WHITE PAPER

What is Optimal?

Striving for Optimal Blood Chemistry Results and Optimal Health

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Abstract

Clinical chemistry utilizes blood samples to create a snapshot "report" of what is going on biochemically and physiologically in the body. Assessing and monitoring changes over time provides valuable diagnostic and prognostic information. In fact, most medical decisions are based on laboratory results and interpretation.

In the 1960s, "cornerstone" assays included glucose, urea, creatinine, electrolytes, total protein, albumin, globulin, cholesterol, and basic enzymes.[1] Today, clinical blood chemistry has developed into an essential branch of medicine with an expanding array of biomarkers.

Technically, biomarkers are "biological molecules that represent health and disease states… are able to detect sub-clinical disease and are used to monitor clinical and sub-clinical disease burden and response to treatments." [2] In some cases, even just a drop of blood can provide valuable insight into metabolic processes.

Detecting sub-clinical disease is the fundamental goal of functional blood chemistry so that early metabolic dysfunction is identified, addressed, and corrected. We must be sure to use these tools of the trade to the greatest extent possible to promote optimal health and prevent chronic disease.

Introduction

Bloodwork is the Window into the Body and Soul…

Patients are often eager to have their bloodwork assessed, seeking clues to why they aren't feeling up to their full health potential.

If told their lab results are "within normal range," they are often disappointed that their bloodwork can't explain their fatigue, weight gain, indigestion, pain, inflammation, hormone disruption, and other subtle or overt physical symptoms.

However, functional medicine practitioners reviewing that same bloodwork may discover that results are indeed not optimal. Instead, levels deemed "normal" may be trending toward compromised thyroid function, blood glucose dysregulation, altered liver function, sex hormone dysfunction, dehydration, inflammation, metabolic acidosis, etc.

For this reason, it is imperative that practitioners assess bloodwork from an optimal perspective, offering patients the opportunity to take proactive steps to restore optimal health. Comparing results to an optimal range that reflects physiological balance is preferable to simply accepting results within the standard or "average" reference interval.

What Do Standard Reference Intervals Reflect?

Standard Reference Intervals:[3 4 5 6 7]

- ✓ Represent *normal distribution* of results but not necessarily normal physiological function
- ✓ Reflect a wide range of values for 95% of individuals presumed to be healthy
- ✓ Do not necessarily correlate with clinical outcomes

- ✓ Vary from lab-to-lab due to variations in testing equipment, technique, geographic area, etc.
- ✓ Reflect population averages in the vicinity of the testing laboratory, and reflect increasing prevalence of disease and dysfunction in that local population
- ✓ Only detect overt pathology once the "damage is done"
- ✓ Fail to highlight or reveal subclinical imbalances or metabolic issues
- ✓ Different researchers may define different reference intervals, even when the same data are assessed[8]
- ✓ "...For most lab tests, there is no universally applicable reference value."[9]

Revision of standard reference intervals and values takes place slowly. For example, in the 1970s, the threshold for diagnosing diabetes was a fasting blood glucose of 140 mg/dL (7.77 mmol/L) or above. However, currently, a level of 100-125 mg/dL (5.6-6.9 mmol/L) is considered prediabetes and 126 mg/dL (7 mmol/L) is considered diabetes.

What is considered "normal" for thyroid stimulating hormone (TSH) is changing as well. Practitioners now recognize that a TSH within "normal" range can be associated with persistent symptomatology, metabolic syndrome, and hyperlipidemia.

Homocysteine levels provide another example of the need to utilize optimal blood chemistry ranges. Results deemed "normal" in the past are now recognized as being associated with blood vessel damage and endothelial dysfunction.

How are Standard Reference Intervals Determined?

A standard reference interval is based on a reference population with similar characteristics (e.g., age, gender, health status, race). Results from a set number of people, at least 120 subjects, are analyzed and "typical" results are determined based on the middle 95% of that population.[10] *Researchers recognize that some of those test subjects may have subclinical disease but are still deemed "healthy."* [11]

Standard reference intervals may literally become so broad that they lose their clinical relevance as they miss early signs of dysfunction and sub-clinical disease. It is recommended that the literature be reviewed regularly to determine updated or relevant guidelines for determining reference intervals beyond a simple statistical derivation.[12] However, such in depth analysis does not appear to be taking place in a timely manner.

Optimal Ranges:

- ✓ Represent a narrower range of acceptable results
- ✓ Reflect laboratory results associated with optimal health and physiology
- ✓ Detect early changes in metabolism and trends toward dysfunction
- ✓ Provide the clinician with an opportunity to explore imbalances before they progress into disease

How are Optimal Ranges Determined?

The best way to determine optimal ranges is to identify levels associated with optimal health or, at the very least, the absence of disease.[13] Almost as an afterthought, research will sometimes note that certain levels observed during clinical studies were associated with an improvement in health. This valuable information can be gathered and catalogued to help establish a useable database of optimal ranges. Optimal ranges can then be reviewed and updated according to published studies.

Of course, it is first necessary for clinicians to recognize exactly what a biomarker represents

and how it relates to patient outcomes. Indeed, *"understanding the relationship between measurable biological processes and clinical outcomes is vital to expanding our arsenal of treatments for all diseases, and for deepening our understanding of normal, healthy physiology."*[14]

Biomarker results may reflect underlying deficient, insufficient, suboptimal, adequate, or excess nutrient status. For example, elevated homocysteine may indicate insufficiency of vitamins B6, B12, riboflavin, and folate.[15] A suboptimal alkaline phosphatase level may be indicative of suboptimal zinc status.[16] A working knowledge of biochemical pathways and cofactors helps clinicians understand these intricate relationships.

Monitoring trends toward or away from optimal values can help identify underlying nutrient insufficiencies before outright deficiency and morbidity occur.

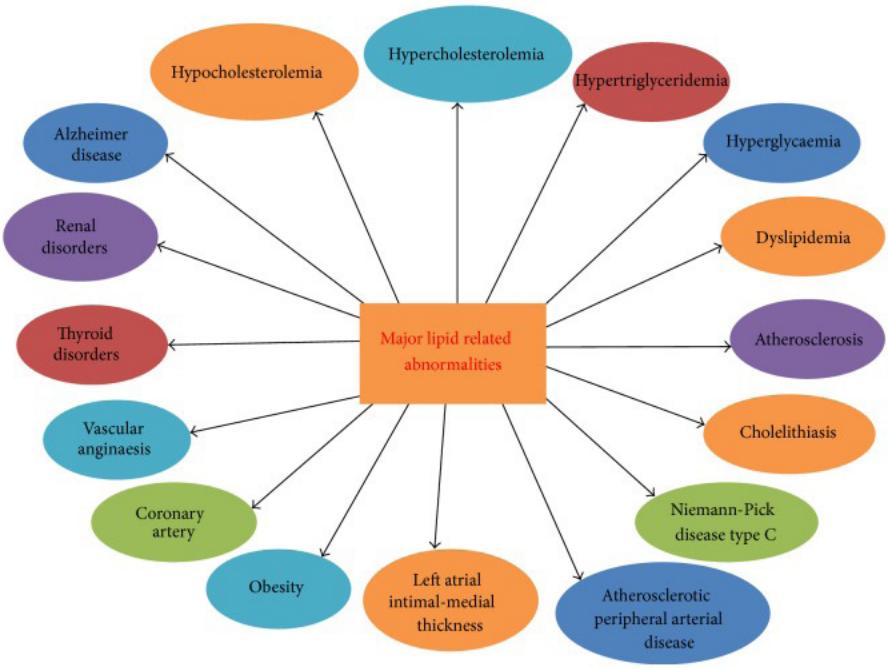
It is important to note that laboratory technique, specimen handling, additives, anticoagulants, lipemia, stress, and diurnal variations can influence some biomarkers no matter which reference interval is being used. It is prudent to repeat labs and use the same laboratory to get the best assessment of a patient's metabolic profile.[17]

The History of Optimal Blood Chemistry Reference Intervals and Patterns

Application of functional blood chemistry analysis can be traced back to one of its pioneers, Harry Eidenier, Ph.D. At Michigan State University, Dr. Eidenier and his M.D. and Ph.D. colleagues conducted an in depth review of more than 10,000 case studies, incorporating laboratory results, symptoms, physical exam, and medical history.[18]

Some of the most salient observations to emerge from this extensive work was a database of laboratory references intervals that aligned most closely with health versus disease. Patterns highlighting the interrelationship between biomarkers emerged. These patterns and associations were catalogued to assist the practitioner in uncovering early signs of dysfunction that warrant further investigation.

Researchers note that ranges and patterns are not diagnostic in, and of themselves, and must be combined with other aspects of a patient's clinical picture. However, it is equally important to recognize that many chronic diseases share similar biochemical patterns that should be fully investigated and addressed in order to optimize physiological function.



Upadhyay, Ravi Kant. "Emerging risk biomarkers in cardiovascular diseases and disorders." Journal of lipids vol. 2015 (2015): 971453. doi:10.1155/2015/971453 [R] This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Fundamental training in nutritional biochemistry, physiology, and functional medicine should accompany all medical training in order for clinicians to recognize and utilize optimal biomarker matrices.

What Does the Research Say?

Optimal ranges reflect normal physiological function and are narrower than standard reference intervals which often reflect two standard deviations (SD) from the mean.

Statistically speaking:[19]

- 68.3% of the distribution falls within 1 SD of the mean
- 95.4% of the distribution falls between mean- 2 SD and mean+ 2 SD
- 99.7% of the distribution falls between mean - 3 SD and mean + 3 SD

Digging into the research can reveal health complications when lab results edge toward "low normal" or "high normal," as they deviate from the mean.

Examples of the Optimal Range in Practice

Using a tighter optimal range to assess and treat dysfunction before it becomes a disease sounds simple enough. But there is a multitude of biomarkers out there, each with different characteristics, interactions, and significance.

To demonstrate what the use of Functional Blood Chemistry Analysis (FBCA) looks like in practice, let's review six representative blood biomarkers:

- Glucose
- Homocysteine
- Iron
- TSH
- Vitamin D
- Magnesium

We'll examine how "normal" levels of these blood biomarkers are often associated with dysfunction and disease and how levels that fall within the optimal range are associated with better patient outcomes. By examining these biomarkers in detail, we can gain a clearer picture of what optimal ranges are and why Functional Blood Chemistry Analysis is the best tool for guiding patients' blood biomarker levels back to healthier levels.

Blood Glucose

Elevated blood glucose is a classic sign of metabolic dysfunction. It is associated not only with diabetes but with cardiometabolic risk factors such as visceral obesity, high blood pressure, and dyslipidemia,[20] as well as cardiovascular disease itself.

The need to periodically update standard reference intervals to reflect dysfunction is illustrated by updates in the diagnostic guidelines for diabetes.

In 1979, diabetes wasn't diagnosed until fasting plasma glucose reached 140 mg/dL (7.77 mmol/L) or higher. This means that early asymptomatic dysfunction and outright disease were present but not accounted for due to outdated reference intervals.[21] [22]

Even traditional medical practice recognizes that a fasting blood glucose that had previously been defined as "normal" is now categorized as "prediabetes," with increased likelihood of progressing to overt diabetes. The functional blood chemistry approach addresses levels that are trending toward dysfunction instead of waiting for it to arrive.

Current 2021 ADA Guidelines[23 24 25 26]	Normal	Prediabetes	Diabetes
Fasting plasma glucose **(No caloric intake for at least 8 hours)**	70 – 99 mg/dL 3.9 – 5.5 mmol/L	100 – 125 mg/dL 5.6 – 6.9 mmol/L	126 mg/dL or higher 7 mmol/L or higher
Hemoglobin A1c	Less than 5.7% Less than 39 mmol/mol	5.7-6.4% 39-47 mmol/mol	6.5% or higher 48 mmol/mol or higher
Oral glucose tolerance test **2-hour result following 75 g anhydrous glucose dissolved in water**	Less than 140 mg/dL Less than 7.8 mmol/L	140 – 199 mg/dL 7.8 – 11 mmol/L	200 mg/dL or higher 11.1 mmol/L or higher Or random glucose >199 mg/dL >11 mmol/L
Other **If symptomatic for hyperglycemia**			Random plasma glucose of 200 mg/dL or higher 11.1 mmol/L or higher
Hypoglycemia			Level 1 54-70 mg/dL 3-3.9 mmol/L Level 2 Less than 54 mg/dL 3 mmol/L

Prediabetes must be addressed early on. Progressive nutrition and lifestyle changes that bring blood glucose biomarkers into optimal range can help avoid progression to an inevitable diagnosis of diabetes.

Research from 2008 based on 46,578 individuals with "normal" fasting plasma glucose (FPG) less than 100 mg/dL (5.6 mmol/L) revealed:[27]

- "Diabetes risk increases as FPG levels increase, *even within the currently accepted normal range."*
- Four FPG categories were defined:
  - Less than 85 mg/dL (4.7 mmol/L)
  - 85-89 mg/dL (4.7 – 4.9 mmol/L)
  - 90-94 mg/dL (5-5.2 mmol/L)
  - 95-99 mg/dL (5.3-5.5 mmol/L)
- Subjects with levels 90-99 mg/dL were significantly more likely to progress to diabetes than those with a FPG of 89 mg/dL (4.9 mmol/L) or lower.
- Those with FPG 90-94 mg/dL were 49% more likely to progress to diabetes.
- Those with FPG of 95-99 mg/dL had a 2.33 greater chance of progressing to diabetes than those with a FPG below 85 mg/dL (4.7 mmol/L).
- Each mg/dL (0.56 mmol/L) increased diabetes risk by 6%.

The importance of creating narrower ranges to better identify disease risk is being recognized by

the mainstream. For example, defining prediabetes in those with a hemoglobin A1c of 5.7-6.4% instead of 6-6.4% helps identify more individuals at increased risk of cardiovascular disease and, of course full-blown diabetes.[28]

Optimal Levels can Translate into Optimal Health

Earlier research from 1999 reveals that fasting glucose above 85 mg/dL (4.7 mmol/L) is associated with health risks including increased risk of cardiovascular disease and myocardial infarction. A 22-year follow-up study of healthy non-diabetic men demonstrates that higher than optimal levels of blood glucose may literally be a matter of life and death.[29]

The prospective study, published in Diabetes Care in 1999, revealed that those with a fasting blood glucose of 86-109 mg/dL (4.8–6 mmol/L), the highest glucose quartile defined, had a

> "significantly higher mortality rate from cardiovascular diseases compared to the three lowest quartiles… even after adjusting for age, smoking habits, serum lipids, blood pressure, forced expiratory volume in 1 s, and physical fitness."

- Quartile I 52-73 mg/dL 2.9-4 mmol/L
- Quartile II 74-79 mg/dL 4.1-4.4 mmol/L
- Quartile III 80-85 mg/dL 4.44-4.7 mmol/L
- Quartile IV 86-109 mg/dL 4.8-6 mmol/L

20 years later…

A 2019 study of 19,630 individuals assessing Long-term Absolute Risk for Cardiovascular Disease Stratified by Fasting Glucose Level, revealed the risk associated with "normal" fasting glucose levels.[30]

- ✓ Participants had no history of a prior CVD event
- ✓ Incidence for each CVD end point was lowest among those with fasting blood glucose of less than 90 mg/dL (<5.0 mmol/L) and highest among those meeting criteria for diabetes.
- ✓ Conversion of prediabetes to diabetes was associated with a 1.3-3.6 fold increased cardiovascular risk including coronary heart disease and stroke

Recognition of elevated blood glucose as a cardiovascular risk factor has been documented in the literature for decades though its importance has been overlooked:

- "Subjects with fasting glucose levels in the high normal range of 95–99 mg/dL (5.3-5.5 mmol/L) had an increased CVD risk when compared with levels <80 mg/dL (HR 1.53;CI 95% [1.22–1.91], P < .001)."[31]
- "Plots of stroke mortality rates versus blood glucose identified an upward inflection in risk of death from stroke at about 83 mg/dL (4.6 mmol/L)…An 18 mg/dL (1 mmol/L) increase in blood glucose after this point was associated with a 27% increase in risk of death from stroke."[32]

As you can see, assessing fasting blood glucose levels through an optimal lens provides the opportunity for early detection of metabolic abnormalities that can otherwise advance to chronic disease. While standard lab values for a "normal" fasting blood glucose range from 65-99 mg/dL (3.6-5.5 mmol/L),[33] a healthier, optimal range would be 75-86 mg/dL (4.2- 4.8 mmol/L).

Functional medicine by nature emphasizes the need to consider optimal ranges for patients' bloodwork in order to optimize prevention. Fortunately, ongoing research and observation is confirming the functional medicine approach to detecting and addressing blood glucose parameters beyond what was traditionally considered normal.[34] [35]

Homocysteine

Elevated homocysteine (Hcy) has been recognized as a risk factor for cardiovascular disease considering its negative effect on vascular endothelial integrity and its promotion of oxidative stress.[36] It is an independent risk factor for atherosclerosis (cerebral, coronary, and peripheral) so an excess can have harmful consequences throughout the body.[37]

Acceptable levels of Hcy have varied over time. In the past, hyperhomocysteinemia had been defined as a level above 15 umol/L, with moderate hyperhomocysteinemia being defined as 16-30 umol/L, intermediate 31-100 umol/L, and severe hyperhomocysteinemia above 100 umol/L.[38] However, researchers now recognize that a level of 10 umol/L or above can be considered hyperhomocysteinemia and warrants further assessment. [39]

Unfortunately, as we've seen, research does not quickly translate into updated reference intervals. Even today, "normal" lab values for homocysteine can range from 0 to a high of 21.3 umol/L for individuals over 80 years of age.[40] However, a significant decline in cognitive function was observed when Hcy rose above 11 umol/L, with an 88% increased risk of decline with Hcy of 20 umol/L. Researchers conclude that elevated homocysteine is a "strong modifiable risk factor for vascular dementia and Alzheimer's."[41]

Higher than optimal homocysteine has been associated with a variety of negative health outcomes. Levels of homocysteine previously accepted as "normal" with a mean of 10.5 umol/L, were associated with atherosclerotic regions in the carotid arteries of healthy individuals.[42] Atherosclerosis of the carotid artery is considered a strong predictor for stroke and cardiovascular disease.[43]

In a randomized double-blind placebo controlled trial of overweight women with vitamin D deficiency, homocysteine levels greater than 10 umol/L were significantly associated with elevated CRP, AST, urea, and creatinine, as well as decreased 25(OH) vitamin D.[44]

In a study of 396 individuals with an average age of 64, homocysteine was considered an independent risk factor for CVD. Levels positively correlated with LDL-C, uric acid, BMI, waist circumference, and blood pressure, and negatively correlated with HDL-C. In the study, homocysteine below 11 umol/L was considered low, and above 14.3 umol/L was considered high.[45]

A tighter range for cutoff values may help predict risk of cardiovascular morbidity and mortality. A higher homocysteine was also associated with shorter sleep duration, a potential cardiovascular risk factor. Note Hcy cutoff values from various studies:[46]

9.47 umol/L for cardiovascular events

9.74 umol/L associated with short sleep duration

11.84 umol/L for all-cause death

$\geq$ 15 umol/L significantly predicted cardiovascular events

Along with vitamin B6 deficiency, elevated hs-CRP, elevated IL-6, and shortened telomeres, Hcy is considered a marker of oxidative stress and systemic inflammation and contributes to morbidity and mortality. Homocysteine levels of 9.8 umol/L or higher were associated with a 28% greater risk of all-cause mortality, including CVD, when compared to those with concentrations below 9.8 umol/L.[47]

A study of 4177 subjects with prehypertension (SBP 120-139 mmHg, DBP 80-89 mmHg) demonstrated an independent association between homocysteine levels and arterial stiffness. Quartiles of Hcy were defined as: ≤9.19; 9.20–10.86; 10.87–12.79; and ≥12.80 umol/L.[48]

Brachial-ankle pulse wave velocity, a marker for arterial stiffness, increased progressively as Hcy increased, suggesting increased risk of progression from prehypertension to hypertension. BMI, waist circumference, serum glucose, uric acid, triglycerides, HDL, and LDL cholesterol differed significantly between quartiles as well.

Data analyzed from the NHANES III studies suggest that when highest and lowest quintiles of homocysteine were compared (11.5-98.1 versus 3-6.4 umol/L), risk of hypertension increased twofold for men and threefold for women with higher Hcy.[49] Researchers note that sufficiency of vitamins B6, B12, and folate can influence homocysteine and blood pressure levels.

As we can see from a variety of studies, as homocysteine begins to increase above 9 umol/L, disease risk increases as well. It is important to closely monitor and intervene in those trending toward dysfunction before disease begins to manifest.

Homocysteine should not be demonized completely as it is important as a sulfur depot and a methyl transfer molecule. Low or insufficient homocysteine should be addressed as it may reflect compromised ability to synthesize glutathione, which will increase risk of oxidative stress. Low homocysteine may also be associated with peripheral neuropathy.[50]

Researchers have observed a U-shaped curve with regard to homocysteine and elevated blood pressure. Risk of hypertension appeared to increase with increasing homocysteine, but risk also appeared to increase with lower homocysteine, especially in males.[51]

According to Mosby's guidelines, a homocysteine below 4 umol/L would be considered low.[52] An optimal goal for homocysteine would be ~ 5-7.2 umol/L.

Iron and Iron Deficiency

Assessment of iron status is a good illustration of using tighter ranges to identify early subclinical deficiencies that are likely to progress to disease.[53]

Biomarker values decrease in iron deficiency much earlier than clinical symptoms appear. Early biochemical changes are reflected in the defined stages of iron deficiency anemia. Noticeable physical symptoms may not appear until stage 5.

Stage 1	Decreased stores of bone marrow iron
	Ferritin drops below 20 ng/mL (45 pmol/L)
	Serum iron and hemoglobin within normal limits
Stage 2	Impaired erythropoiesis
	Serum iron falls below 50 ug/dL (9 umol/L)
	Transferrin saturation drops below 16%
	Serum transferrin receptor level rises above 8.5 mg/L
	Transferrin increases
Stage 3	Anemia with normal-appearing red blood cells
Stage 4	Microcytosis and hypochromia develop
Stage 5	Deficiency of iron affects tissue, manifests in physical signs and symptoms including dizziness, fatigue, weakness, loss of stamina, pallor, and restless leg syndrome.

A review of the research indicates that healthy individuals with replete bone marrow stores of iron maintained a serum ferritin level of 70 ng/mL.[54] However, ferritin levels can vary significantly with pathologies such as rheumatoid arthritis, alcoholism, and blood disorders so a comprehensive history and clinical assessment must accompany evaluation of iron status.

Since a low ferritin may be the earliest sign of iron insufficiency, research suggests a low end cut-off of 30 ng/mL.[55] However, researchers suggest that a ferritin below 100 ng/mL may warrant further evaluation of iron insufficiency. Other biomarkers should be evaluated as well, including mean corpuscular volume, hemoglobin, hematocrit, TIBC, and transferrin saturation as serum iron alone is insufficient for assessing status. At present, serum erythropoietin and hepcidin are being evaluated as pertinent biomarkers.[56]

Serum ferritin can also be used to assess iron overload as ferritin reflects liver stores which can be damaging at high levels. A ferritin above 160 ng/mL may be indicative of mild iron overload, and 290 ng/mL may indicate severe iron overload.[57] Ferritin levels can increase temporarily during inflammation and infection. Therefore, further assessment of elevated ferritin is warranted.

	Mosby's[58]	Merck Manual[59]	Quest standard ranges[60]	Optimal ranges
Serum Iron	Men 80-180 ug/dL 14-32 umol/L Women 60-160 ug/dL 11-29 µmol/L	Men 75-150 µg/dL 13–27 umol/L Women 60–140 µg/dL 11–25 umol/L	Men 50-195 ug/dL 9-35 umol/L Women 40-190 ug/dL 7-34 umol/L	85-130 ug/dL 15-23 umol/L
Total iron-binding capacity	250-460 ug/dL 45-82 umol/L	250–450 µg/dL 45–81 umol/L	250–425 ug/dL (45–76 µmol/L)	250–350 ug/dL 45-76 umol/L
Ferritin	Men 12-300 ng/mL 27-674 pmol/L Women 10-150 ng/mL 22-337 pmol/L	30–300 ng/mL 67-674 pmol//L	Men 24-380 ng/mL 54-854 pmol/L Women 16-288 ng/mL 36-647 pmol/L	30–70 ng/mL 67-157 pmol/L
Transferrin saturation	Men 20-50% Women 15-50%	20–50%	Men 20–48% Women 16-45%	24–35%

Thyroid Stimulating Hormone

Biochemical assessment of thyroid function has undergone important changes. For instance, "normal" serum levels of T4 and T3 with abnormal fluctuations in TSH have been recognized as subclinical thyroid disease

Also, thyroid markers that vary overtime within the standard reference interval may reflect abnormal function and should be explored in conjunction with symptomatology and clinical presentation.[61]

Subtle hints about thyroid function can be revealed when reviewing historical blood chemistry results. Individuals may experience variations in thyroid biomarkers, but if values remain "normal," then those changes may be overlooked until overt disease occurs.[62]

Signs and Symptoms of Hypothyroidism may Include[63]

Anxiety

Attention deficit

Brittle hair and nails

Carpal tunnel syndrome

Cerebellar ataxia

Cold intolerance

Constipation, prolonged gastric emptying

Decreased sweating

Depression

Dry skin

Edema

EEG abnormalities

Fatigue, listlessness, lack of energy, drowsiness

Headache

Hearing loss

Hypocoagulability, prolonged bleeding, bruising

Mental dullness

Memory deficits

Menstrual disturbances

Musculoskeletal cramps

Myxedema madness (schizoid or affective psychoses)

Nervousness, irritability

Tinnitus

Paresthesias

Sleep apnea

Urticaria (especially in Hashimoto's)

Weight gain

Serum elevations in cholesterol, oxidized cholesterol, LDL cholesterol, triglycerides, ALT, AST, GGT, LDH even if TSH within "normal" range

TSH Evaluation of Thyroid Status

As long as pituitary and hypothalamus function are normal, TSH is considered a sensitive marker of thyroid dysfunction that can be easily assessed.[64]

Clinicians may be surprised to learn that the historic upper range for TSH was once 10 uU/mL before it was lowered to 4.5. As research progressed, it was recognized that TSH between 4.5-9.9 uU/mL (mU/L), previously accepted as "normal", was associated with dyslipidemia, vascular alterations, and diastolic dysfunction in young and middle aged subjects.[65]

Presently, evaluating TSH in terms of optimal ranges is becoming more mainstream. While the "normal" reference interval for TSH for a non-pregnant adult is 0.45–4.5 uU/mL, therapeutic targets range from 0.3- 3.0 uU/mL, reinforcing the value of a more optimal range.[66] Updated reproducibility studies confirm that a TSH of 0.44-3.19 uU/mL, rather than the standard reference interval, better reflects normal thyroid function.[67]

Further research suggests that even a TSH of 2.5-4.5 uU/mL, in the upper end of the standard reference interval, was associated with obesity, hypertriglyceridemia, and increased metabolic syndrome risk.[68]

A TSH above 2.5 uU/mL has also been associated with depression, a syndrome that shares clinical characteristics with hypothyroidism.[69] Research reveals that antithyroid antibodies are more prevalent when TSH levels rise above 2.5 uU/mL.[70]

Even the National Academy of Clinical Biochemists (NACB) recognizes that 95% of subjects without indication of thyroid disease maintain a TSH below 2.5 uU/mL.[71]

Case studies have demonstrated that classic hypothyroid symptoms may persist despite TSH within the standard interval, including a level of 2.65 uU/mL. In one case, symptoms of dry skin, constipation, compromised thyroid function, and low energy resolved, and TSH decreased from 2.65 uU/mL to 1.95 uU/mL, with thyroid hormone support incorporating T3 (5 ug) and T4 (25 ug).[72]

One prospective survey indicates that actual thyroid dysfunction was lowest with a serum TSH between 1 and 1.9 uU/mL.[73]

Based on research that included a 20 year follow up period, researchers note that an increase in TSH above 2 uU/mL increases the probability of developing hypothyroidism, especially in the

presence of TPO antibodies. Norwegian research observed a significantly increased odds ratio of developing hypothyroidism in women when TSH increased above 1.5 uU/mL and in men when TSH rose above 2 uU/mL.[74] Here again see that while lab results were "normal," health was far from optimal.

Currently even conventional experts are recommending lowering the upper range to 3, possibly even 2, closer to what functional practitioners currently recommend.[75] [76] [77]

Vitamin D

Evolving recommendations for vitamin D illustrate the need to assess serum biomarkers from an optimal perspective. Evaluation of both optimal vitamin D levels and intake have been gaining attention.

Traditionally, serum 25-hydroxyvitamin D (25(OH)D) levels above 20 ng/mL (50 nmol/L) were accepted as "normal." Insufficiency was defined as 12-20 ng/mL (30-50 nmol/L), and deficiency was defined as a value lower than 12 ng/mL (30 nmol/L).[78]

However, over time, research revealed that minimum sufficiency wasn't achieved until levels reached above 30 ng/mL (75 nmol/L),[79] [80] while levels of 40 ng/mL (100 nmol/L) or greater were associated with a reduction in all-cause mortality.[81]

Corroborating these findings, research during the COVID-19 pandemic revealed that a 25(OH) D level of 30 ng/mL (75 nmol/L) or greater was associated with reduced disease severity and mortality.[82] Researchers recommend maintaining a serum 25(OH)D level of 55 ng/mL (137 nmol/L) or greater to reduce cancer risk.

How much is too much? Serum 25(OH)D does not reflect tissue stores and toxicity is a potential concern, though at what level it may occur is debated. Pharmacokinetics research suggests that while levels of 25(OH)D must "rise above 300 ng/mL (750 nmol/L) to produce vitamin D toxicity, the more prudent upper limit of 100 ng/mL (250 nmol/L) might be retained to ensure a wide safety margin."[83] Serum calcium levels should also be assessed as 25(OH)D levels rise.

Currently, conventional lab normal range is 30–100 ng/mL (75-250 nmol/L),[84] with an optimal goal of 50-90 ng/mL (125-225 nmol/L).[85]

Vitamin D Intake and Supplementation

Recommended intake of vitamin D has been a subject of debate as well.

The US recommended dietary allowance (RDA) for vitamin D remains fairly low at 600-800 IU/ day (15-20 ug) with a tolerable upper intake of 4000 IU (100 ug) per day.[86] However, researchers indicate that due to statistical error, the estimated RDA for vitamin D was set too low and will not promote serum vitamin D levels consistent with optimal health. Research and reanalysis of the data suggests:[87]

- 8895 IU/day (222 ug) was needed for 97.5% of individuals to achieve 20 ng/mL (50 nmol/L) or greater
- 6201 IU/day (155 ug) was needed to achieve 30 ng/mL (75 nmol/L)
- 9122 IU/day (228 ug) was needed to reach 40 ng/mL (100 nmol/L)
- 8000 IU/day (200 ug) is general recommendation for adults
- In general, each 1000 IU (25 ug) dose of vitamin D3 should increase blood levels by 10 ng/mL (25 nmol/L).[88]

Vitamin D status should be evaluated as part of a general health checkup considering its wide range of effects and functions including musculoskeletal health, immune regulation, skin health, cardiovascular integrity, apoptosis, and cell proliferation and differentiation.[89]

Vitamin D also plays an important role in homocysteine metabolism as it activates the cystathionine synthase gene which facilitates one of the biochemical pathways for processing Hcy. Supplementation with vitamin D, 50,000 IU/week for two months, significantly decreased Hcy, CRP, AST, and ALT in vitamin D deficient women. Results also indicated an increase in urea to 12 mg/dL (4.3 mmol/L) and creatinine to 0.65 mg/dL (57.5 umol/L), and a decrease in eGFR to 167.6 mls/min though values remained within optimal range.[90]

According to the Endocrine Society, vitamin D deficient adults should be treated with 50,000 IU (1250 ug) of vitamin D weekly [equal to 7143 IU (179 ug) daily] for eight weeks to achieve a blood level greater than 30 ng/mL (75 nmol/L). Maintenance therapy thereafter should be at least 1500-2000 IU (38-50 ug) per day.

In obesity, malabsorption syndromes, or medication-induced depletions, higher doses of 6000-10000 IU (150-250 ug) per day may be needed to reach 30 ng/mL (75 nmol/L), with maintenance therapy of 3000-6000 IU (75-150 ug) per day.[91]

Classification of Serum 25(OH)D Levels:[92]

Classification	Nanograms	Nanomoles	Recommended D
Danger of toxicity	>100 ng/m*	>250 nmol/l	Hold
Normal or optimal	>30 ng/ml	>75 nmol/l	400–4,000 IU/day
Insufficient	21–29 ng/ml	51–74 nmol/l	4,000–6,000 IU/day
Deficient	11–20 ng/ml	26–50 nmol/l	7,000 IU/day
Severely deficient (often not distinguished from deficient)	<10 ng/ml	25 nmol/l	10,000 IU/day x 1 month or 500,000 IU x 1
NIH target	30 ng/mL	75 nmol/L	2000 IU/day
Prevention of respiratory infection	40-60 ng/mL	100-150 nmol/L	6000 IU/day normal weight until goal 7000-8000/day obese
Reduce risk CVD, hypertension	50-80 ng/mL	125-200 nmol/L	4000-10000 IU/day until goal
COVID-19	40-60 ng/mL	100-150 nmol/L	5000-10000 IU/day until goal

*some sources found that 150 ng/ml was not harmful.

Benskin, Linda L. "A Basic Review of the Preliminary Evidence That COVID-19 Risk and Severity Is Increased in Vitamin D Deficiency." *Frontiers in public health* vol. 8 513. 10 Sep. 2020, doi:10.3389/fpubh.2020.00513 [R]

Endogenous production of vitamin D is stimulated when a cholesterol compound in the skin is exposed to UVB light, with subsequent hydroxylation and activation at the liver and kidney level. From 10000 to 25000 IU of vitamin D can be produced endogenously when exposed to one erythemal dose of UV radiation (leaves a slight pinkness in the skin 24 hours following exposure). Endogenous vitamin D remains in the blood longer than ingested vitamin D.[93]

Keep in mind that a wide range of variables can influence serum 25(OH)D including age, gender, body weight, obesity, genetic factors, skin pigmentation, sun exposure, sunblock, season, geographic location/latitude, physical activity, diet, and lifestyle factors.[94] [95] [96] [97] Vitamin D deficiency is more likely in those with fair to poor health status, diabetes, obesity, no college education, smokers, and individuals with dark skin.[98]

A literature review of randomized trials, systematic reviews, meta-analyses, and international consensus conferences was conducted and published in March 2021. Researchers conclude that optimal serum 25(OH)D levels be maintained above 50 ng/mL (125 nmol/L).[99]

Magnesium

Accurate assessment of magnesium status is another prime example of where standard lab ranges can fall short. Magnesium is an essential mineral required by most organs for a wide variety of metabolic functions. Its insufficiency contributes to hypertension, atherosclerosis, cardiovascular disease, insulin resistance, type 2 diabetes, neurological dysfunction, osteoporosis, low grade inflammation, and electrolyte imbalance among other dysfunctions.[100]

Insufficiency may be subtle but widespread as less than half of the population in the United States consumes adequate magnesium. Not surprisingly, subclinical magnesium deficiency was suspected even at "acceptable" serum magnesium levels of 1.82 - 2.3 mg/dL (0.75–0.95 mmol/L) based on 1974 NHANES I data.[101]

Unfortunately, some standard lab ranges for magnesium currently have an even lower acceptable cut-off, making it more difficult to identify suboptimal status:

- Quest Diagnostics[102] 1.5 - 2.5 mg/dL (0.62 – 1.03 mmol/L)
- Labcorp[103] 1.6 - 2.3 mg/dL (0.66 – 0.95 mmol/L)
- Mosby's[104] 1.6 - 2.6 mg/dL (0.65-1.07 mmol/L, 1.3-2.1 mEq/L)
- Merck Manual[105] 1.8 to 2.6 mg/dL (0.74 to 1.07 mmol/L)

Researchers suggest magnesium deficiency is likely with a serum magnesium of less than 2 mg/dL (0.82 mmol/L), especially coupled with decreased urinary magnesium. A urinary magnesium of 40-80 mg/day reflects intake of less than 250 mg/day while excretion of 80-160 mg/day reflects intakes of more than 250 mg/day.[106]

Magnesium insufficiency is suspected in primary hypertension, the most common form of high blood pressure. A 2021 systematic review of the literature noted the cardiovascular benefits of magnesium supplementation: [107]

- 240 mg/day or more successfully reduced blood pressure in uncontrolled medicated hypertensives.
- 600 mg/day or more were needed to reduce blood pressure in uncontrolled untreated hypertensives.
- Supplementation in normotensive subjects didn't lower blood pressure further but significantly improved serum magnesium, lipoprotein levels, CRP, fasting glucose, insulin resistance, sodium excretion, and retinal vasospasm.
- The current US tolerable upper limit (UL) for supplemental magnesium was set at 350 mg/day based on limited evidence.
- The potential for mild diarrhea in a minority of subjects at levels of 360-380 mg/day prompted the limited UL.
- Exceedingly high doses of 5000 mg/day or more can cause serious side effects.

Clinicians must look beyond standard reference intervals and not wait for a pathological diagnosis, if we are to help patients improve their metabolic profile now to prevent disease later.

Interrelationships Between Biomarkers

No biomarker is an island unto itself. Instead, it is just the tip of the metabolic iceberg…or perhaps the volcano. Ongoing research confirms the inherent value of monitoring key biomarkers and groups of biomarkers to assess health and disease…and even predict all-cause mortality.[108]

For example, elevated "prediabetes" levels of blood glucose have an impact beyond diabetes risk, and are associated with abdominal/visceral obesity, hypertension, and dyslipidemia such as high triglycerides and/or low HDL cholesterol.[109] The takeaway can no longer be "Well, at least you don't have diabetes."

Endothelial dysfunction is another example of the interrelatedness of biomarkers. A common pattern associated with this disorder, which underlies atherosclerosis and most cardiovascular disease, includes:

Endothelial Dysfunction	
Elevated	**Decreased**
Homocysteine[110] [111]	Omega-3 index[128]
Fibrinogen[112]	Adiponectin[129]
CRP[113]	Testosterone[130]
Serum iron[114]	
Ferritin[115]	
GGT[116]	
Neutrophil/Lymphocyte ratio[117]	
Oxidized LDL[118] [119] [120]	
ADMA[121]	
Myeloperoxidase[122]	
Malondialdehyde[123]	
Post-prandial glucose[124]	
Two-hour glucose in OGTT[125]	
Impaired fasting glucose and HbA1C[126]	
*Oscillating glucose[127]	
Oscillating glucose between 90 and 270 mg/dL (5 and 15 mmol/L) (endothelial dysfunction was reversed by vitamin C infusion 3mg/min).	

Assessing key biomarkers within a matrix creates an important tool for assessing overall health, disease, and risk for all-cause and specific causes of mortality.

Readily available serum biomarkers provide a snapshot of metabolic function and include comprehensive metabolic panel, CBC with differential, lipid panel, mineral panel, hemoglobin A1c, and inflammatory biomarkers.

Researchers have begun to develop various tools to assess groups of biomarkers and their relation to disease risk and overall mortality. These include the Intermountain Risk Score (IMRS) and the Health Status Metric (HSM). The latter is found to predict all-cause mortality and specific causes of mortality such as diabetes, kidney disease, and liver disease.[131]

Examples of FBCA Patterns:

Dysfunction	Elevated	Decreased
Adrenal hyperfunction	Sodium, chloride, CO2, BUN	Potassium, cholesterol, triglycerides
Adrenal hypofunction	Potassium, cholesterol, triglycerides	Sodium, chloride, blood glucose
Anemia- B12/folate deficiency	MCH, MCV, RDW, serum iron, LDH, MMA, homocysteine	RBCs, Hct, Hgb, WBCs, neutrophils, uric acid
Arthritis	ESR, CRP, globulin, platelets, albumin (or normal)	Decreased or normal albumin
Atherosclerosis	Increased triglycerides, cholesterol (or normal), oxidized cholesterol, small dense LDL particles, uric acid, platelets. CRP, ApoB/Apo A-1 ratio, Lp(a)	HDL cholesterol Antioxidant status
Insulin resistance	Glucose, insulin, C-peptide, HgbA1C, total cholesterol, triglycerides, triglyceride/HDL ratio, HOMA2-IR greater than 1.8	Adiponectin
Metabolic syndrome	Glucose, insulin, HgbA1C, total cholesterol, triglycerides, also obesity and blood pressure	HDL cholesterol
Polycythemia	RBCs, Hct, Hgb, total bilirubin, uric acid, WBCs, basophils, alkaline phosphatase	MCV (or normal), MCH (or normal), serum iron (or normal)

Reaching beyond reference intervals that define disease, it is the functional practitioner's goal to assess these same serum biomarkers in a matrix based on optimal ranges. This approach is believed to best provide a picture of health and optimal metabolic function instead of just diagnosing disease and predicting mortality. Such an assessment provides the clinician with a valuable tool to detect subtle preclinical changes that can then be addressed and corrected.

Implications for Clinicians and Patients

The most pressing reason for analyzing blood chemistry and laboratory results from a functional perspective is that an estimated 60-70% of medical decisions are based on laboratory results. Unfortunately, teaching critical thinking outside the box and outside the accepted reference intervals has not become mainstream yet.[132]

Functional Blood Chemistry Analysis can be defined as the process by which complex and comprehensive blood biomarkers are organized, analyzed, and interpreted to provide a comprehensive assessment of the state and trends of the main body systems, the supporting body accessory systems, along with the status of nutrients and trends towards and away from clinical dysfunction.

Using tighter functional physiological ranges, this approach not only recognizes that "normal" is not optimal, but provides the tools and guidance needed to uncover the underlying biochemical imbalances that may be contributing to a patient's clinical picture.

With advanced functional blood chemistry analysis, the functional practitioner can assess and integrate biomarker indices into a comprehensive program for health improvement and optimization.

The OptimalDX software provides a wide range of biomarkers, clinical overviews, and optimal ranges to help focus the clinical picture and provide guidance down the road to optimal health.

It is imperative that clinicians and patients detect, address, and resolve early changes in metabolism that, if left unchecked, can develop into disease and pathology. The implications of evaluating a patient's blood chemistry and laboratory data through an optimal lens are relevant and far-reaching. The implications of dismissing levels of biomarkers that may be representative of subclinical disease may translate into "First, doing some harm." Using a more comprehensive approach can help identify trends towards disease and dysfunction well before clinical symptoms and consequences appear.

Optimal Takeaways

- ✓ The majority of medical decisions are based on lab results and blood chemistry analysis. However, standard biomarker reference intervals can fail to identify early dysfunction, subclinical disease, or latent deficiencies.
- ✓ Standard reference intervals reflect normal or average distribution of values in a geographic population but not necessarily normal physiology.
- ✓ Functional blood chemistry analysis provides valuable tools for assessing an individual's biochemistry, physiology, metabolism, and risk of chronic disease.
- ✓ Early trends away from optimal values can be identified and addressed before overt symptoms or dysfunction occur.
- ✓ Monitoring results over time and using the same laboratory for repeat bloodwork will provide the most relevant data for a comprehensive blood chemistry analysis.
- ✓ Optimal ranges should be utilized for detecting risk of and progression toward
    - Diabetes, metabolic syndrome, insulin resistance, cardiovascular disease, thyroid disease, endothelial dysfunction, nutrient insufficiency, etc.
- ✓ Patterns of associated biomarkers can help guide clinical evaluation.
- ✓ Functional blood chemistry is not considered diagnostic and must be used as part of a matrix addressing each patient's clinical presentation history, symptoms, and blood chemistry changes over time.
- ✓ Remember to promote optimal function on the inside to achieve optimal health on the outside.

OPTIMAL DX SOFTWARE STATEMENT

WHY BLOOD TESTING?

Blood has a lot to tell us about our state of health and the blood chemistry and CBC / hematology test is the most commonly ordered medical lab test worldwide.

These blood tests are an integral part of Western clinical medicine and are used to aid in the diagnostic decision-making process.

Patients understand and are educated that blood testing is the norm for health assessment. However, many, many people start to feel unwell long before a traditional blood test becomes diagnostic and more often than not, our patients are told by their physician that "everything on your blood test looks normal."

"NORMAL" IS NOT OPTIMAL

Most patients who feel "unwell" will come out "normal" on a blood test. Clinical experience suggests that these people are by no means "normal" and are a far cry from being functionally optimal. They may not yet have progressed to a known disease state but they are what we call dysfunctional, i.e. their physiological systems are no longer functioning properly and they are starting to feel un-well.

The issue is not that the blood test is a poor diagnostic tool, far from it.

The issue is that the ranges used on a traditional lab test are based on statistics and not on whether a certain value represents good health or optimal physiological function.

The problem is that "normal" reference intervals usually represent "average" populations rather that the optimal level required to maintain good health.

Many “normal” ranges are too broad to adequately detect health problems before they become pathology and are not useful for detecting the emergence of dysfunction.

THE FUNCTIONAL APPROACH

The functional approach to chem screen and CBC analysis is oriented around changes in physiology and not pathology. We use ranges that are based on optimal physiology and not the “normal” population. This results in a tighter “Functional Physiological Range”, which allows us to evaluate the area within the “Normal” range that indicates that something is not quite right in the physiological systems associated with this biomarker. This gives us the ability to detect patients with changes in physiological “function”. We can identify the factors that obstruct the patient from achieving optimal physiological, biochemical, and metabolic functioning in their body.

Another thing that separates the Functional Blood Chemistry Analysis from the Traditional approach is we are not simply looking at one individual biomarker at a time in a linear report of the data. Rather, we use trend analysis between the individual biomarkers to establish otherwise hidden trend towards or away from a functional health optimal.

THE FUNCTIONAL HEALTH REPORT

The Functional Health Report is the result of a detailed algorithmic analysis of your blood test results. Our analytical and interpretive software analyzes the blood test data for its hidden meaning and reveals the subtle, web-like patterns hidden within the numbers that signal the first stages of functional change in the body.

SUMMARY

In closing, Blood testing is no longer simply a part of disease or injury management. It’s a vital component of a comprehensive Functional Medicine work up and plays a vital role in uncovering hidden health trends, comprehensive health promotion and disease prevention.

The OptimalDX Difference

Discover how to bring real meaning to your blood test results.

The OptimalDX Software: Your End-to-End Functional Blood Chemistry Analysis Tool

What makes one medical practitioner stand out in a patient's mind? Easy: It's the ability to provide answers — faster, more accurately, and at less cost. The Optimal DX Software enables you to do just that. By supporting the analysis, interpretation and tracking of patient blood test results, this software tool accelerates your ability to deliver insights into your patients' health and generate intuitive, comprehensive Functional Health Reports.

SEE A DEMO >

FBCA Mastery Course

This 12-week online course provides you the tools for assessing, diagnosing and evaluating your patients from a functional perspective with the expertise of Dr. Weatherby. Featuring lifetime access to 12 core training modules and additional training from leading functional medicine experts, this course will set you up for success in blood chemistry analysis. Evaluate and diagnose your patients better byusing Dr. Dicken Weatherby's step-by-step approach to Functional Blood Chemistry Analysis.

REGISTER NOW >

Why Use the OptimalDX Software in Your Practice?

Using the Optimal DX Software, you gain more time in your day to dedicate towards treating patients, growing your practice and keeping up with the latest medical developments. The software platform expedites the process of Functional Blood Chemistry Analysis; its features include automatic analysis and assisted interpretation, enhanced tracking and storage, automated and customizable report generation and more.

SIGN UP FOR A FREE TRIAL >

Dr. Dicken Weatherby, Founder and CEO of OptimalDX

OptimalDX.com

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