

Bilirubin, Total (serum)

Normal: 0.2-1.5 mg/dl
Optimum: 0.5-0.8 mg/dl

Abstract:

Total serum bilirubin is the sum total of indirect, unconjugated bilirubin from the breakdown of red blood cells and direct, conjugated bilirubin that is used in the synthesis of bile.

A slightly elevated level in adults indicates either oxidative stress within the red blood cells or some interruption in the conjugation of bilirubin. Telling the difference requires having access to the direct and indirect readings. If the elevation is credited to direct bilirubin then it is due to some interruption in bile flow, causing oxidative stress. However, if the elevation is credited mostly to indirect bilirubin then red blood cell fragility is at fault. The latter is preferred, as indirect bilirubin doubles as an important antioxidant for protecting LDL. Such a reading nevertheless signals oxidative stress within red blood cells, in which case it will be accompanied by a low normal G-6-PD reading.

A clearly elevated total bilirubin is most always indicative of liver disease.

A low total bilirubin reflects oxidative stress just as a high normal to slightly elevated level may reflect oxidative stress.

(In babies total bilirubin is naturally high for two reasons. The turnover of red blood cells is very fast, and there is some difficulty at birth of converting unconjugated bilirubin in the liver to conjugated bilirubin so that it can be made into bile. Since direct bilirubin can be a major source of oxidative stress, the difficulty at birth in making direct bilirubin is mostly protective.)

Background:

Each day the body makes about 250 to 400 mg bilirubin. About 3/4ths of this total is derived from the degradation of hemoglobin. Other hemoproteins include catalase, cytochrome P450, and myoglobin. None of these other sources, however, are known to contribute to total bilirubin in disease.

In the synthesis of bilirubin from the heme portion of hemoglobin, during hemoglobin breakdown, biliverdin is the first bile pigment to arise. The reducing agent NADH converts biliverdin to bilirubin via enzyme activity.

Total bilirubin is a breakdown product and reflects the amount of circulating bile pigment. A high total bilirubin then is either a reflection of liver disease, blockage in the gall bladder, interruption in bile synthesis, or the degree of RBC fragility. RBC fragility is often associated with G-6-PD deficiency, high oxidant content in the blood (Hg, Fe, Pb, for instance), or antibodies that attach to and prematurely destroy RBC's. If the increase in total bilirubin, then,

is due to RBC fragility, it will be associated with an enlarged spleen, as the spleen serves as a burial ground for RBC's.

Although knowledge has long been with us that indirect bilirubin serves as an antioxidant, to what extent this is true has only recently been known. A high normal level of total bilirubin, where 90% is credited to indirect bilirubin, has been shown to suppress oxidation to an even greater extent than vitamin E. (Science 235: 1043, 1987). Its action is enhanced when combined with albumin as an albumin/bilirubin complex. In this state it is particularly active as a chain breaker for peroxy radicals, and as a copper binding agent—binding far better than albumin would alone. (Hulea, S.A., Wasowicz, E., and Kummerow, F.A., "Inhibition of metal-catalyzed oxidation of low-density lipoprotein by free and albumin-bound bilirubin," Biochem et Biophysica Acta 1259: 29-38, 1995.)

To further test the oxidative protection offered by bilirubin, Dr. Paul Hopkins and colleagues at the Cardiovascular Genetics Research Clinic in Salt Lake City, UT, measured total bilirubin in 120 men and 41 women who had heart attacks or were being treated for CAD and compared the data with a control group of 155 men and women without CAD. The average blood level of bilirubin in the CAD group was 9 micromol/L compared to 12 micromol/L in the control group. Although the differences were small when the two groups were lumped together, there were marked differences among individuals. Men and women in the top fifth of bilirubin levels (who did not have a high direct reading) experienced an 80% reduction in CAD risk compared to individuals in the lowest fifth. (Arteriosclerosis, Thrombosis and Vascular Biology 16: 250-5, 1996.) Bilirubin, then, clearly exerts a protective effect on the arteries.

Based on this background information it is easier to see why a low to low normal total bilirubin might be seen in people who have an exceptionally high level of oxidative stress occurring aboard lipoproteins. The bilirubin reserve was used up trying to neutralize the oxidant catalysts. Paradoxically, a high normal bilirubin due to a rise in indirect bilirubin may on the one hand be a sign of oxidative stress within red blood cells while simultaneously providing antioxidant protection against oxidative stress in the arterial wall.

A clearly elevated total bilirubin (≥ 2.0) in adults is associated with

- Liver disease/liver failure
- Gall bladder disease
- Hepatitis

A moderately elevated total bilirubin (1.3-1.9) is associated with

- Fasting
- Carbohydrate restriction
- Extreme physical exertion
- Gilbert's Syndrome

Gilbert's Syndrome:

In some people the liver does not convert indirect (unconjugated) bilirubin to direct (conjugated) bilirubin as efficiently as it should. So on certain occasions, such as after drinking alcohol, during a fast, or while restricting carbohydrate intake, there is a temporary rise, or bilirubin bottleneck. This can lead to a yellowing, often notable in the eyes. In a day or so, things revert to normal without the doctor ever really knowing the cause for this short term accumulation, or bottleneck, of bilirubin.

One possible cause: A high intake of beta carotene, which is believed to interfere with bilirubin conjugation in some people.

A high normal to slightly increased total bilirubin is associated with:

- RBC fragility
- G-6-PD deficiency
- Oxidative protection of the LDL particle

A low to low normal total bilirubin is associated with

- Oxidative stress
- Increased risk to coronary artery disease.