Micro-Nutrient Needs in Down Syndrome: A peer-reviewed science base © 2014

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Down Syndrome results from a (third arm) on chromosome 21.

This trisomy is associated with changes in:

- neurological development
- physical growth
- muscle to fat ratio
- immunity and resistance to infection
- risk of leukemia
- risk of celiac disease
- risk of thyroid dysfunction
- risk of diabetes and blood sugar abnormalities
- precocious aging
- Alzheimer-like lesions
Down Syndrome: an Analogy

A 2-arm chromosome (normal) is like a recipe:
X volume of ingredients $\rightarrow$ Y volume of product.

A 3-arm chromosome (trisomy) increases production by 50%:
Y + 50% volume of product $\rightarrow$ requires X + 50% volume ingredients.

X + 50% ingredients $\rightarrow$ faster depletion of ingredient stores
$\rightarrow$ ‘stealing’ ingredients from other functions

$\rightarrow$ decreased ingredients for growth + development
$\rightarrow$ decreased ingredients for disease prevention
$\rightarrow$ decreased ingredients for healthy aging
1. 50% overproduction of products coded on Chromosome 21
   *(50% more products produced)*

2. 50% increase in production causes a 50% increase in requirements for raw ingredients (vitamins, minerals, amino acids, etc)
   *(50% more ingredients needed)*

3. There is also an increase in the byproducts (mess), requiring increased antioxidants to neutralize the excess byproducts
   *(50% more garbage produced + 50% more antioxidants needed).*
There are three well-documented enzymes coded on Chromosome 21 which increase requirements for zinc, selenium and vitamin B12:

1) Cu-Zn SuperOxide Dismutase (SOD): a zinc dependent enzyme.
2) Glutathione Peroxidase: a selenium dependent enzyme
3) Cysteine Beta Synthase (CBS): a folate and B12 dependent enzyme

Additionally, there is an increased production of free radicals and consequently an increased requirement for anti-oxidants such as:

3) glutathione, vitamin A, vitamin C, vitamin E
Copper-Zinc Superoxide Dismutase (SOD) in Down Syndrome
Superoxide Dismutase (SOD) levels can be normal in mosaic Down Syndrome (Biol Trace Elem Res 2001)

Superoxide Dismutase (SOD) levels are increased in full expression Down Syndrome (Mayo Clin Proc 2005)

Overproduction of Superoxide Dismutase (SOD) increases oxidative stress and increases oxidative damage to proteins in children with Down Syndrome. (Clin Chem Lab Med 2006)
Consequences of Low Zinc in Down Syndrome
Low zinc status in Down Syndrome is associated with:

1) decreased immune status
2) decreased growth and lean tissue ratios
3) thyroid dysfunction
4) celiac disease
5) altered taste perception and appetite
Zinc and Immunity
18 children with Down Syndrome
Hx respiratory, ear and skin infections

2 cycles of zinc supplementation 10 months apart
1 mg elemental zinc/kg/day x 2 months each

Decreased infections and increased school attendance

Despite normal plasma zinc before supplementation
No effect on copper status

12 children with Down’s Syndrome
Low serum zinc and immune deficiency

Zinc sulfate supplementation @ 135 mg zinc/d x 2 months

Immune improvements in 11/12 children

30 children with Down Syndrome
63.2% with low plasma zinc

Supplementation with zinc sulfate x 20 mg/kg/day x 2 months

Normalized immunity (lymphocyte response) x 6 months
But, immunity decreasing 22 months after supplementation ended

Zinc and Growth
Meta-analysis of 33 zinc supplementation studies and childhood growth.

Highly significant improvements in height
Highly significant improvements in weight

Greatest improvements among children with lowest height-for-age scores.

35 children with Down Syndrome

No difference in protein intake, carb or fat intake
Zinc intake adequate in 40% of Down Syndrome and 67% controls

Lower plasma zinc in Down Syndrome.

Shorter height in Down Syndrome.

22 children with Down Syndrome

Supplemented with zinc sulphate for 6-9 months.

Increased growth percentile and increased growth hormone levels

Increased growth velocity (23.84 -> 40.80 mm/6 months).

Zinc and Body Composition
9 female elite athletes

% fat mass is negatively associated with plasma zinc.

% fat mass is positively associated with the plasma copper/zinc ratio.

30 adolescents with Down Syndrome

No difference in protein, fat, carb or zinc intake

No difference in plasma zinc

Greater zinc losses in urine in Down Syndrome.

Greater overweight (26.7%) and obesity (6.6%) in Down Syndrome.

Zinc and Thyroid
Down Syndrome: Zinc and Thyroid

25 children with Down Syndrome
Lower plasma zinc
Higher TSH
No difference in T3 or T4

4 months zinc sulphate supplementation
Plasma zinc normalized
TSH on par with control children

51 children with Down Syndrome

4 months of zinc sulphate supplementation:
Normalized plasma zinc and TSH

1 year after zinc supplementation stopped:
Plasma zinc decreasing
TSH increasing

Zinc and Celiac Disease
43 children with Down Syndrome

Lower zinc
Lower immune function
Higher TSH
Higher coeliac disease

Zinc lowest in children with celiac disease and decreased immune status

Zinc and Taste/Appetite
22 patients with altered taste acuity (hypoguesia)

Zinc acetate supplementation x 50 mg zinc/day

Improvement in plasma zinc

Improvement in taste perception for sweet, salt and bitter.

Zinc Safety
Meta-analysis of preventive zinc supplementation studies among infants, preschoolers and older prepubertal children.

Decreased diarrhea x 20%
Decreased acute respiratory infections x 15%
Decreased mortality in children > 1 yr x 18%
Increased growth in height

No adverse effect on iron or copper status.

Zinc Testing
Zinc Assessment

1) Serum/plasma zinc
   -> recent intake only
   -> many confounding variables

2) Alkaline phosphatase (zinc enzyme)
   -> functional zinc status
   -> unreliable if recent growth as alk phos is mobilized into blood during growth

3) Best approach
   -> combination of serum/plasma zinc AND alkaline phosphatase
Dietary Sources of Zinc
Zinc Sources in Diet

Absorption blocked by calcium, iron, fibre, phytate.

Richest food sources:
Seafood
Fish
Liver
Beef, Pork, Chicken
Beans
Cashews
Cheese

US National Institutes of Health, 2013
Glutathione Peroxidase (GPx) in Down Syndrome
18 children with Down Syndrome
RBC GPx was significantly increased.
Serum selenium was significantly decreased.

29 children with Down Syndrome
RBC GPx in red cells was significantly increased
Plasma selenium was significantly decreased

RBC GPx levels were significantly greater in the DS group
RBC GPx was significantly correlated with memory function.
Brugge K et al. Biol Psychiatry 1999; 46(12): 1682-9
Consequences of Low Selenium in Down Syndrome
Low selenium levels in Down Syndrome are associated with:

1) impaired thyroid status

2) decreased immune status
Selenium and Thyroid
109 healthy individuals

Decreased serum selenium

Decreased T3/T4 ratio

Decreased conversion of T4 to T3 because of low selenium status

18 adults with Down Syndrome

Decreased serum selenium

Decreased T4

Increased TSH

Kanavin OJ et al. Biol Trace Elem Res 2000; 78(1-3):35-42. Thyroid hypofunction in Down’s Syndrome: is it related to oxidative stress?
Selenium and Immunity
1a) Natural Killer (NK) activity is low in Down Syndrome.

1b) Supplementation with Se increases natural killer (NK) cell activity in the mouse.

2a) The T-lymphocyte activation response is patients with dysmorphic disorders.
   Cruz et al. Ann Allergy Ashtma Immunol 2009

2b) Selenoprotein deficiency suppresses T-lymphocyte response.
Selenium Testing
Selenium Assessment

1) Serum/plasma selenium -> only recent selenium intake

2) RBC selenium -> longer term selenium status

3) But, there are no established ‘normal ranges’ for either test

Dietary Sources of Selenium
Selenium Sources in the Diet

Richest food sources:

Brazil Nuts
Mixed Nuts and Seeds
Oysters
Fish
Liver
Beef, Pork, Lamb, Chicken
Eggs
Beans

Canadian Nutrient File 2012
Cystathione Beta Synthase (CBS) in Down Syndrome
Cystathione beta synthase (CBS) levels are increased by approximately three times in the Down Syndrome brain.

High CBS causes homocysteinuria, which is characterized by mental retardation and vascular disease.

The high CBS may explain the cognitive abnormalities in Down Syndrome, and the vulnerability to Alzheimer’s Disease.

42 children with Down Syndrome

CBS overexpression in lymphoblasts altered homocysteine metabolism with decreased homocysteine content, and decreased glutathione.

Addition of methyl-folate, methyl-B12 or dimethylglycine improved this profile

Folate in Down Syndrome
Down Syndrome: Folate Status

Canadian Health Measures Survey

5248 people 6-79 years + 1162 women 15-45 years

‘Folate deficiency is virtually nonexistent in the Canadian population’
Very high folate among 40% of the Canadian population

New reference range for ‘normal’ RBC folate: 305-1360 nmol/L

Following folate fortification of flour in US:

- Significant increase in maternal folate status
- Normal serum and RBC folate in infants with Down Syndrome
- Significant decrease in neural tube defects and cleft palate
- 7% increase in Down Syndrome (where no prenatal DS testing)

Down Syndrome: Folate Status

10 children with Down Syndrome
No difference in serum and RBC folate between Down Syndrome and controls

50 children with Down Syndrome
No difference in serum or RBC folate between Down Syndrome and controls

113 patients with Down Syndrome
No difference in serum of RBC folate between Down Syndrome and controls
Folate Assessment

1) Serum/plasma folate -> only recent folate intake

2) RBC folate -> longer term folate status

   Reference range for Canadians: 305-1360 nmol/L

   Caution if RBC folate > 1360 nmol/L

Folate Sources in the Diet

All flour and flour products in Canada are fortified with flour
All multi-B, multivitamin and prenatal vitamins contain folate
Many protein powders and alternate non-dairy milks are folate fortified.

Richest unfortified dietary sources:

Liver
Beans and lentils
Dark green vegetables
Sunflower seeds
Potatoes
Fruit

Canadian Nutrient File 2010
B12 Status in Down Syndrome
50 children with Down Syndrome

Increased hemoglobin
Increased mean cell volume (MCV)

No difference in serum or RBC folate
No difference in serum iron or ferritin
No difference in serum B12 (but no test for functional B12 status)

‘Macrocytosis (is) an expression of an altered folate remethylation pathway, secondary to enhance CBS activity, the gene for which is present on chromosome 21’

113 patients with Down Syndrome
Increased mean cell volume (MCV)
Decreased serum B12
No difference in serum of RBC folate

10 children with Down Syndrome
Increased hematocrit
Increased mean cell volume (MCV)
Decreased white blood cells (WBC)
No B12 testing
No difference in serum and RBC folate
Down Syndrome: B12 Status

28 adults with Down Syndrome
Increased mean cell volume (MCV)
Increased mean platelet volume (MPV)
De Alarcon PA et al. Ped Res 1984; 18: 235A. Down’s Syndrome and increased mean corpuscular volume (MCV), mean platelet volume (MPV) and neutrophil alkaline phosphatase (NAP).

61 adults with Down Syndrome
Increased mean cell volume (MCV)
Decrease red cell survival

147 adults with Down Syndrome
Increased mean cell volume (MCV) in 48%
Decreased white blood cells (WBC) and neutrophils in 20%
B12 deficiency and Abnormal Hematology
Vitamin B12 deficiency can cause profound alterations in the bone marrow.

These alterations can **mimic the more serious diagnosis of acute leukemia**.

Two patients were suspected of having acute leukemia or myelodysplasia on the basis of bone marrow smear.

They were both found to have vitamin B12 deficiency

Parenteral vitamin B12 resulted in normalization of the bone marrow.

205 children with pancytopenia (decreased red cells, white cells and/or platelets)

Hematological malignancies = 24%
Megaloblastic anemia = 20%

‘Leukemia and bone marrow failure are the most common causes.’
But ‘megaloblastic anemias are treatable and reversible causes of pancytopenia

Plasma concentrations of methycobalamin was significantly lower in CML patients than the reference population.

Low methylcobalamin was associated with a poor prognosis.


In the mouse model of L1210 leukemia, vitamin B12 + C inhibited cell growth and increased survival.

B12 and Myelination
14 cases of early-onset cobalamin deficiency

Mental retardation was identified in most cases

A variable degree of white matter atrophy was detected
Selective white matter involvement seems to be the most consistent finding of cobalamin deficiency

The white matter atrophy may be related to a reduced supply of methyl groups, possibly caused by the dysfunction of the methyl-transfer pathway.

Biancheri et al. Neuropediatr 2001
1) The brain of a child with Down Syndrome develops differently from a normal one, attaining a form reduced in size and altered in configuration.

2) Directly related to the mental retardation are neuronal modifications manifest as alterations in cortical lamination (myelination).

Becker et al. Prog Clin Biol Res 1991

120 children with Down Syndrome
Delayed myelination in 22.5%

18 month old infant with Down Syndrome
Brain myelination equivalent to an 11-month infant.
Koo et al. J Child Neurol 1992
B12 Assessment

1) No gold standard has emerged for the diagnosis of cobalamin deficiency.

2) Therapeutic trials with pharmacologic doses of cobalamin are suggested when findings consistent with cobalamin deficiency are present regardless of the results of diagnostic tests.

Solomon LR. Blood Rev 2007

Normal serum B12 can be repeatedly normal in the presence of haematological and neurological symptoms of B12 deficiency.


There is concern that high intakes of folic acid from fortified food and dietary supplements might mask the macrocytic anemia of vitamin B12 deficiency, thereby eliminating an important diagnostic sign.

Johnson MA. Nutr Rev 2007

Occult cobalamin deficiency could become a common disorder.

B12 Assessment

1) Serum B12
   Recent intake -> will show high if supplementation
   Caution if < 400 (Japanese cutoff for serum B12)

2) MCV and MCH
   If high, may indicate folate or B12 deficiency.
   Test for RBC folate to differentiate

3) White cell count (WBC) and subsets, red cell count (RBC) and platelets
   If low, may indicate B12 deficiency.
   Consider testing response to high dose B12 before considering leukemia

4) Homocysteine
   Will be low in Down Syndrome because of CBS overexpression on chromosome 21
Only 1% of dietary B12 is passively absorbed. 99% requires intrinsic factor production in the gut.

Best dietary sources:

- Clams
- Liver
- Seafood
- Trout and Salmon
- Beef and wild game

Canadian Nutrient File 2010
US National Institutes of Health 2011
Human infants with iron deficiency anemia test lower in cognitive, motor, social-emotional, and neurophysiologic development than comparison group infants.


Increased likelihood of mild or moderate mental retardation associated with anemia, independent of birth weight, maternal education, sex, race-ethnicity, the mother’s age, or the child’s age at entry into the US WIC (Women, Infants and Children Supplementation program.

EK Hurtado et al. Am J Clin Nutr 1999; 69(1): 115-119; Early Childhood Anemia and Mild or Moderate Mental Retardation
114 children with Down Syndrome
Iron deficiency in 10%
Iron deficiency anemia in 3%
”Screening should include CBC, transferrin saturation and ferritin”

149 children with Down Syndrome
Anemia in 8.1%
Iron deficiency in 50% with iron tests (19/38)
Iron Assessment

Serum Ferritin
An acute phase reactant -> can be falsely high if infection or inflammation
Can be increased if insufficient B12 for red cell production
Caution if < 30

Mean Cell Volume (MCV) and Mean Cell Hemoglobin
Low MCV and MCH in uncomplicated iron deficiency
May be normal or high if co-existing B12 or folate deficiency
Caution if <75-80 or >90-95
Iron Saturation
May be low if low iron or B12
May be high if macrocytosis (swollen cells) from B12 or folate deficiency

Serum iron
Recent iron intake; not functional iron status

Hemoglobin and hematocrit
If low, may be due to iron, B12 or folate deficiency
Need to test ferritin and RBC folate to determine which deficiency
Iron Sources in the Diet

Heme iron has a higher absorption, and comes from animal products. Non-heme iron absorption may be compromised by the presence of fibre and phytate. Iron absorption is enhanced by vitamin C and decreased by calcium.

Richest dietary sources:
Seafood
Fish
Liver and kidney
Red meat

Beans and Soybeans
Spinach and dark greens
Fortified cereals

Canadian Nutrient File 2010
Vitamin A in Down Syndrome
38 children with Down Syndrome
Serum retinol deficiency (<20mg/dL) in 18.4%

12 patients with Down Syndrome
Lower plasma and red cell retinol.

33 patients with Down Syndrome
No difference in vitamin A intake, serum vitamin A or Vitamin A absorption
But skin symptoms of hypovitaminosis A
Vitamin A

Testing
Serum Vitamin A (retinol): recent intake only

Vitamin A Sources in the Diet
Liver
Cod Liver Oil

Eggs
Goat cheese
Cow cheese

Orange vegetables (sweet potato, pumpkin, carrots)
Green vegetables (spinach, kale, swiss chard)

Canadian Nutrient File 2010
Nutrient-Rich Diet for Down Syndrome

High animal protein (liver, fish, beef, lamb) (unfortified non-GMO whey protein)

High intake of colourful vegetables (dark greens and dark oranges)

High intake of nuts and seeds and lentils

Minimally processed grains

Minimal fruit

Dairy x 2-3 servings/day

Cod liver oil (without Vitamin A and D removed)

¼ tsp of iodized salt/day
Baseline Bloodwork for Children with Down Syndrome

CBC
Serum ferritin -> separate test for serum iron and iron saturation if abnormal
RBC folate

AST & ALT
Alkaline phosphatase

TSH & T4
Ammonia

Fasting blood sugar & triglycerides
HDL and LDL cholesterol (if older than 12 years)

Urinalysis (for occult urinary tract infections or dysurias)
Consider also: vitamin A, serum zinc and serum selenium if appropriate