Casual Friday Series

# Functional Blood Chemistry Series: CBC pt. II

A Biogenetix Clinical Presentation

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- *The information provided in this presentation is for your consideration only as a practicing health care provider. Ultimately you are responsible for exercising professional judgment in the care of your own patients.*

April 2018

# Goldman Sachs asks in biotech research report: 'Is curing patients a sustainable business model?'

"…where the success of [its] hepatitis C franchise has gradually exhausted the available pool of treatable patients," the analyst wrote. "In the case of infectious diseases such as hepatitis C, curing existing patients also decreases the number of carriers able to transmit the virus to new patients, thus the incident pool also declines … Where an incident pool remains stable (eg, in cancer) the potential for a cure poses less risk to the sustainability of a franchise."

https://www.cnbc.com/amp/2018/04/11/goldman-asks-is-curing-patients-a-sustainable-business-model.html?__twitter_impression=true

INVESTING

# Goldman Sachs asks in biotech research report: 'Is curing patients a sustainable business model?'

PUBLISHED WED, APR 11 2018 3:15 PM EDT
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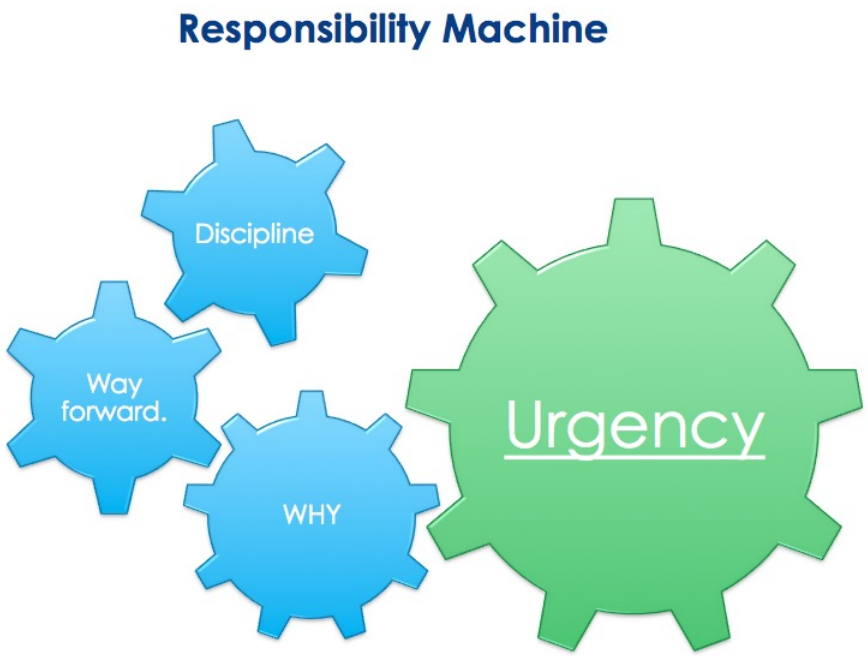
*Yuri Arcurs | Getty Images*

Goldman Sachs analysts attempted to address a touchy subject for biotech companies, especially those involved in the pioneering "gene therapy" treatment: cures could be bad for business in the long run.

"Is curing patients a sustainable business model?" analysts ask in an April 10 report entitled "The Genome Revolution."

# Responsibility Machine

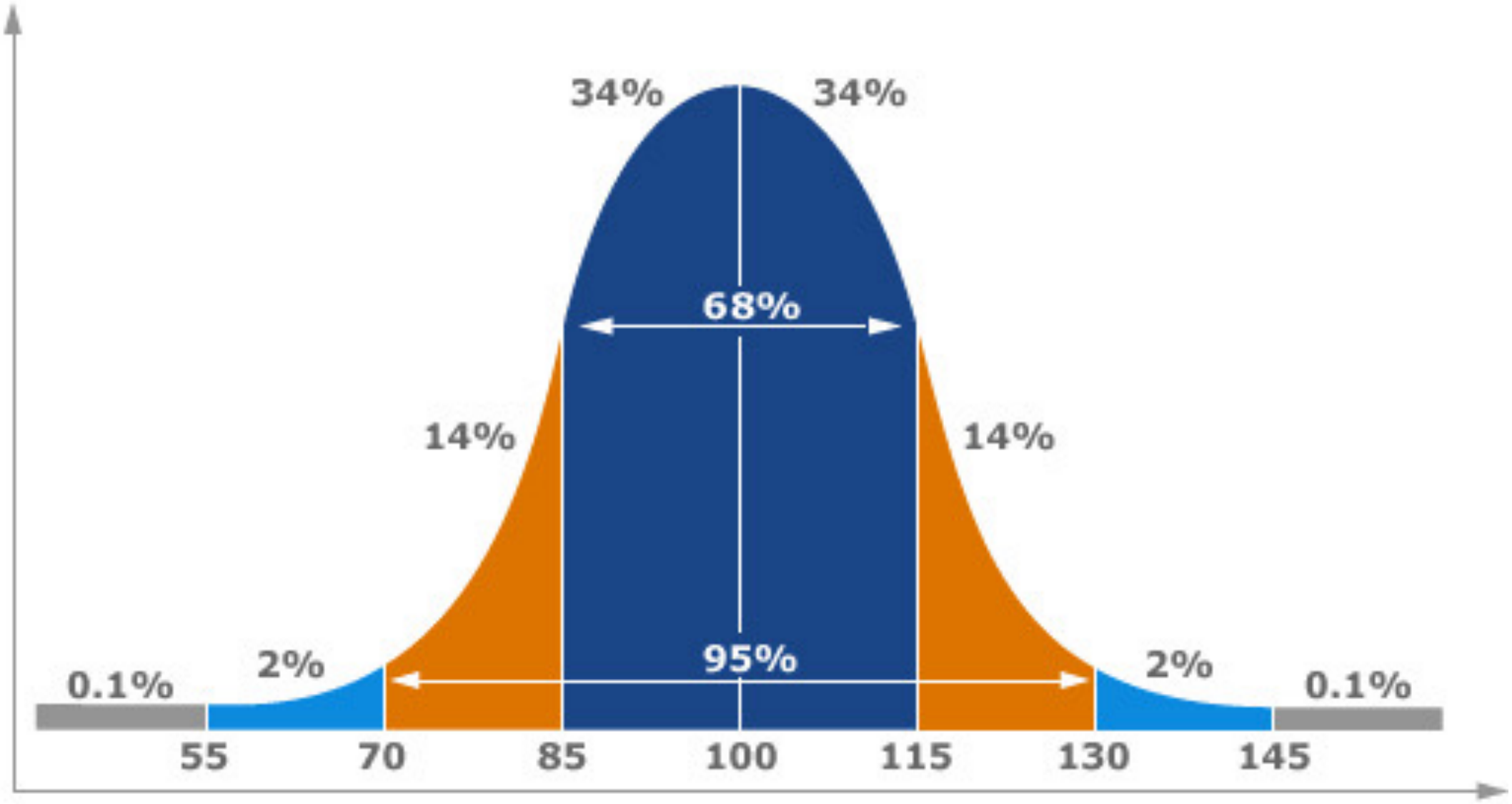
# Applied FM




+


= **Progress.**

# Raw Data



# Optimal Range

A tighter set of ranges designed to help:

1. Identify underlying physiological issues that can help explain symptoms
2. Evaluate health rather than disease
   - Catch potentially more serious disease processes earlier

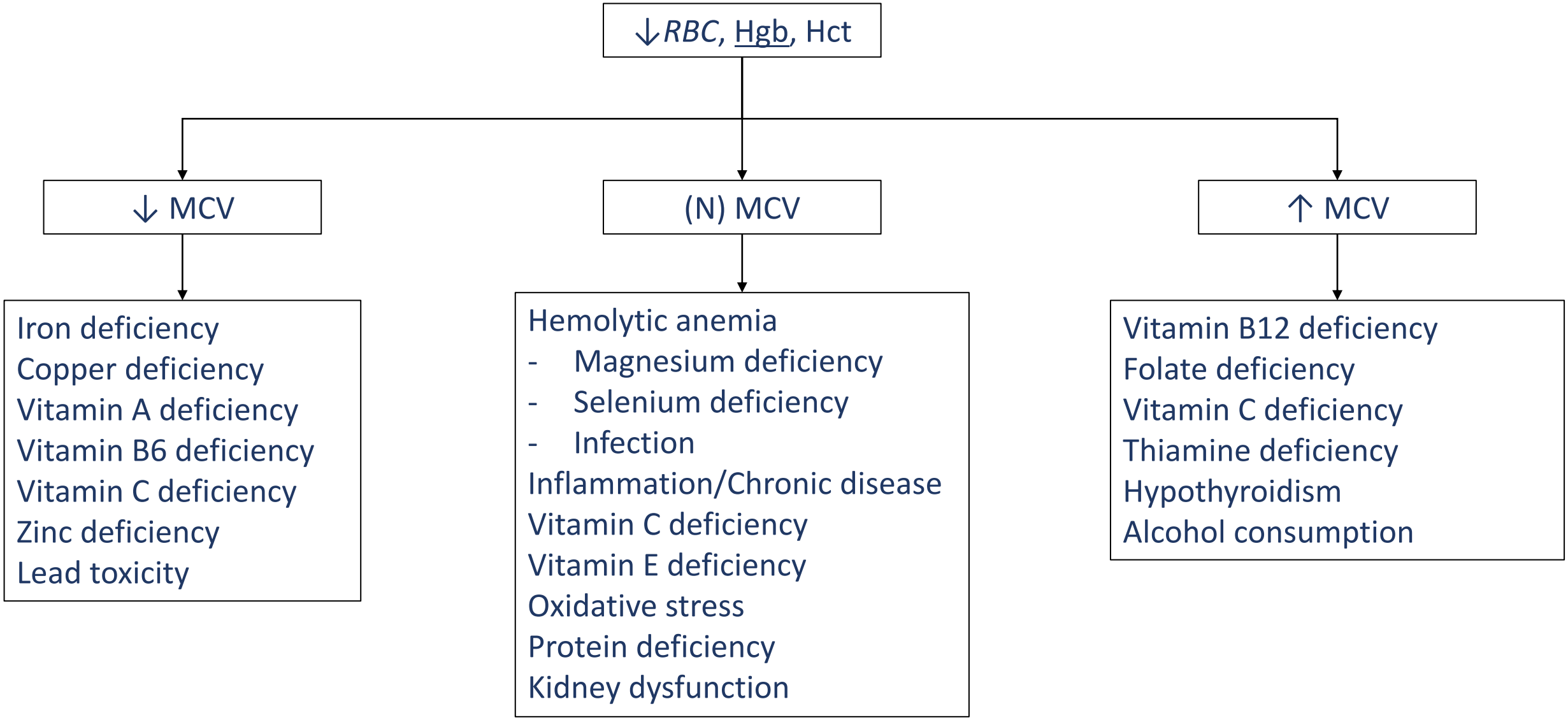
Sodium

Laboratory ref range:

135 – 145 mmol/L

Optimal ref range:

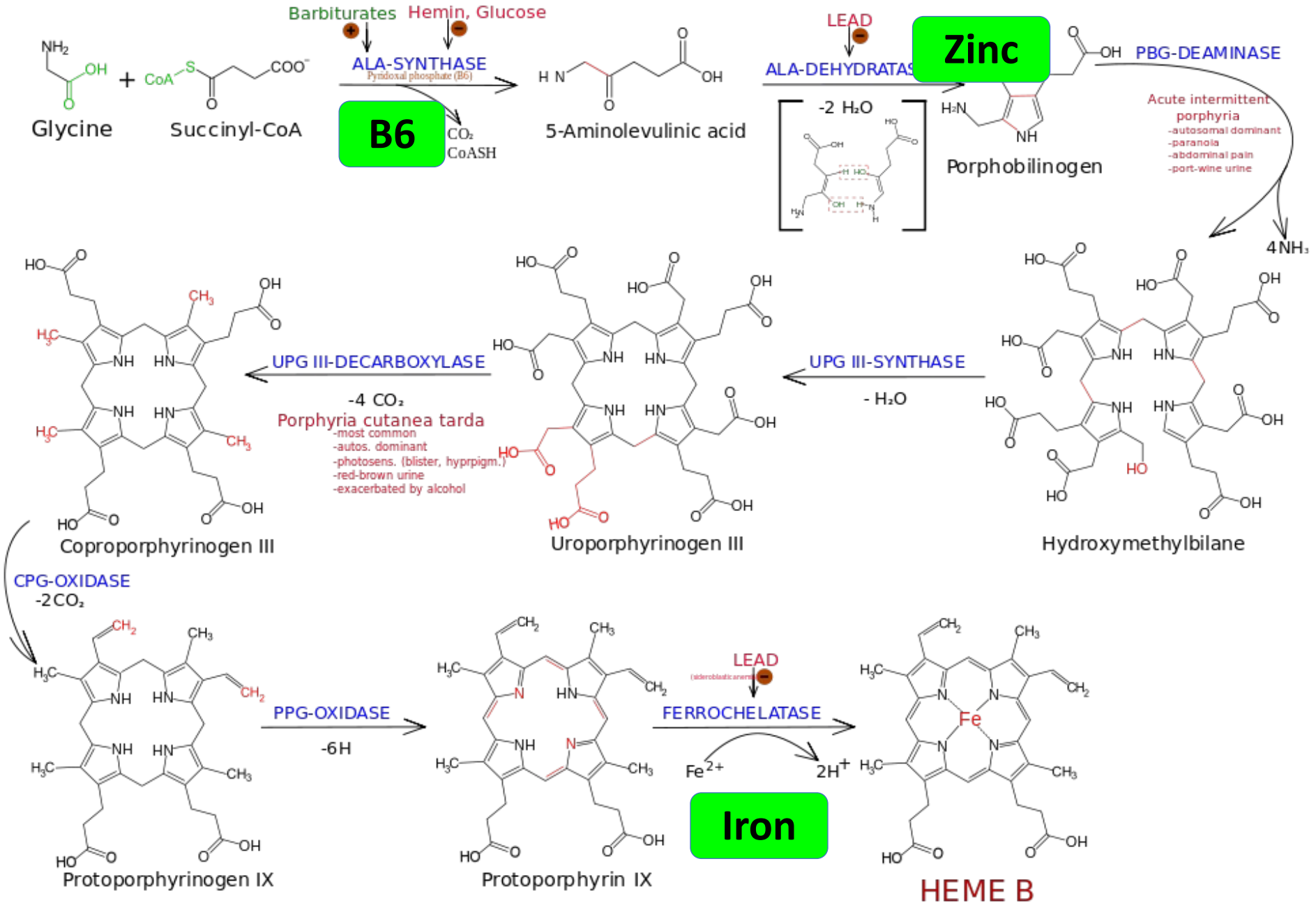
139 – 142 mmol/L


↓*RBC*, Hgb, Hct
↓ MCV
(N) MCV
↑ MCV
Iron deficiency
Copper deficiency
Vitamin A deficiency
Vitamin B6 deficiency
Vitamin C deficiency
Zinc deficiency
Lead toxicity
Hemolytic anemia
- Magnesium deficiency
- Selenium deficiency
- Infection
Inflammation/Chronic disease
Vitamin C deficiency
Vitamin E deficiency
Oxidative stress
Protein deficiency
Kidney dysfunction
Vitamin B12 deficiency
Folate deficiency
Vitamin C deficiency
Thiamine deficiency
Hypothyroidism
Alcohol consumption

# Differentiating Between Destruction and Loss

| | Anemia Due to Blood Loss | Anemia of Inflammation | Hemolytic Anemia | Iron Deficiency |
|---|---|---|---|---|
| RBC | ↓ | ↓ | ↓ | ↓ |
| Hgb | ↓ | ↓ | ↓ | ↓ |
| Hct | ↓ | ↓ | ↓ | ↓ |
| MCV | N | N↓ | N↓ | ↓ |
| MCH | N | N↓ | N↓ | ↓ |
| MCHC | N | N↓ | N↓ | ↓ |
| RDW | N | N | N | ↑ |
| Iron | ↓ | | ↑ | ↓ |
| Ferritin | ↓ | ↑ | ↑ | ↓ |
| TIBC | ↑ | | | ↑ |
| Reticulocyte Count | ↑ | N↓ | ↑ | N↓ |
| Transferrin Receptor | | N↓ | | ↑ |

| | Iron Deficiency | Vitamin A Deficiency | Copper Deficiency | Zinc Deficiency | Vitamin B6 Deficiency | Hemolytic Anemia |
|---|---|---|---|---|---|---|
| RBC | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ |
| Hgb | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ |
| Hct | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ |
| MCV | ↓ | ↓ | ↓ | ↓ | ↓ | N↓ |
| MCH | ↓ | ↓ | ↓ | ↓ | ↓ | N↓ |
| MCHC | ↓ | ↓ | ↓ | ↓ | ↓ | N↓ |
| RDW | ↑ | ↑ | ↑ | ↑ | ↑ | N |
| Iron | ↓ | ↑ | ↓ | ↑ | ↑ | ↑ |
| Ferritin | ↓ | ↑ | ↓ | ↑ | ↑ | ↑ |
| TIBC | ↑ | ↓ | ↑ | ↓ | ↓ | ↓ |
| Reticulocyte Count | ↓ | ↓ | ↓ | ↓ | ↓ | ↑ |
| Transferrin Receptor | ↑ | | ↑ | | | |
| Ceruloplasmin/ Copper | | | ↓ | | | |
| AST | | | | | ↓ | |
| ALT | | | | | ↓ | |
| Neutrophils | | | ↓ | | | |
| Homocysteine | | | | | ↑ | |
| Alkaline Phosphatase | | | | ↓ | | |


Barbiturates
Hemin, Glucose
ALA-SYNTHASE
Pyridoxal phosphate (B6)
B6
Glycine
Succinyl-CoA
CO₂
CoASH
5-Aminolevulinic acid
LEAD
ALA-DEHYDRATASE
Zinc
-2 H₂O
Porphobilinogen
PBG-DEAMINASE
Acute intermittent porphyria
-autosomal dominant
-paranoia
-abdominal pain
-port-wine urine
4 NH₃
Hydroxymethylbilane
UPG III-SYNTHASE
- H₂O
Uroporphyrinogen III
UPG III-DECARBOXYLASE
-4 CO₂
Porphyria cutanea tarda
-most common
-autos. dominant
-photosens. (blister, hyprpigm.)
-red-brown urine
-exacerbated by alcohol
Coproporphyrinogen III
CPG-OXIDASE
-2 CO₂
Protoporphyrinogen IX
PPG-OXIDASE
-6H
Protoporphyrin IX
LEAD
FERROCHELATASE
Fe2+
2H+
Iron
HEME B

SCIENTIFIC REPORTS

Red blood cell distribution width (RDW) is the coefficient of variation of red blood cell size, considered to be associated with cardiovascular disease (CVD). This study aimed to comprehensively synthesize previous studies on RDW and CVD outcomes through an overall and dose-response meta-analysis

Twenty-seven articles, consisting of 28 studies and 102,689 participants (mean age 63.9 years, 63,703 males/36,846 females, 2,140 gender-unmentioned subjects) were included in the present meta-analysis.

The pooled HRs are 1.12 (95% CI = 1.09–1.15) for the association of all-cause mortality (ACM) per 1% increase of RDW, 1.12(95% CI = 1.08–1.17) for major adverse cardiac events (MACEs) per 1% increase of RDW.

For every 1-unit increase of RDW, there is an increased risk of occurrence of ACM and MACEs. This study indicates RDW may be a prognostic indicator for CVD outcomes.

Edith Cowan University, Perth, Australia. [2]Ruijin Hospital, Shanghai Jiao Tong University, Shanghai, 200025, China. [3]Affiliated Hospital, Taishan Medical University, Taian, 271000, China. *These authors contributed equally to this work. Correspondence and requests for materials should be addressed to H.H. (email: hfhou@163.com) or D.L. (email: dli@tsmc.edu.cn)

# Combined Iron and B12 Deficiency

- If both iron and B12 are deficient, the MCV might be normal
  - Iron deficiency leads to microcyosis (low MCV), B12 deficiency leads to macrocytosis (high MCV)
- Research suggests the platelet/MCH ratio can help differentiate between the two
  - In patients with iron deficiency (low ferritin), a platelet/MCH ratio >12.0 was indicative of a possible B12 deficiency as well
  - Platelets 350, MCH 26: 350/26 = 13.5

# Iron

- Serum iron concentration measures iron bound to transferrin.
- This value represents approximately one-third of the total iron binding capacity (TIBC) of transferrin protein, which is made largely in the liver.
- TIBC measures the iron-binding capacity of transferrin.
- In iron deficiency anemia, TIBC will increase due to an increase in production of transferrin.

# Iron

- Iron by itself is a relatively poor marker of iron status and can fluctuate considerably.
- Iron has many functions in the body including:
  - Hemoglobin and myoglobin
  - Cytochrome enzymes in the Electron Transport Chain (ATP synthesis)
  - Monooxygenase enzmes (dopamine and serotonin synthesis)
  - Peroxidases (catalase, myeloperoxidase, thyroperoxidase)
  - Collagen and carnitine synthesis

# Iron

Can also create *massive* amounts of oxidative stress via a process called the Fenton reaction

Iron absorption is enhanced by sugars (fructose), acids (ascorbic), meat.

Iron absorption is inhibited by polyphenols (tannins), oxalic acid (spinach, tea), phytates, other minerals (zinc, calcium)

# Iron

Traditional Reference Range

40-155 mcg/dL

Optimal Reference Range

80-100 mcg/dL

Transferrin saturation % = (serum iron X 100)/TIBC

Example:

- Serum iron = 100
- TIBC = 300 mcg/dL
- Transferrin saturation = 33%
  - The lower the saturation, the more likely iron deficiency exists

# Iron - Elevated

| Cause | Reason | Additional Inquiry |
|---|---|---|
| **Hemosiderosis, hemochromatosis** | Genetic conditions clients are likely already aware of. Iron overload. | Client history. |
| **Hemolytic anemia** | If RBCs break-down, iron will be released and can increase in the serum. | Evaluate CBC markers. |
| **Liver damage** | Liver and spleen are major sources of iron storage. Thus if there is active liver inflammation iron levels may increase. | Evaluate liver markers. |
| **Vitamin B6 deficiency** | If B6 is not available for heme synthesis, iron will not be used and can increase. | Evaluate AST, ALT. |

# Iron - Decreased

| Cause | Reason | Additional Inquiry |
|---|---|---|
| **Poor intake** | | Diet journal. |
| **Poor absorption** | | Diet journal. |
| **Chronic blood loss** | Heavy menstruation, GI bleed | Client history. Reticulocytes. CBC. |
| **Chronic disease and/or chronic infection** | Iron either becomes depleted or sequestered. | Client history. |
| **Progesterone birth control pills** | Association | Client history. |

# Transferrin/TIBC - Elevated

| Cause | Reason | Additional Inquiry |
|---|---|---|
| **Iron deficiency** | Increased production. | Evaluate ferritin. |
| **Pregnancy** | | |
| **Elevated estrogen** | Estrogen tends to increase plasma protein production, including transferrin. | Client history for exogenous use. Evaluate T3 Uptake. |

# Transferrin/TIBC - Decreased

| Cause | Reason | Additional Inquiry |
|---|---|---|
| **Anemia of Chronic Disease** | Transferrin is a negative acute phase reactant, meaning it will tend to decrease during chronic inflammation and/or infection | Client history. |
| **Chronic infection** | Same as above | Client history. Evaluate WBCs. |
| **Liver dysfunction** | Poor production. | Evaluate liver markers. |

# Ferritin

- Ferritin is considered to be the body's stored form of iron.
- It is the ferrous form of iron ($Fe^{2+}$) complexed with a protein, apoferritin, storing it in the ferric state ($Fe^{3+}$).
- Most reliable indicator of total-body iron status.
- Ferritin is an *acute phase reactant,* in that it will increase during inflammation or infection.

# Ferritin

Traditional Reference Range
Men: 18-270 ng/mL or 18-270 ug/L
Women: 18-160 ng/mL or 18-160 ug/L

Optimal Reference Range
50-150 ng/mL (Iron Disorders Institute's Scientific & Medical Advisory Board)
Women: 50-100 ng/mL?*
Men: >100 ng/mL?*

*British Journal of Nutrition* (2009), **102**, 594–600
© The Authors 2009
doi:10.1017/S000711450922085X

# Is serum ferritin within the reference range a risk predictor of cardiovascular disease? A population-based, long-term study comprising 2874 subjects

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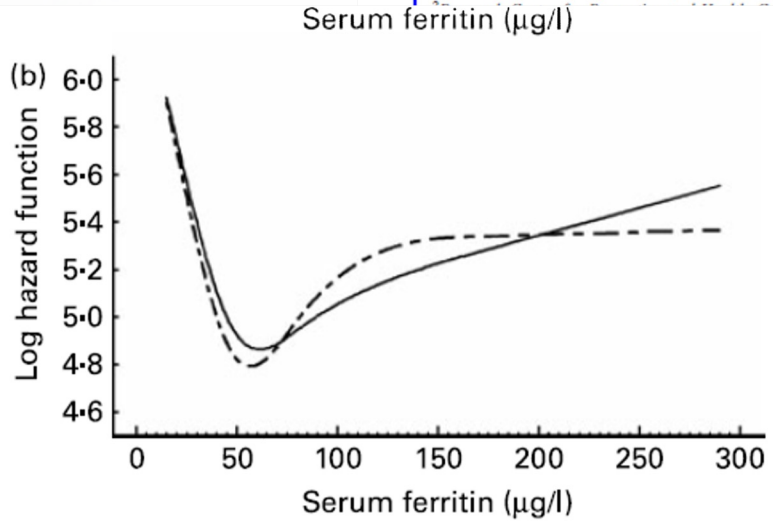


**Fig. 1.** Predicated log hazard function for CVD as a function of serum ferritin in men (a) and women (b). Results of Cox proportional hazard regression models with restricted cubic splines adjusted for age (- – -) and fully adjusted (—). The full model was adjusted for age, smoking, alcohol consumption, diabetes, hypertension, serum cholesterol levels and systolic blood pressure.

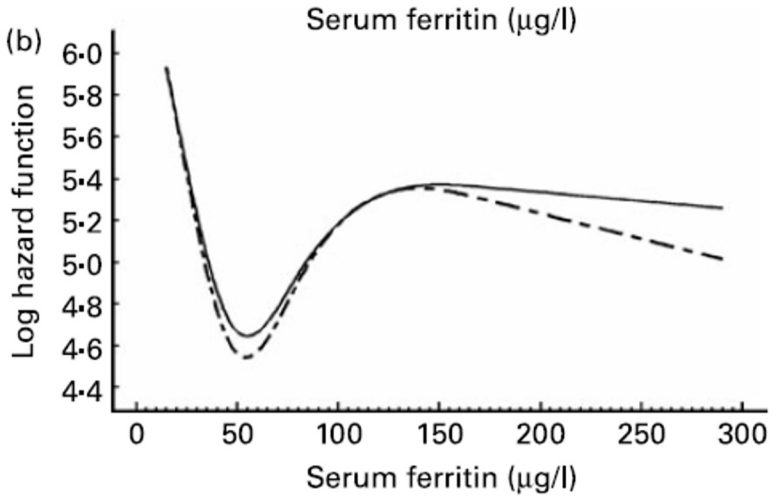


**Fig. 2.** Predicated log hazard function for IHD as a function of serum ferritin in men (a) and women (b). Results of Cox proportional hazard regression models with restricted cubic splines adjusted for age (- – -) and fully adjusted (—). The full model was adjusted for age, smoking, alcohol consumption, diabetes, hypertension, serum cholesterol levels and systolic blood pressure.

that ferritin represents a strong predictor of myocardial infarction (relative hazard per unit 1·002 (95 % CI 1·001, 1·003). Furthermore, this study reported a 2·2-fold increased risk of myocardial infarction among men with serum ferritin levels > 200 μg/l[8] compared with men with lower levels. Against the original Fe hypothesis, which did not precisely define the association between ferritin and IHD, this paper studies mentioned[8,9,15,17] considered the full serum ferritin range. However, the effects of pathological serum ferritin levels are well investigated[20–23]. Therefore, the objective of the present study was to investigate the associations between serum ferritin levels within the reference range and the risks of non-fatal and fatal CVD as well as IHD in 2874 Danish subjects who were followed for 10 years.

**Abbreviations:** DAN-MONICA, Monitoring of Trends and Determinants in Cardiovascular Disease, Danish part; HR, hazard ratio.

* **Corresponding author:** Dr Nele Friedrich, fax +49 3834 866684, email nele.friedrich@uni-greifswald.de

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PII S0002-9270(98)00103-8

# Serious Gastrointestinal Pathology Found in Patients With Serum Ferritin Values ≤ 50 ng/ml

TABLE 2
*Serious Gastrointestinal Pathology Found in Patients With Serum Ferritin Values ≤ 50 ng/ml*

| | |
|---|---|
| Upper gastrointestinal tract | 53 (40% of total 132 patients) |
| Cancer | 2 |
| Esophagitis (grades III, IV) | 15 |
| Ulcers and erosions of the stomach and/or duodenum | 31 |
| Multiple angiodysplasia | 5 |
| Lower gastrointestinal tract | 29 (23% of total of 125 patients) |
| Cancer | 13 |
| Adenoma > 1 cm | 6 |
| Colitis | 4 |
| Erosions/ulcers | 2 |
| Multiple angiodysplasia | 4 |

Endoscopic examination of the gastrointestinal tract in patients with unexplained iron deficiency anemia shows that approximately half have serious gastrointestinal pathology, including cancer, large polyp, and peptic ulcer disease. In most cases, an evaluation of the gastrointestinal tract is indicated, usually with colonoscopy and/or esophagogastroduodenoscopy (EGD) (1–6). Although the definitive di-

*Received July 18, 1997; accepted Dec. 22, 1997.*

The study data were abstracted from the medical records, endoscopy database, and/or interview of the patient and the primary care physician for eligible patients who were already undergoing gastrointestinal evaluation. The remaining subjects were contacted after obtaining permission from their primary care physicians and asked to undergo colonoscopy and/or EGD at their earliest convenience. We did not deliberately select patients for evaluation based on any particular laboratory or clinical features, but rather enrolled the subjects in the order they were identified.

# Ferritin

Traditional Reference Range

Men: 18-270 ng/mL or 18-270 ug/L

Women: 18-160 ng/mL or 18-160 ug/L

Optimal Reference Range

50-150 ng/mL (Iron Disorders Institute's Scientific & Medical Advisory Board)

Women: 50-100 ng/mL?*

Men: >100 ng/mL?*

# Ferritin - Elevated

| Cause | Reason | Additional Inquiry |
|---|---|---|
| **Hemosiderosis, hemochromatosis** | Genetic conditions clients are likely already aware of. Iron overload. | Client history. |
| **Inflammatory diseases** | Acute phase reactant. | Evaluate other inflammation markers. |
| **Liver damage** | Liver and spleen are major sources of iron storage. Thus if there is active liver inflammation iron levels may increase. | Evaluate liver markers. |
| **Hemolytic anemia, sideroblastic anemia** | Iron is being lost or unused from RBCs, thus leading to excess iron. | Evaluate CBC. |

# Ferritin - Decreased

| Cause | Reason | Additional Inquiry |
|---|---|---|
| **Poor intake** | | Diet journal. |
| **Poor absorption** | | Diet journal. |
| **Chronic blood loss** | Heavy menstruation, GI bleed | Client history. |
| **Chronic disease and/or chronic infection** | Iron either becomes depleted or sequestered. | Client history. |
| **Progesterone birth control pills** | | Client history. |

# Reticulocyte Count

- Reticulocytes are early red blood cells that are formed in the bone marrow, enter the blood stream and, after 1-2 days become fully matured red blood cells.
- They do not contain a nucleus, but rather have nucleic acid remnants, which are not found in fully formed red blood cells.
- Reticulocytes tend to be elevated in blood loss and/or hemolytic anemia but normal, or even low, in anemia of nutrient deficiency
  - Poor RBC production due to low nutrient deficiency – they cannot make more
  - But respond rapidly to nutrient supplementation by increasing production
    - Thus reticulocytes can be helpful in seeing if nutrient supplementation is working or not

# Reticulocyte count - Increased

| Cause | Reason | Additional Inquiry |
|---|---|---|
| **Hemolytic anemia** | Breakdown of red blood cells leads to low oxygen state, which is sensed by the kidneys and increases EPO production | |
| **Blood loss** | Same | Client history. |

# Reticulocyte count - Decreased

| Cause | Reason | Additional Inquiry |
|---|---|---|
| **Untreated nutrient deficiency anemia (iron, B12)** | Nutrient deficiency leads to poor RBC production, despite attempts by the body to increase production | Evaluate nutrient-related markers. |
| **Anemia of chronic disease** | Inflammation suppresses the ability to make more red blood cells. | Evaluate other inflammatory markers. |
| **Alcoholism** | Causes nutrient deficiency | History |

# White Blood Cell Count

- Refers to total amount of white blood cells
- The CBC with differential includes the five major types of white blood cells:
  - Neutrophils, lymphocytes, monocytes, eosinophils, basophils
- The WBC count is of limited value without the differential
- In general, an elevated WBC indicates an infection of an acute nature, and a decreased WBC count indicates an infection of a more chronic nature.
  - Decreased WBCs are often seen in autoimmune conditions and pernicious anemia as well.
- Interestingly, high-normal white blood cell counts, along with neutrophils, can indicate possible endothelial dysfunction and peripheral artery disease

# White Blood Cell Count

Interfering factors include:

- Stress: epinephrine response can increase white blood cells
- Time of day:  lower in the morning, higher in the evening
- Other:  age, gender, exercise, pregnancy, pain, temperature and altitude can all affect results
- Early infection/inflammation: Migration out of blood may temporarily lower serum numbers before compensation takes place

ORIGINAL INVESTIGATION

# Leukocyte Count as a Predictor of Cardiovascular Events and Mortality in Postmenopausal Women

## *The Women's Health Initiative Observational Study*

*Karen L. Margolis, MD, MPH; JoAnn E. Manson, MD, DrPH; Philip Greenland, MD; Rebecca J. Rodabough, MS; Paul F. Bray, MD; Monika Safford, MD; Richard H. Grimm, Jr, MD, PhD; Barbara V. Howard, PhD; Annlouise R. Assaf, PhD; Ross Prentice, PhD; for the Women's Health Initiative Research Group*

**Background:** Increasing evidence supports a role for inflammation in the atherosclerotic process. The role of the leukocyte count as an independent predictor of risk of a first cardiovascular disease (CVD) event remains uncer-

L), women in the fourth quartile (6.7-15.0×10⁹ cells/L) had over a 2-fold elevated risk for CHD death (hazard ratio, 2.36; 95% confidence interval, 1.51-3.68), after mul-

deaths, 701 nonfatal myocardial infarctions, 738 strokes, and 1919 deaths from all causes. Compared with women with WBC counts inthe first quartile (2.5-4.7×10⁹ cells/

rently identified by traditional CVD risk factors.

*Arch Intern Med. 2005;165:500-508*

The WBC count, a stable, well-standardized, widely available and inexpensive measure of systemic inflammation, is an independent predictor of CVD events and all-cause mortality in postmenopausal women. A WBC count greater than 6.7 x 10(9) cells/L may identify high-risk individuals who are not currently identified by traditional CVD risk factors. (Approximately 50% increase in risk.)

INCREASING EVIDENCE SUPPORTS A role for inflammation in the atherosclerotic process.[1,2] Initiation, growth, and complications of atherosclerotic plaques are each judged to be an inflammatory response to vascular injury,[3,4] and inflammatory markers and cytokines originating in the heart, vessel walls, macrophages, adipose tissue, and liver have been associated with the risk of coronary events.[5] In light of the multitude of pathobiological factors involved in inflammation, a large number of targets for measurement have been proposed to identify and monitor the inflammatory process in patients with, or at risk for, coronary heart disease (CHD). These include proinflammatory factors such as oxidized low-density lipoproteins, proinflammatory cytokines (eg, interleukin 1 and tumor necrosis factor-α), adhesion molecules (eg, intercellular adhesion molecule 1 and selectins), inflammatory stimuli with hepatic effects (eg, interleukin 6), or the products of the hepatic stimulation, such as serum amyloid A, C-reactive protein (CRP), and other acute-phase reactants.[6] In addition, indicators of cellular responses to inflammation, such as elevated white blood cell (WBC) count, have also been considered.[6]

*For editorial comment see page 487*



**Author Affiliations** are listed at the end of this article. A complete listing of the Women's Health Initiative Research Group is given in a box at the end of this article.

**Financial Disclosure:** Dr Assaf is an employee of Pfizer Inc.

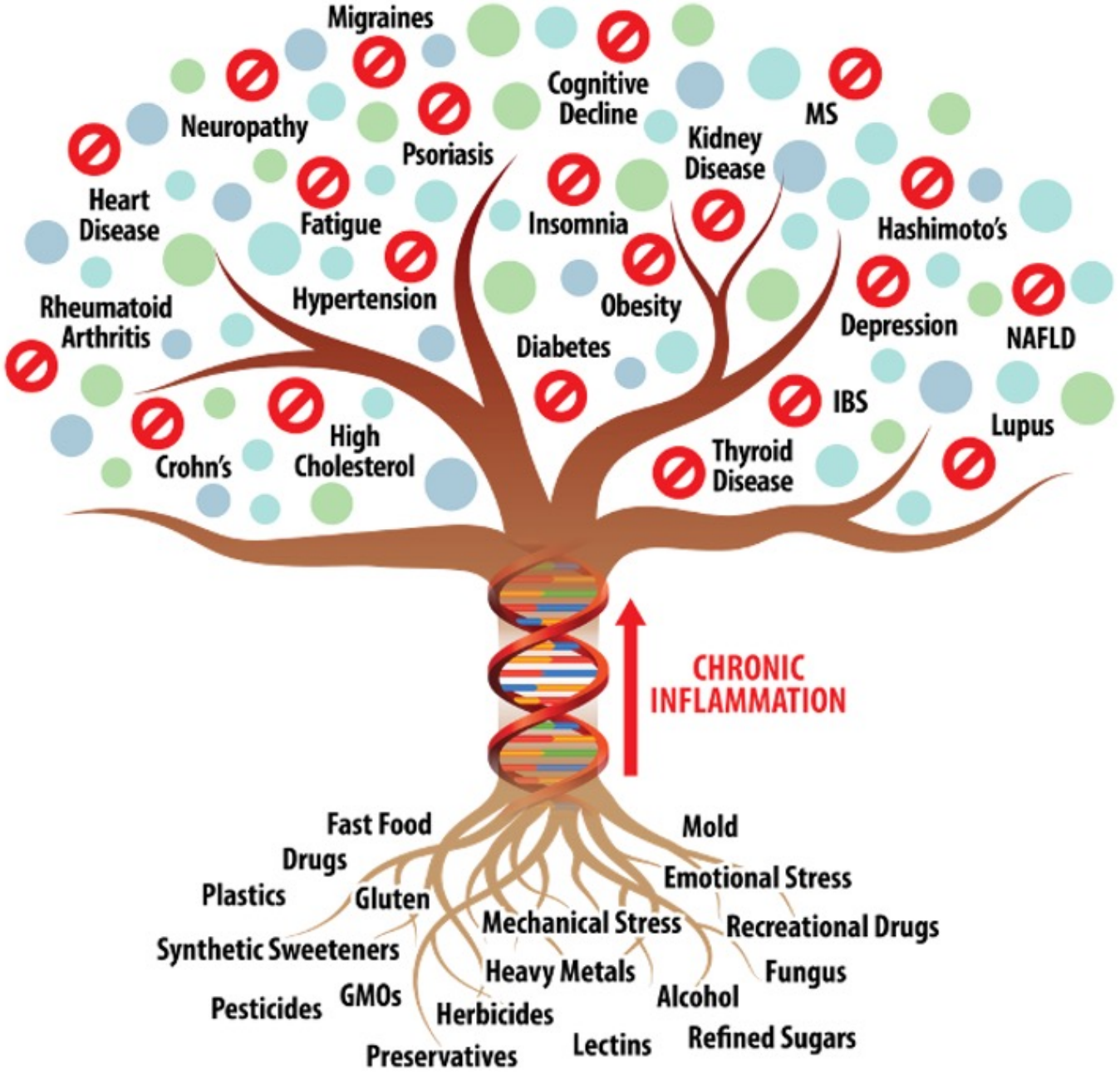
# White Blood Cell Count

Traditional Reference Range:

3.4-10.8 x10E3/uL

Optimal Reference Range

4.5 – 6.5 x10E3/uL


Migraines
Neuropathy
Psoriasis
Cognitive Decline
MS
Kidney Disease
Heart Disease
Fatigue
Insomnia
Hashimoto's
Hypertension
Obesity
Depression
NAFLD
Rheumatoid Arthritis
Diabetes
IBS
Lupus
Crohn's
High Cholesterol
Thyroid Disease
CHRONIC INFLAMMATION
Fast Food
Mold
Drugs
Emotional Stress
Plastics
Gluten
Mechanical Stress
Recreational Drugs
Synthetic Sweeteners
Heavy Metals
Fungus
Pesticides
GMOs
Herbicides
Alcohol
Preservatives
Lectins
Refined Sugars

# The Wedge Protocol