KRESSER INSTITUTE FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

# Impaired Liver Function - Part Two

## Autoimmune hepatitis

| Prevalence | Risk factors | Comments |
|---|---|---|
| Prevalence varies geographically; in Hong Kong <1% of those with chronic hepatitis have autoimmune form; in Germany and Austria 34–62%; in North America, 11–23% and overall incidence is 0.68 cases per 100,000 people/year | More common in women and those with other autoimmune diseases | Diagnosis by exclusion of viral hepatitis, pathologic findings, and presence of autoimmune markers such as antinuclear antibodies, smooth muscle antibody, liver-kidney microsomal antibodies |

Autoimmune hepatitis is another cause of elevated AST and ALT. The prevalence varies a lot geographically. In Hong Kong, less than 1 percent of those with chronic hepatitis have the autoimmune form, but in Germany and Austria, it's between 34 and 62 percent, obviously much higher there in Europe. In North America, it's somewhere between 11 and 23 percent of cases, and the overall incidence is 0.68 cases per 100,000 people per year. So, it's pretty rare in North America, but it certainly does occur, and we've seen it in our practice. It's much more common in Europe.

Risk factors include sex, female sex, and those with other autoimmune diseases. Diagnosis is often by exclusion of viral hepatitis, pathologic findings, and then presence of some autoimmune markers such as antinuclear antibody, smooth muscle antibodies, and liver-kidney microsomal antibodies.

## Wilson disease

| Prevalence | Risk factors | Comments |
|---|---|---|
| Estimated prevalence of Wilson disease is 1 in 40,000 to 1 in 100,000 worldwide | Anyone under age 40 with abnormal liver enzymes should be evaluated, even in absence of neurologic or ocular findings; routine screening rarely helpful in patients over age 50 | Genetic testing limited value because of large # of potential mutations of ATP7B gene; if patient does have WD, screening of family members indicated |

Wilson disease is another cause of elevated AST and ALT. We talked about this briefly in a case study back in the iron overload unit. This is a disease of excess copper storage. The estimated prevalence of Wilson disease is between 1 in 40,000 to 1 in 100,000 worldwide. Risk factors are anyone under age 40 with abnormal liver enzymes, essentially, even in the absence of neurologic or ocular findings. Routine screening is rarely helpful in patients over age 50 because it would have manifested by then in the vast majority of cases. Wilson's is such a serious disease, and the prognosis is so much better if it is detected early that it should always be ruled out in cases with abnormal liver enzymes under the age of 40 who don't have a clear pathology.

Genetic testing is of limited value for Wilson disease because of the large number of potential mutations of the ATP7B gene, which is implicated. If the patient does have Wilson disease, screening of family members is definitely indicated because there is a strong genetic connection there.

## Alpha-1-antitrypsin deficiency

| Prevalence | Risk factors | Comments |
|---|---|---|
| 1 of every 1,600 to 1,800 live births | Patients with emphysema or with a young sibling with liver failure | Common cause of liver disease in young children, but only a portion develop liver failure as adults |

Alpha-1-antitrypsin deficiency can cause elevated AST and ALT. It's present in 1 of every 1,600 to 1,800 live births. Patients with emphysema or with a young sibling with liver failure are at higher

risk, and it's a common cause of liver disease in young children, but only a portion of adults with this condition will develop liver failure in adulthood. Alpha-1-antitrypsin is a protease inhibitor made in the liver that protects both the liver and the lungs. About 10 percent of infants with alpha-1-antitrypsin deficiency will go on to develop liver disease, and approximately 15 percent of adults with alpha-1-antitrypsin deficiency develop liver damage.

## Drug- and toxin-related liver diseases

| Prevalence | Risk factors | Comments |
|---|---|---|
| Unknown | A variety of prescription and nonprescription drugs can damage the liver | NSAIDs |
| | | Antibiotic |
| | | Statins |
| | | Valproic acid |
| | | SSRIs |
| | | PPIs |
| | | Losartan |
| | | Lisinopril |
| | | Acetaminophen |
| | | Some botanicals *(kava kava and germander)* |
| | | Amiodarone |
| | | Trazodone |

Then, of course, there are several drugs and toxins that can harm the liver and cause high AST and ALT. The prevalence is unknown. It depends on the drugs and the toxins. You should note that many of the drugs that can damage the liver are among the most commonly used drugs such as NSAIDs, statins, antibiotics, SSRIs, PPIs, losartan and other blood pressure medications, acetaminophen, some botanicals such as kava kava and germander, and psych meds such as trazodone and valproic acid. There is obviously some level of awareness to this in the medical community, but you might be surprised how many patients I've seen who are taking these drugs and have liver damage or elevated AST and ALT and were not aware that the drugs that they were on could cause this problem.

## Extra-hepatic causes

| Prevalence | Comments |
|---|---|
| Thyroid disorders | Screen for thyroid antibodies and run full thyroid panel |
| Celiac disease | Test tissue transglutaminase levels |
| Hemolysis | Test LDH and haptoglobin levels, reticulocyte count; infection is possible cause |
| Muscular disorders | Test CK and aldolase levels; screen for SLE |

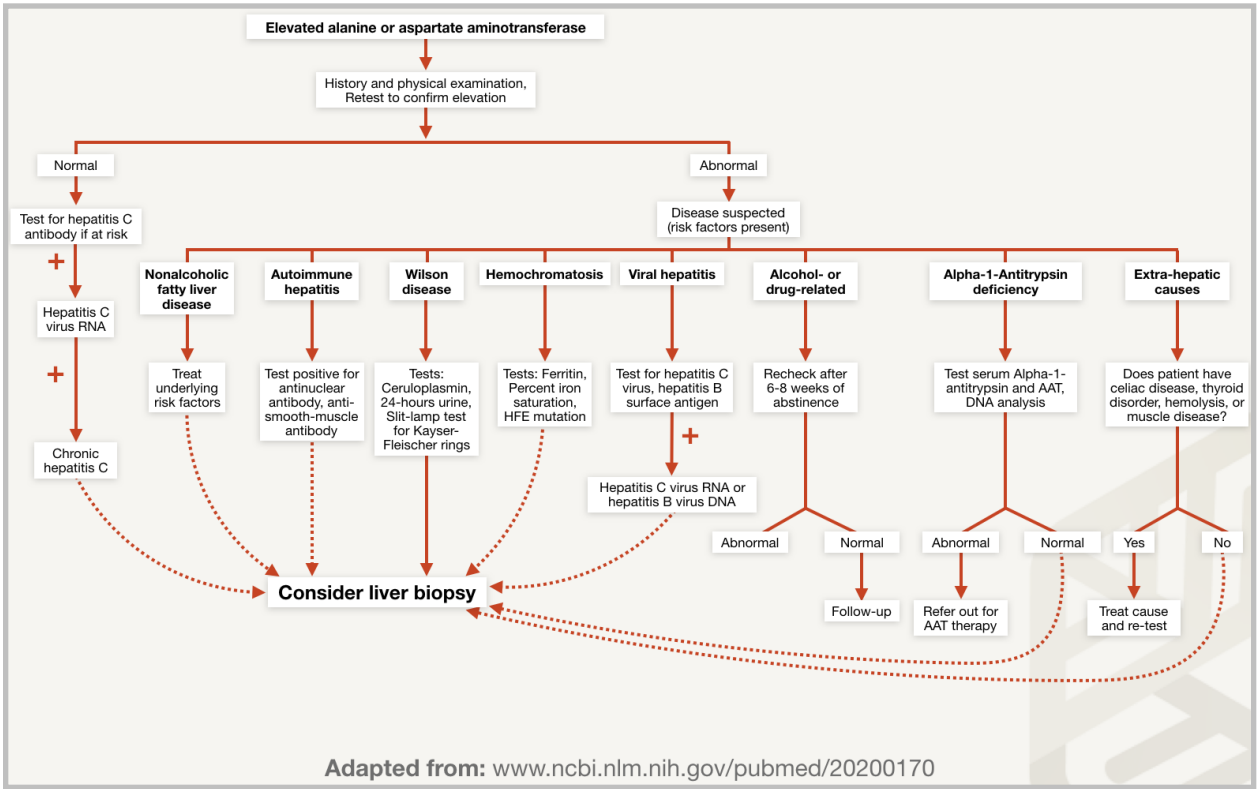
Finally, there are extrahepatic causes of elevated AST and ALT, so thyroid disorders are one, a lesser known cause, so if you see a patient with hypothyroidism, particularly Hashimoto's, and they have elevated AST and ALT and none of the other conditions we just talked about, then it's a likely cause. Celiac disease can lead to elevated AST and ALT. I've seen it also in patients with nonceliac gluten sensitivity who are still eating gluten. Hemolysis can lead to high ALT and AST. You can test LDH and haptoglobin levels and do a reticulocyte count, and infection is one possible cause of hemolysis that can lead to that. Muscular disorders—there you could test creatine kinase and aldolase levels and screen for things such as lupus.

Before we dive into cases, I want to present an algorithm for evaluating elevated aminotransferases. There are so many potential causes, so we really need a systematic approach here. One study suggested that 31 percent of patients with mildly elevated aminotransferases had either hepatitis B or hepatitis C or iron overload, and the elevation in the remaining patients was unexplained, but many had markers of metabolic dysfunction. That tells you right there that hepatitis B, hepatitis C, iron overload, and probably nonalcoholic fatty liver disease are the most common causes of elevated AST and ALT.

**After other causes were excluded, >90% of patients with mildly elevated aminotransferases had NAFLD.**

Along those lines, another study found that fatty liver was the cause of mildly elevated aminotransferases in over 90 percent of cases after other causes such as hepatitis B, hepatitis C, and iron overload were excluded. If you're able to exclude iron overload, hepatitis B, and hepatitis C, it's virtually certain that the patient has nonalcoholic fatty liver, especially if you can rule out Wilson disease with copper, ceruloplasmin, and urine copper testing.

With this in mind, the goal in working up patients is, of course, to exclude those other causes, and once you've done that, again, it is highly likely that fatty liver is the cause, especially if markers of metabolic dysfunction are present, and the patient has normal copper, ceruloplasmin, and urine copper levels. This can, of course, be confirmed with a liver ultrasound, which can show the infiltration of fat in the liver.




**Adapted from:** www.ncbi.nlm.nih.gov/pubmed/20200170

Here is the algorithm. It looks worse than it is. It's actually fairly simple. As in many other cases, the first step when you see high AST and ALT is to retest to confirm that the elevation is persistent. History is really important here as well because it can provide important clues on potential causes of elevation; for example, if they have a relative with hemochromatosis or Wilson disease, you'd obviously want to put that higher on the list. If they have traveled to an endemic area for hepatitis B, then you'd want to put that higher on the list. If they are consuming alcohol or have alcoholism in the family, you'd want to put that higher on the list. History, as always, is very important. If the enzymes are normal on retest, it's still probably good to screen for hepatitis C antibody if risk factors are present because ALT and AST levels can fluctuate in hepatitis and will occasionally be

normal. That takes you to the left branch here, if you're looking at this diagram. If they have antibodies for hepatitis C, of course, you'd continue to work that up.

If the liver enzymes are abnormal again on the retest, then you need to go into this right branch here where you want to start looking for all of these other potential causes. As we discussed on the last slide, the most important things to do first are to test for hepatitis and to test for iron overload, which you already do during the case review blood panel. If they don't have iron overload, and then you run follow-up testing for hepatitis and they are normal for that, then you'd want to make sure to look at their serum copper, probably test their ceruloplasmin level and 24-hour urine copper. If all of that is normal, then you're almost certainly looking at nonalcoholic fatty liver disease if they are not drinking. That's especially true if they have markers for metabolic dysfunction.

If all of the known causes of elevated AST and ALT are ruled out and they remain elevated, and this has definitely happened to me in several cases in practice, you can monitor the patient for three to up to six months as you address other underlying causes that are identified in the case review. In many situations, you'll see the aminotransferases come down as you address those causes, even if they aren't documented causes of high ALT and AST. Especially if the elevation is mild, it's safe to monitor for three to six months if you've ruled out Wilson's, hepatitis, and other more serious causes and just see if what you are doing with the patient can drop those levels down.

All right, now for some cases. This patient is a 25-year-old female with chief complaint of bloating, postnasal drip, PCOS, anxiety, and overweight.

| TESTS | RESULT | FLAG | UNITS | REFERENCE INTERVAL | LAB |
|---|---|---|---|---|---|
| **Thyroid Profile II** | | | | | |
| TSH | 2.030 | | uIU/mL | 0.450 - 4.500 | 01 |
| Thyroxine (T4) | 5.1 | | ug/dL | 4.5 - 12.0 | 01 |
| T3 Uptake | 27 | | % | 24 - 39 | 01 |
| Free Thyroxine Index | 1.4 | | | 1.2 - 4.9 | |
| Triiodothyronine (T3) | 71 | | ng/dL | 71 - 180 | 01 |
| **BUN** | 20 | | mg/dL | 6 - 20 | 01 |
| **Creatinine, Serum** | | | | | |
| Creatinine, Serum | 0.74 | | mg/dL | 0.57 - 1.00 | 01 |
| eGFR If NonAfricn Am | 113 | | mL/min/1.73 | >59 | |
| eGFR If Africn Am | 130 | | mL/min/1.73 | >59 | |
| **AST (SGOT)** | 24 | | IU/L | 0 - 40 | 01 |
| **ALT (SGPT)** | **58** | **High** | IU/L | 0 - 32 | 01 |
| **Triiodothyronine,Free,Serum** | 2.1 | | pg/mL | 2.0 - 4.4 | 01 |

Her case review blood panel showed lab-high levels of ALT, poor thyroid function, and a high BUN-to-creatinine ratio, so we retested. Her ALT level was 58, which is out of the lab range and well above the functional cutoff of 20. Her AST was 24, which is in the lab range but just barely above

the functional cutoff of 23. Her TSH was high-normal in the functional range, 2.0, but her total and free T3 were low in the functional range. Given her PCOS, insulin resistance, and weight issues, fatty liver is the most likely cause of her elevated aminotransferases here. She had no signs of hepatitis and did not have iron overload or Wilson disease.

If the patient is overweight and/or has insulin resistance, then you can address that with diet, lifestyle, and supplements and then retest the aminotransferases in a couple of months afterwards.

| Marker | Value | Functional Range | Lab Range |
|---|---|---|---|
| Glucose | 111 | 75 - 90 | 65 - 99 |
| Hemoglobin A1c | 6.3 | 4.4 – 5.4 | 4.8 - 5.6 |
| Uric Acid | 5.2 | 3.2 - 5.5 | 2.5 - 7.1 |
| BUN | 21 | 13 – 18 | 6 - 24 |
| Creatinine | 0.63 | 0.85 – 1.1 | 0.57 - 1 |
| BUN/Creatinine Ratio | 33 | 9 – 23 | 9 - 23 |
| Sodium | 143 | 135 – 140 | 134 - 144 |
| Potassium | 4.3 | 4.0 – 4.5 | 3.5 - 5.2 |
| Chloride | 103 | 100 – 106 | 97 - 108 |
| C02 | 25 | 25 – 30 | 18 - 29 |
| Calcium | 9.2 | 9.2 – 10.1 | 8.7 - 10.2 |
| Phosphorus | 3.4 | 3.5 – 4.0 | 2.5 - 4.5 |
| Magnesium | 2.0 | 2.0 – 2.6 | 1.6 - 2.6 |
| Protein, total | 7.0 | 6.9 – 7.4 | 6.0 - 8.5 |
| Albumin | 4.6 | 4.0 – 5.0 | 3.5 - 5.5 |
| Globulin | 2.4 | 2.4 – 2.8 | 1.5 - 4.5 |
| A/G ratio | 1.9 | 1.5 – 2.0 | 1.1 - 2.5 |
| Bilirubin, total | 0.3 | 0.1 – 1.2 | 0.0 - 1.2 |
| Alkaline Phosphatase | 106 | 42 – 107 | 39 - 117 |
| LDH | 133 | 140 - 180 | 119 - 214 |
| AST | 32 | 10 - 30 | 0 - 40 |
| ALT | 51 | 10 - 22 | 0 - 32 |
| GGT | 65 | < 15 | 0 - 60 |
| TIBC | 373 | 275 – 425 | 250 - 450 |
| UIBC | 292 | 175 - 350 | 150 - 375 |
| Iron | 81 | 40 – 135 | 40 - 155 |
| Iron saturation | 22 | 17 – 45 | 15 - 55 |
| Ferritin | 49 | 30 - 100 | 15 - 150 |
| Vitamin D, 25-hydroxy | 27.5 | 35 - 60 | 30.0 - 100.0 |
| Cholesterol, total | 177 | 150 - 250 | 100 - 199 |
| Triglycerides | 161 | 50 – 100 | 0 - 149 |
| HDL | 43 | 55 – 85 | > 39 |
| LDL | 102 | 0 - 175 | 0 - 99 |
| T. Chol / HDL Ratio | 4.1 | < 3 | 0 - 4.4 |
| Triglycerides / HDL Ratio | 3.74 | < 2 | < 3.8 |
| TSH | 1.120 | 0.5 – 2.5 | 0.45 - 4.50 |
| T4, total | 8.8 | 6.0 – 12 | 4.5 - 12.0 |
| T3 Uptake | 27 | 28 - 35 | 24 - 39 |
| T3, Total | 113 | 100 – 180 | 71 - 180 |
| WBC | 6.2 | 5.0 – 8.0 | 3.4 - 10.8 |
| RBC | 4.36 | 4.4 – 4.9 | 3.77 - 5.28 |
| Hemoglobin | 13.3 | 13.5 - 14.5 | 11.1 - 15.9 |

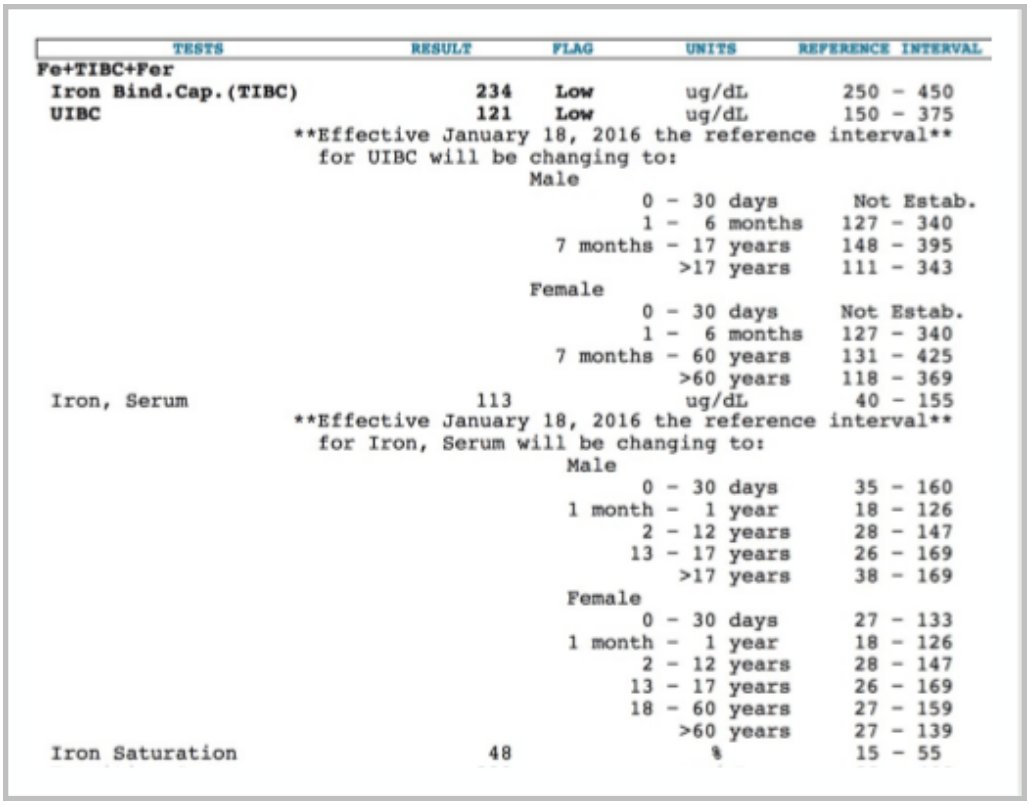
The next patient is a 59-year-old female with chief complaint of prediabetes, weight gain, joint pain, and GERD. Her ALT is out of the lab range at 51, and AST is out of the functional range at 32.

Alkaline phosphatase is normal, and LDH is low in the functional range, which can occur in reactive hypoglycemia, as you may recall from the blood sugar section. Triglycerides, glucose, A1c, and HDL are all indicative of prediabetes. This is another case where the cause of high AST and ALT is almost certainly fatty liver, so you could help them lose weight and improve their insulin sensitivity and retest.

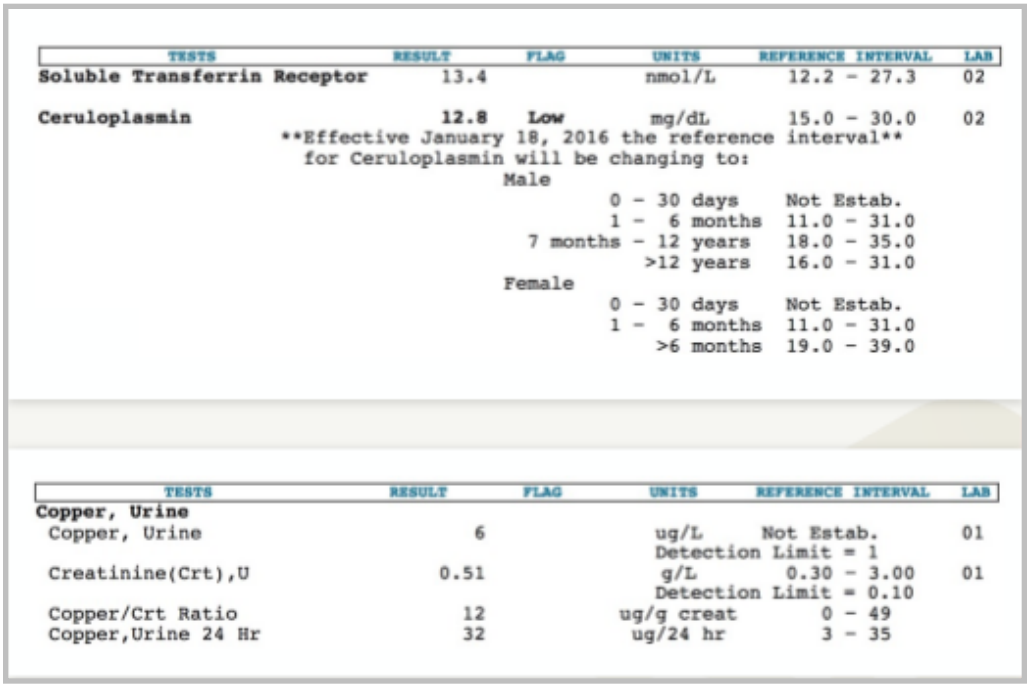
| Marker | Value | Functional Range | Lab Range |
|---|---|---|---|
| Glucose | 92 | 75 - 90 | 65 - 99 |
| Hemoglobin A1c | 5.5 | 4.4 – 5.4 | 4.8 - 5.6 |
| Uric Acid | 6.3 | 3.7 – 6.0 | 3.7 - 8.6 |
| BUN | 20 | 13 – 18 | 6 - 24 |
| Creatinine | 0.94 | 0.85 – 1.1 | 0.76 - 1.27 |
| BUN/Creatinine Ratio | 21 | 8 – 19 | 8 - 19 |
| Sodium | 142 | 135 – 140 | 134 - 144 |
| Potassium | 3.9 | 4.0 – 4.5 | 3.5 - 5.2 |
| Chloride | 101 | 100 – 106 | 97 - 108 |
| C02 | 25 | 25 – 30 | 18 - 29 |
| Calcium | 9.6 | 9.2 – 10.1 | 8.7 - 10.2 |
| Phosphorus | 3.2 | 3.5 – 4.0 | 2.5 - 4.5 |
| Magnesium | 2.3 | 2.0 – 2.6 | 1.6 - 2.3 |
| Protein, total | 6.7 | 6.9 – 7.4 | 6.0 - 8.5 |
| Albumin | 4.6 | 4.0 – 5.0 | 3.5 - 5.5 |
| Globulin | 2.1 | 2.4 – 2.8 | 1.5 - 4.5 |
| A/G ratio | 2.2 | 1.5 – 2.0 | 1.1 - 2.5 |
| Bilirubin, total | 1.1 | 0.1 – 1.2 | 0.0 - 1.2 |
| Alkaline Phosphatase | 48 | 42 – 107 | 39 - 117 |
| LDH | 150 | 140 - 180 | 121 - 224 |
| AST | 81 | 10 - 30 | 0 - 40 |
| ALT | 48 | 10 - 29 | 0 - 44 |
| GGT | 15 | < 15 | 0 - 65 |
| TIBC | 321 | 275 – 425 | 250 - 450 |
| UIBC | 161 | 175 - 350 | 150 - 375 |
| Iron | 160 | 40 – 135 | 40 - 155 |
| Iron saturation | 50 | 17 – 45 | 15 - 55 |
| Ferritin | 70 | 30 - 100 | 30 - 400 |
| Vitamin B-12 | 460 | 450 – 2000 | 211 - 946 |
| Vitamin D, 25-hydroxy | 76.1 | 35 - 60 | 30.0 - 100.0 |
| Cholesterol, total | 186 | 150 - 240 | 100 - 199 |
| Triglycerides | 46 | 50 – 100 | 0 - 149 |
| HDL | 99 | 55 – 85 | > 39 |
| LDL | 78 | 0 - 175 | 0 - 99 |
| T. Chol / HDL Ratio | 1.9 | < 3 | 0 - 5.0 |
| Triglycerides / HDL Ratio | 0.46 | < 2 | < 3.8 |
| CRP-hs | 0.96 | < 1.0 | 0.00 - 3.00 |
| Homocysteine | 11.5 | < 7.0 | 0.0 - 15.0 |

| Marker | Value | Functional Range | Lab Range |
|---|---|---|---|
| TSH | 1.650 | 0.5 – 2.5 | 0.45 - 4.50 |
| T4, total | 7.3 | 6.0 – 12 | 4.5 - 12 |
| T3 Uptake | 37 | 30 - 38 | 24 - 39 |
| T3, Total | 84 | 100 – 180 | 71 - 180 |
| Copper | 58 | | 72 - 166 |
| Zinc | 136 | | 56 - 134 |
| Zinc / Copper Ratio | 2.34 | > 0.85 | |
| Serum Methylmalonic Acid (MMA) | 70 | 0 - 325 | 0 - 378 |
| WBC | 4.3 | 5.0 – 8.0 | 3.4 - 10.8 |
| RBC | 5.04 | 4.4 – 4.9 | 4.14 - 5.8 |
| Hemoglobin | 15.5 | 14 - 15 | 12.6 - 17.7 |
| Hematocrit | 45.3 | 40 - 48 | 37.5 - 51.0 |
| MCV | 90 | 85 – 92 | 79 - 97 |
| MCH | 30.8 | 27.7 – 32.0 | 26.6 - 33.0 |
| MCHC | 34.2 | 32 – 35 | 31.5 - 35.7 |
| RDW | 13.7 | 11.5 – 15.0 | 12.3 - 15.4 |
| Platelets | 212 | 150 – 415 | 150 - 379 |
| Neutrophils | 44 | 40 – 60 | |
| Lymphocytes | 44 | 25 – 40 | |
| Monocytes | 8 | 4.0 – 7.0 | |
| Eosinophils | 3 | 0.0 – 3.0 | |
| Basophils | 1 | 0.0 – 3.0 | |

This is a 29-year-old male with GI issues, including bloating and constipation. He had depression and anxiety symptoms for most of his life. Both AST and ALT were out of range. AST is significantly higher than ALT but not more than the 2:1 ratio that you see in alcoholism. This patient did not consume any alcohol at all. Blood sugar is slightly elevated in the functional range, but follow-up testing indicated normal insulin sensitivity, and the patient was lean. Note that his copper was low, and zinc was high, and his iron markers are elevated. You may remember this patient from the iron overload unit.



| TESTS | RESULT | FLAG | UNITS | REFERENCE INTERVAL |
|---|---|---|---|---|
| **Fe+TIBC+Fer** | | | | |
| **Iron Bind.Cap.(TIBC)** | **234** | **Low** | ug/dL | 250 - 450 |
| **UIBC** | **121** | **Low** | ug/dL | 150 - 375 |
| **Effective January 18, 2016 the reference interval** for UIBC will be changing to: | | | | |
| Male | | | | |
| 0 - 30 days | | | | Not Estab. |
| 1 - 6 months | | | | 127 - 340 |
| 7 months - 17 years | | | | 148 - 395 |
| >17 years | | | | 111 - 343 |
| Female | | | | |
| 0 - 30 days | | | | Not Estab. |
| 1 - 6 months | | | | 127 - 340 |
| 7 months - 60 years | | | | 131 - 425 |
| >60 years | | | | 118 - 369 |
| Iron, Serum | 113 | | ug/dL | 40 - 155 |
| **Effective January 18, 2016 the reference interval** for Iron, Serum will be changing to: | | | | |
| Male | | | | |
| 0 - 30 days | | | | 35 - 160 |
| 1 month - 1 year | | | | 18 - 126 |
| 2 - 12 years | | | | 28 - 147 |
| 13 - 17 years | | | | 26 - 169 |
| >17 years | | | | 38 - 169 |
| Female | | | | |
| 0 - 30 days | | | | 27 - 133 |
| 1 month - 1 year | | | | 18 - 126 |
| 2 - 12 years | | | | 28 - 147 |
| 13 - 17 years | | | | 26 - 169 |
| 18 - 60 years | | | | 27 - 159 |
| >60 years | | | | 27 - 139 |
| Iron Saturation | 48 | | % | 15 - 55 |



| TESTS | RESULT | FLAG | UNITS | REFERENCE INTERVAL | LAB |
|---|---|---|---|---|---|
| **Soluble Transferrin Receptor** | 13.4 | | nmol/L | 12.2 - 27.3 | 02 |
| **Ceruloplasmin** | **12.8** | **Low** | mg/dL | 15.0 - 30.0 | 02 |
| **Effective January 18, 2016 the reference interval** for Ceruloplasmin will be changing to: | | | | | |
| Male | | | | | |
| 0 - 30 days | | | | Not Estab. | |
| 1 - 6 months | | | | 11.0 - 31.0 | |
| 7 months - 12 years | | | | 18.0 - 35.0 | |
| >12 years | | | | 16.0 - 31.0 | |
| Female | | | | | |
| 0 - 30 days | | | | Not Estab. | |
| 1 - 6 months | | | | 11.0 - 31.0 | |
| >6 months | | | | 19.0 - 39.0 | |

| TESTS | RESULT | FLAG | UNITS | REFERENCE INTERVAL | LAB |
|---|---|---|---|---|---|
| **Copper, Urine** | | | | | |
| Copper, Urine | 6 | | ug/L | Not Estab. | 01 |
| | | | Detection Limit = 1 | | |
| Creatinine(Crt),U | 0.51 | | g/L | 0.30 - 3.00 | 01 |
| | | | Detection Limit = 0.10 | | |
| Copper/Crt Ratio | 12 | | ug/g creat | 0 - 49 | |
| Copper,Urine 24 Hr | 32 | | ug/24 hr | 3 - 35 | |

Follow-up testing showed low ceruloplasmin and borderline-high 24-hour urine copper and also confirmed mild iron overload. If you recall, I referred this patient out, and he did have Wilson disease, so this was someone who we were able to catch. He didn't really have any significant symptoms or any organ damage from the copper deposition, so we were really fortunate to be able to catch it.