ve gebelik döneminde sağlıklı beslenmenin ve normal vücut ağırlığının korunması erken dönem koruyucu stratejiler açısından önem taşımaktadır. Emzirmenin koruyucu bir faktör olduğu gösterilmiş; özellikle altı ay ve üzeri emzirme süresi metabolik sendrom riskinde anlamlı azalma ile ilişkilendirilmiştir (4). Ayrıca emzirme süresi uzadıkça obezite, bel çevresi artışı, dislipidemi, hipertansiyon, diyabet, glukoz intoleransı ve insülin direnci riskinin azaldığı bildirilmektedir (10). Anne sütünde bulunan insülin, IGF-1 ve leptin gibi biyoaktif bileşenler metabolik programlamayı olumlu yönde etkileyerek enerji dengesi ve iştah düzenlenmesine katkı sağlamaktadır (11). Emzirmenin sağlıklı beslenme ve düzenli fiziksel aktivite ile desteklenmesi, çocuk ve ergenlerde metabolik sendromun önlenmesinde güçlü bir koruyucu temel oluşturmaktadır (3)

Metabolik sendromun taraması özellikle tip 2 diyabet ve kardiyovasküler hastalık riski yüksek olan fazla kilolu ve obez çocuklar için önerilmektedir. Risk faktörleri ebeveyn obezitesi, ailede tip 2 diyabet öyküsü (birinci, ikinci derece), ırk/etnik köken (Asyalı, Latin, Afrikalı Amerikalı), insülin direnci göstergeleri (akantozis nigrikans, hipertansiyon, polikistik over sendromu, dislipidemi), küçük gestasyonel haftada doğum ve annede gestasyonel diyabet öyküsü olmasıdır. Bu faktörlerden iki tanesinin varlığı tarama yapılması gerektiğini gösterir (4).

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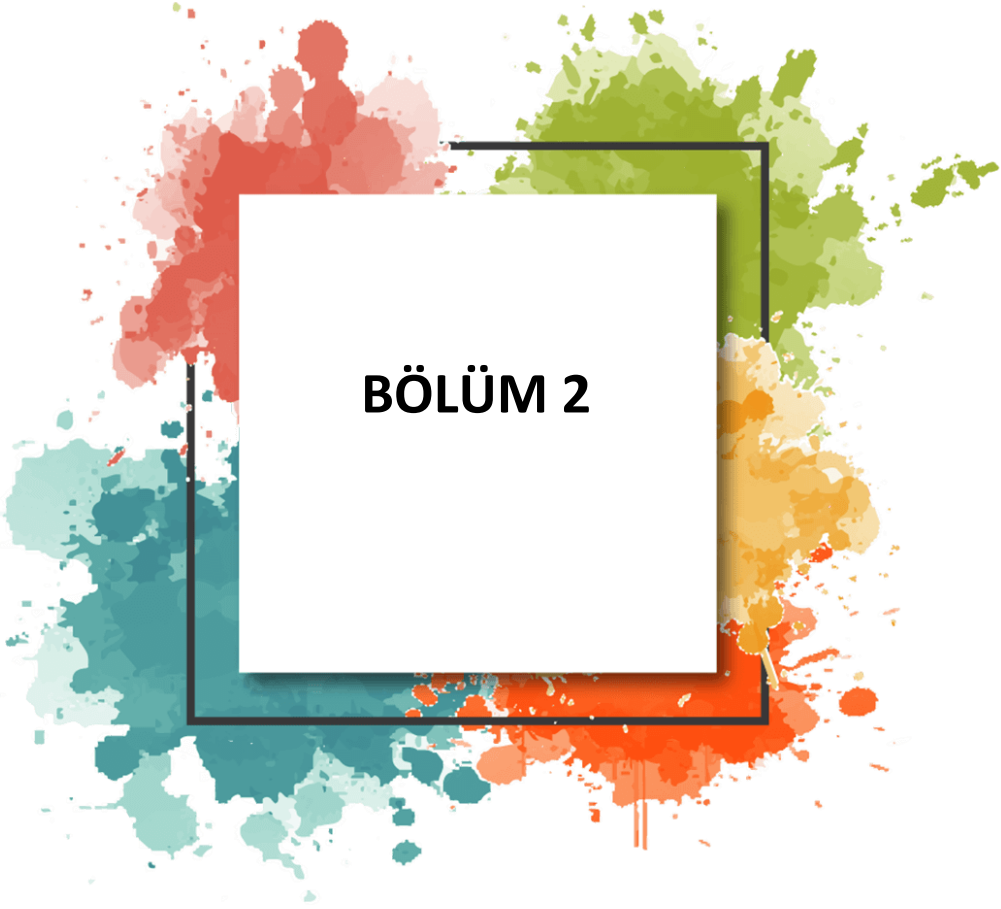
BÖLÜM 2

Vitamin B12 Deficiency in Children: Etiology, Diagnosis, and Treatment Approaches

Selen Ceren Çakmak[1]

1. Introduction

Vitamin B12, also known as cobalamin, is an essential water-soluble micronutrient that serves as a critical cofactor in two pivotal enzymatic reactions: the conversion of methylmalonyl-CoA to succinyl-CoA—a step integral to the catabolism of odd-chain fatty acids and certain amino acids—and the remethylation of homocysteine to methionine, which is fundamental to one-carbon metabolism and DNA synthesis (Green et al., 2017). These biochemical roles render B12 indispensable for normal hematopoiesis and neurological function; deficiency in either pathway gives rise to the hallmark clinical features of the condition.

In the pediatric population, vitamin B12 deficiency constitutes a significant and underappreciated public health concern. Despite its potentially devastating consequences—particularly for the developing nervous system—the condition is frequently overlooked in routine clinical practice, partly due to the non-specific nature of early symptoms and partly because of the widespread reliance on diagnostic thresholds established for adults. A growing body of evidence now suggests that these thresholds are inadequate for children and adolescents, in whom the physiological demands for cobalamin are proportionally higher relative to body mass and metabolic turnover (Plattel et al., 2024).

Nutritional vitamin B12 deficiency in infancy remains prevalent in low- and middle-income countries, where plant-based diets predominate; however, it is increasingly recognized in higher-income settings as vegetarian and vegan dietary patterns gain popularity. Infants exclusively breastfed by cobalamin-deficient mothers represent the highest-risk group, as maternal B12 status is the primary determinant of milk cobalamin content. Beyond nutritional causes, a spectrum of malabsorptive conditions, genetic disorders of cobalamin metabolism, and iatrogenic factors may also underlie deficiency in children.

The clinical presentation varies considerably with age. In infants under six months, acute neurological deterioration may occur with remarkable rapidity;

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older children may present with more indolent manifestations including developmental regression, irritability, and fatigue. The hematological picture—macrocytic megaloblastic anemia—is a late finding that may be absent in the early stages, particularly in infants whose iron co-deficiency masks macrocytosis.

Treatment of vitamin B12 deficiency has historically relied on intramuscular (IM) administration, a route that bypasses the gastrointestinal absorption mechanism and ensures reliable delivery. However, accumulating evidence from randomized controlled trials and meta-analyses now supports oral high-dose cobalamin as an effective alternative in most clinical scenarios, including those involving absorption defects, provided that passive diffusion mechanisms remain intact. This paradigm shift has significant practical implications for both patient experience and healthcare resource utilization.

This chapter aims to synthesize current evidence on pediatric vitamin B12 deficiency—from molecular pathophysiology to clinical management—with the goal of equipping clinicians with a practical framework for early recognition and treatment.

2. Etiology and Risk Factors

2.1 Nutritional Deficiency

The most common cause of vitamin B12 deficiency in children worldwide is inadequate dietary intake, either directly—as in strict vegetarian or vegan children—or indirectly, through breastfeeding by a B12-deficient mother. Cobalamin is found exclusively in animal-derived foods; plant sources contain no bioavailable B12 unless fortified. Lacto-ovo-vegetarians generally maintain adequate intake, but vegans—particularly those who do not supplement—are at significant risk (Pawlak et al., 2013).

Breastfed infants represent a particularly vulnerable subgroup. Breast milk cobalamin concentration correlates directly with maternal serum B12 levels. In populations with low meat consumption or high rates of maternal B12 deficiency, exclusively breastfed infants may develop symptomatic deficiency within the first six months of life, even when the mother herself appears asymptomatic (Stabler, 2013). This phenomenon—sometimes termed "occult maternal deficiency"—underscores the importance of screening maternal cobalamin status during pregnancy and lactation.

2.2 Malabsorption

Normal absorption of dietary cobalamin is a complex, multistep process requiring intact gastric, pancreatic, and intestinal function. The principal mechanisms are: (1) release of protein-bound B12 by gastric acid and pepsin; (2) binding to intrinsic factor (IF), a glycoprotein secreted by gastric parietal cells;

(3) receptor-mediated endocytosis of the IF-B12 complex at the distal ileal mucosa via cubilin receptors. Any disruption along this pathway may cause malabsorption.

In pediatric practice, relevant causes of malabsorption include: inflammatory bowel disease (particularly Crohn's disease with ileal involvement), celiac disease, short bowel syndrome, post-surgical resection of the terminal ileum, and chronic proton pump inhibitor or metformin use. Selective cobalamin malabsorption (Imerslund-Gräsbeck syndrome) is a rare autosomal recessive condition caused by mutations in the genes encoding cubilin or amnionless, presenting in early childhood with proteinuria and megaloblastic anemia unresponsive to oral supplementation.

2.3 Inherited Disorders of Cobalamin Metabolism

A heterogeneous group of inborn errors of cobalamin transport, absorption, and intracellular processing may cause functional B12 deficiency despite normal dietary intake and absorption. These include transcobalamin II deficiency, methylmalonic acidemia, homocystinuria due to CBS deficiency, and the cobalamin C, D, E, F, G, and J disorders. These conditions typically present in early infancy with severe metabolic derangements and require specialized management beyond standard B12 supplementation.

2.4 Other Causes

Helicobacter pylori infection in older children may impair gastric acid secretion and intrinsic factor production. Chronic nitrous oxide exposure—increasingly relevant given recreational misuse in adolescents—irreversibly oxidizes cobalamin cobalt, rendering it inactive. Immune-mediated destruction of parietal cells causing juvenile pernicious anemia is rare but described in children, sometimes in association with autoimmune polyglandular syndromes.

3. Pathophysiology

3.1 Biochemical Mechanisms

Vitamin B12 functions as a cofactor for two enzymes: methionine synthase (MTR) and methylmalonyl-CoA mutase (MUT). Methionine synthase catalyzes the remethylation of homocysteine to methionine using methyltetrahydrofolate as the methyl donor; this reaction is critical for maintaining the pool of active tetrahydrofolate required for nucleotide synthesis. Deficiency leads to functional folate deficiency—the "methyl trap" hypothesis—resulting in impaired DNA synthesis and megaloblastic changes in rapidly dividing cells, most prominently hematopoietic precursors and gastrointestinal epithelium.

Methylmalonyl-CoA mutase converts methylmalonyl-CoA to succinyl-CoA in mitochondria. Impairment leads to accumulation of methylmalonic acid (MMA) and propionyl-CoA, which interfere with fatty acid synthesis and myelin formation. Elevated MMA is now recognized as the most sensitive functional marker of intracellular B12 deficiency and may be elevated even when serum B12 concentrations appear borderline normal (Allen, 2009).

3.2 Neurological Consequences

The nervous system is exquisitely sensitive to cobalamin deficiency, particularly during periods of rapid myelination in early childhood. Subacute combined degeneration of the spinal cord—a classic manifestation in adults—may present atypically in children as peripheral neuropathy, pyramidal tract signs, or cognitive regression. In infants, the predominant manifestation is neurodevelopmental delay or regression, which may be irreversible if treatment is delayed beyond a critical window. Demyelination has been demonstrated on MRI as T2-hyperintense white matter changes, particularly in the posterior columns and corticospinal tracts (Dror & Allen, 2008).

The pathophysiology of neurological injury in B12 deficiency is not fully elucidated. Current evidence implicates the accumulation of MMA, which is neurotoxic at elevated concentrations, as well as impaired S-adenosylmethionine (SAM)-dependent methylation reactions required for myelin basic protein synthesis and neurotransmitter metabolism. Elevated homocysteine also contributes to neurological injury through endothelial dysfunction and excitotoxicity.

4. Clinical Manifestations

4.1 Hematological Features

The classical hematological presentation of vitamin B12 deficiency is megaloblastic anemia, characterized by macrocytosis (elevated mean corpuscular volume, MCV), hypersegmented neutrophils on peripheral blood smear, and elevated serum lactate dehydrogenase (LDH). Thrombocytopenia and leukopenia may occur in severe cases, presenting as pancytopenia. However, the absence of anemia or macrocytosis does not exclude significant B12 deficiency; in particular, concurrent iron deficiency—common in the pediatric population—may normalize the MCV, masking megaloblastic changes.

4.2 Neurological Features

Neurological manifestations are the most clinically consequential aspect of pediatric B12 deficiency and may precede or occur independently of hematological changes. In infants (0–12 months), the presentation typically includes: hypotonia, poor feeding, developmental regression or failure to achieve

milestones, irritability, and seizures. Tremor, myoclonus, and altered consciousness may occur in severe cases. Older children may present with peripheral neuropathy (paresthesias, decreased deep tendon reflexes), gait disturbance, cognitive impairment, behavioral changes, and affective symptoms.

A striking feature of infantile B12 deficiency is the rapidity of neurological deterioration and, conversely, the potential for substantial recovery with early treatment. However, outcomes are variable; longitudinal follow-up studies have documented persistent cognitive and language deficits in a proportion of infants who experienced prolonged deficiency, even after biochemical normalization (von Schenck et al., 1997).

4.3 Other Manifestations

Gastrointestinal symptoms including anorexia, glossitis, and recurrent aphthous stomatitis may be presenting features. Growth faltering and failure to thrive are commonly observed in infants with nutritional deficiency. In older children, fatigue, exercise intolerance, and pallor are non-specific but important clinical clues. Skin hyperpigmentation, particularly over the dorsum of the hands and feet, has been described in infants and is thought to reflect altered melanin metabolism secondary to impaired methionine synthesis.

5. Diagnosis

5.1 Serum Vitamin B12

Serum total cobalamin remains the most widely used first-line screening test for B12 deficiency. However, its limitations are well-recognized: it measures both biologically active and inactive forms of cobalamin (approximately 80% of circulating B12 is bound to haptocorrin and metabolically inactive), and its sensitivity and specificity for functional deficiency are suboptimal. The conventional lower reference limit of 200 pg/mL (148 pmol/L) was derived from adult populations and may not reflect the physiologically higher requirements of growing children.

Plattel et al. (2024), in a landmark case report and review, highlighted that children and adolescents may exhibit functional B12 deficiency with clinical and biochemical manifestations despite serum B12 levels within the adult normal range. This underdiagnosis phenomenon is particularly problematic because it may delay treatment during critical windows of neurological development. Age-stratified reference ranges are needed, though not yet universally adopted in clinical practice.

5.2 Functional Markers

Holotranscobalamin (holoTC)—the biologically active fraction of serum B12 bound to transcobalamin II—is considered a more sensitive early marker of cobalamin depletion. Methylmalonic acid (MMA) and total homocysteine (tHcy) are downstream functional markers that reflect the metabolic consequences of intracellular B12 deficiency; they remain elevated even when serum B12 is borderline normal. The combination of low holoTC with elevated MMA and/or tHcy provides the most specific diagnosis of functional B12 deficiency.

In clinical practice, however, MMA and holoTC are not universally available. A pragmatic approach involves measuring serum B12, folate, complete blood count with peripheral smear, and homocysteine as initial workup, with MMA reserved for cases where the diagnosis remains uncertain.

5.3 Diagnostic Algorithm

A practical diagnostic approach for pediatric B12 deficiency includes: (1) clinical history focusing on dietary intake (maternal and child), feeding practices, and symptom timeline; (2) complete blood count with differential and peripheral smear; (3) serum B12, folate, and homocysteine; (4) if available, holoTC and MMA; (5) assessment for underlying causes (anti-intrinsic factor antibodies, anti-parietal cell antibodies, celiac serology, inflammatory bowel markers) as clinically indicated.

A serum B12 <200 pg/mL is generally considered deficient. Values between 200 and 400 pg/mL may represent borderline deficiency, particularly in the presence of clinical symptoms or elevated functional markers. In infants with neurological symptoms and a suspicious dietary history, empirical treatment should not await complete laboratory confirmation, as delay carries significant risk of irreversible neurological injury.

6. Treatment

6.1 Intramuscular Administration

Intramuscular (IM) cyanocobalamin or hydroxocobalamin has been the traditional route of treatment for vitamin B12 deficiency, particularly in settings where malabsorption is suspected or confirmed. IM administration entirely bypasses the gastrointestinal absorption mechanism, ensuring complete bioavailability regardless of intrinsic factor status or intestinal integrity. In acute presentations with severe neurological compromise, IM therapy is generally preferred to achieve rapid repletion of tissue stores.

Commonly used regimens include: cyanocobalamin 1000 mcg IM daily for 7 days, then weekly for 4 weeks, then monthly for maintenance; or hydroxocobalamin 1000 mcg IM on alternate days for 2 weeks. Pediatric dosing is typically weight-adjusted, though practice varies considerably across centers.

IM therapy carries the disadvantages of pain, cost, and the need for clinical attendance, which may affect adherence, particularly in infants and young children.

6.2 Oral Administration

High-dose oral cobalamin exploits the passive diffusion absorption pathway, which operates independently of intrinsic factor and functions proportionally to the luminal concentration of the vitamin. At doses of 1000–2000 mcg/day, approximately 1–2% is absorbed via passive diffusion, sufficient to meet daily requirements and replete stores even in the context of malabsorption. This observation has led to a substantial body of evidence supporting oral B12 as an effective alternative to IM therapy in most clinical settings.

A Cochrane systematic review (Wang et al., 2018) and several randomized controlled trials have demonstrated that high-dose oral cobalamin is equivalent to IM injection in normalizing serum B12 levels, MMA, and homocysteine in adults. Data specifically addressing pediatric populations are more limited but accumulating. A 2025 meta-analysis of 6,098 participants across multiple administration routes (oral, sublingual, IM) found that all routes produced significant increases in serum cobalamin (pooled mean difference: +402.6 pg/mL; 95% CI: 293.6–511.5; $p<0.001$), with comparable clinical outcomes, and that IM therapy demonstrated only a statistically—not clinically—superior rise in serum B12 (Abdelwahab et al., 2024).

Oral ampule formulations (cyanocobalamin solution) and tablet preparations are both used in pediatric practice. Practical considerations favor oral therapy for maintenance treatment, for mild-to-moderate nutritional deficiency, and in settings where IM access is limited. IM therapy remains preferred for acute neurological presentations, confirmed malabsorption (e.g., Imerslund-Gräsbeck syndrome), and situations requiring guaranteed adherence.

6.3 Sublingual and Other Routes

Sublingual cobalamin formulations have gained attention as an alternative that may improve absorption compared with oral tablets by delivering the vitamin across the buccal mucosa. Limited evidence suggests efficacy comparable to IM administration in normalizing serum B12 levels in children (Tuğba-Kartal & Çağla-Mutlu, 2020; Orhan Kiliç et al., 2021). However, sublingual preparations are not universally available and the evidence base remains smaller than for oral and IM routes.

6.4 Response Monitoring and Maintenance

Following initiation of treatment, reticulocytosis typically peaks at 5–10 days, indicating a positive hematopoietic response. Serum B12 levels and complete

blood count should be rechecked at 4–6 weeks. Neurological recovery is variable and may be incomplete; however, early treatment—ideally within the first weeks of symptom onset in infants—is associated with better neurodevelopmental outcomes. Maintenance therapy is required when the underlying cause cannot be corrected; the route and dose depend on the etiology and the patient's ability to absorb oral preparations.

For nutritional deficiency, dietary counseling is essential. Breastfed infants of vegan or vegetarian mothers should receive B12 supplementation from birth; weaning foods should include B12-rich or fortified items. Supplementation during pregnancy and lactation for at-risk mothers is a critical preventive measure.

7. Special Considerations

7.1 Infants of Vegetarian and Vegan Mothers

The intersection of increasing vegan dietary practice among reproductive-age women and the vulnerability of the developing infant brain creates a public health imperative for targeted screening and supplementation. National guidelines in several countries now recommend routine B12 supplementation for all vegan pregnant and breastfeeding women and their infants, yet implementation remains inconsistent. Pediatricians should proactively inquire about maternal diet at well-child visits and assess infant B12 status in the context of any developmental concern or feeding difficulty in breastfed infants of plant-based-diet mothers.

7.2 Age-Specific Diagnostic Thresholds

The inadequacy of adult-derived B12 reference ranges for pediatric clinical decision-making is increasingly recognized but not yet resolved. Children and adolescents appear to have physiologically higher demands for cobalamin relative to body size, and emerging evidence suggests that the diagnostic threshold for clinical deficiency should be higher in this population than the conventionally applied 200 pg/mL cutoff. Until age-stratified reference intervals are validated and widely adopted, clinicians should maintain a low threshold for treating borderline-low B12 levels in the presence of compatible clinical features, particularly in the context of neurological symptoms.

7.3 Interaction with Iron Deficiency

Co-existing iron and vitamin B12 deficiency is common in pediatric populations, and the concurrence complicates both diagnosis and interpretation of treatment response. Iron deficiency reduces MCV, potentially masking the macrocytosis of megaloblastic anemia and creating a normocytic or even microcytic picture. Conversely, correction of iron deficiency without addressing concurrent B12 deficiency may unmask macrocytosis and reveal the underlying

megaloblastic process. A comprehensive nutritional assessment, including both iron status and B12, is warranted in children presenting with anemia or nutritional risk.

8. Prevention

Prevention of vitamin B12 deficiency in children operates at multiple levels. Primary prevention targets at-risk populations before deficiency occurs: universal supplementation of vegan/vegetarian pregnant and lactating women; B12 supplementation for breastfed infants of at-risk mothers; food fortification programs in populations with low dietary diversity; and newborn screening in populations with high prevalence of cobalamin C and related disorders.

Secondary prevention involves early identification of asymptomatic or mildly symptomatic deficiency through targeted screening: B12 measurement in infants presenting with developmental delay or faltering growth; periodic assessment in children with malabsorptive conditions; and monitoring in patients on long-term proton pump inhibitors or metformin. Tertiary prevention focuses on preventing the progression of established deficiency to irreversible neurological injury through prompt, appropriate treatment.

9. Conclusion

Vitamin B12 deficiency in children is a preventable cause of potentially irreversible neurological and hematological morbidity. Its clinical spectrum is broad, early symptoms are non-specific, and conventional diagnostic thresholds may fail to identify all affected children—particularly infants and those with borderline serum levels but functional deficiency. A high index of clinical suspicion, informed by nutritional history and contextual risk factors, is essential for timely diagnosis.

Treatment is highly effective when initiated early. Oral high-dose cobalamin has emerged as a viable, evidence-based alternative to intramuscular injection in most settings, improving patient experience and accessibility without compromising clinical outcomes. The choice of route should be individualized based on the severity of presentation, etiology, and the clinical context.

Ongoing research is needed to establish pediatric-specific diagnostic reference intervals, to expand the evidence base for oral therapy in children, and to develop effective public health strategies targeting maternal and infant cobalamin nutrition. Pediatricians are at the frontline of early identification and management of this common but underdiagnosed condition.

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