

**The Misery of Low Lipids:
Choline Deficiency in Clinical Practice**

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ABSTRACT

This paper presents a literature investigation into the causative factors behind choline deficiency, highlighting the biochemical pathways involved with phospholipid production, choline synthesis, and choline absorption. An analysis is provided as to the roles which single nucleotide polymorphisms and estrogen hormone levels play in choline metabolism. Important clinical sequelae of choline deficiency and low lipids in general are also addressed.

Key Terms: Choline Deficiency, Single Nucleotide Polymorphisms, Fatty Liver, Cell Membrane, Low Cholesterol, Low Triglycerides, Depression, Infertility

Introduction

Choline is an important and fascinating nutrient that is critical for physical, chemical and mental health. It is a B vitamin-like compound necessary for membrane stability, myelin formation, bile acid production, neurotransmission, and more. Without choline the body would be unable to absorb and process fats, myelin sheaths would degenerate, and neurologic signals would be interrupted with serious, life-threatening consequences. It has often been said that our health depends first and foremost on the health of our cell walls. And if that is true then choline must be considered among the most important nutrients in the body since phosphatidylcholine, a choline-rich phospholipid molecule, is the most common building block of all the cell walls and membranes in our body.¹ Healthy cell walls are critical as they allow the body to keep what is supposed to be inside the cell separated from what needs to be kept outside the cell. And choline's unique properties make it essential for membrane function. Choline is such an important nutrient that the body has the ability to produce it *de novo* via the methylation-dependent enzyme PEMT. However, this important enzyme is susceptible to single nucleotide polymorphic variations (SNPs) which slow it down. The *de novo* synthesis of choline is also estrogen-dependent, since the PEMT enzyme cannot function without adequate levels of estrogen. Thus both genetics and sex hormones influence the production of this fascinating molecule.

After all, the human body is just a series of fatty walls or membranes separating bodies of water. From our skin, to our organs, and right down to the cell itself, each system within the body depends on the membrane for function and survival. Yet despite choline's importance in maintaining membrane homeostasis, choline deficiency is a major as-yet-unrecognized health problem. The reasons for choline deficiency are varied – low lipids, methylation imbalances, hormone deficiencies, genetic SNPs, poor gut health, and improper food selection. This paper will address the main causes of choline deficiency and the health implications of choline deficiency. As you will see, the choline connection is anything but a boring ride!

Low Lipids as a Common Cause of Choline Deficiency

Choline is an amazing molecule and one that is very important for optimum health. Choline is both absorbed from the diet and produced inside the body through the methylation process. Even though the body can make choline or absorb it from the diet, there are many common health challenges that can cause choline deficiencies. And first among those challenges are phospholipid deficiencies. Because once the body has absorbed or created a molecule of choline, it must attach it to a molecule of phosphatidylethanolamine (PE) in order to form phosphatidylcholine (PC). There must be an ample supply of TG in order for the body to

make phospholipids, including PE. To better understand this “supply chain” relationship between dietary inputs and PC levels, please refer to the illustrations in Figures 1.1 and 1.2.

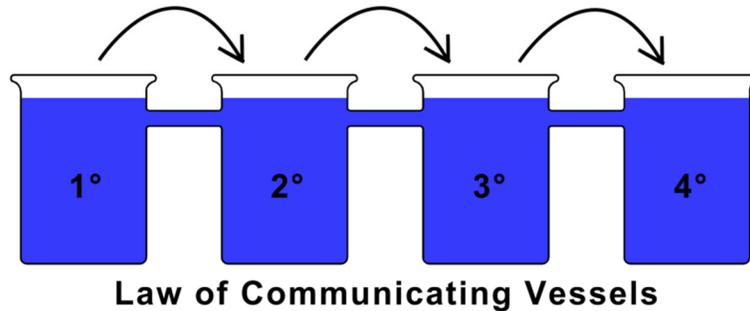


Figure 1.1 – The Law of Communicating Vessels – discovered by Blaise Pascal in the 17th Century, describes how liquid poured into communicating vessels will raise to the same height in each. This is a perfect metaphor for biochemical pathways. The primary vessel must be full or “saturated” with substrate before any products show up in the secondary vessel. Again, the secondary vessel must be saturated before the third vessel, third before the fourth, and so on.

When a person has low TGs they are going to produce fewer phospholipids, fewer molecules of PE, and fewer molecules of PC. This is due to the fact that TGs act as the fatty backbone of every phospholipid molecule in the body, including PC.² Without adequate TG being produced, every single cell in the body will be forced to slow down building and repairing the cell wall. If the cell wall isn’t repaired quickly enough, damage from inflammation may cause the cell to malfunction or even be destroyed. Thus this loss of TG production will cause a choline deficiency and will negatively impact multiple systems inside the body.

Every single cell requires large amounts of phospholipids, especially phosphatidylcholine, to build healthy cell walls and function normally. In fact, PC is the most important building-block of the cell wall, and more than 90% of the body’s choline is stored as phosphatidylcholine in the membranes of cells with only a small amount circulating as free choline.³ The body places a premium on choline because it acts both as a structural component and as a cofactor in important methylation reactions. The body stores choline inside the cell wall like a long-term methyl donor savings account. The body tries to manage without dipping into this savings, but under certain conditions, the body will be forced to make a withdrawal. Under conditions where folate is unavailable, choline is removed from the cell membranes, converted into betaine, and used to recycle homocysteine via the BHMT enzyme.³ This relationship illustrates how a primary folate deficiency will lead to a secondary choline deficiency, with broad

consequence on neurological health and membrane stability. And without adequate TGs the body cannot store what choline is available in the cell wall, further compromising methylation resources and cell wall integrity. Simply producing choline inside the body will not guarantee phosphatidylcholine will be produced – that ultimately depends on whether TGs are available to produce PE. In this way the body's supplies of lipids, especially TGs, act as rate-limiting factors in the production and storage of choline. This point is illustrated more clearly in Figure 1.2 shown below.

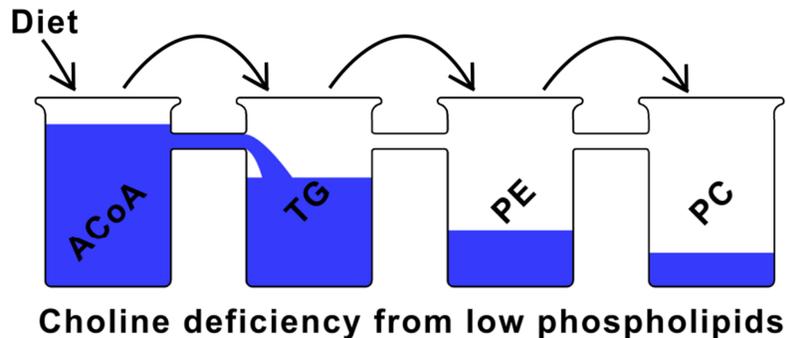


Figure 1.2 – Proposed mechanism showing choline deficiency arising from low lipids. Without adequate triglycerides and phospholipid levels there is not enough phosphatidylethanolamine available for phosphatidylcholine production. The law of communicating vessel highlights the impact that low lipids will have on global body choline stores. ACoA – Acetyl-CoA; TG – Triglycerides; PE – phosphatidylethanolamine; PC – phosphatidylecholine.

Besides TGs, cholesterol levels may also be depressed in persons with a choline deficiency. This is due to the fact that cholesterol and TG share a common biochemical starting point at the molecule Acetyl-CoA. Acetyl-CoA is found in every cell, is produced in the mitochondria and plays a major role in energy and growth.⁴ Acetyl-CoA builds up in the cell when the cell burns sugar, protein or fat for energy. Low Acetyl-CoA levels mean a person is not eating or absorbing enough food from the GI tract and not enough energy is being burned in the cells. In other words they are suffering from hypoglycemia, and likely feel tired, weak, and lightheaded if meals are missed, etc. If there is not enough Acetyl-CoA to produce TG, there will not be enough to manufacture cholesterol either. Again, TG and cholesterol share the same biochemical starting point; low cholesterol and low TG often occur together. Meal skipping, poor digestion and improper food selection are the main causes of low lipids. Taking nutritional supplements with choline without fixing the dietary habits will create frustration and lackluster results. To raise cholesterol and TGs patients will need to eat more frequently than 3 meals per day. One meal every 3 hours is more helpful and is required to boost the blood levels of glucose to the point where the glycolysis pathway becomes saturated. Only by saturating the

glycolysis pathway will levels of Acetyl-CoA rise high enough to start replenishing both TG and cholesterol levels. The solution to low cholesterol and TGs resides in frequent eating, eating fatty and cholesterol-rich foods, and by avoiding excess HPA-axis activation.

The overall strategy to increase lipids back to normal range is to saturate the pathways involved with the production of cholesterol and triglycerides. Due to the law of communicating vessels (Figures 1.1 and 1.2) the upstream biochemical pathways, or pools, must be adequately saturated before any final products will show up downstream. If someone is starting from a deficient standpoint, they are going to need to absorb a lot more nutrients than most clinicians think is necessary in order to start seeing results. This is due to the fact that human biochemistry is not a $1+1 = 2$ system. In fact, there are multiple steps and mechanisms at play with even the most basic processes inside the body. Even cholesterol production requires dozens of chemical reactions to produce a single molecule of cholesterol.⁵ Only by making sure all these precursor pathways are working at their maximum speed will the body be able to cause levels to rise back to normal.

Summary of Low Lipids and Choline Deficiency:

- Anyone with low cholesterol, TG, and/or VLDL is at risk of choline deficiency
- Statins and cholesterol-lowering drugs may cause a choline deficiency
- Low TG is any blood test reading below 75 mg/dL
- Low cholesterol is any blood test reading below 150 mg/dL
- VLDL levels below 15 mg/dL suggest phospholipid deficiency
- Phosphatidylcholine cannot be produced without adequate phospholipids and TGs
- TG levels come from our diet, and are produced in the liver during post-prandial caloric excess
- Cholesterol and TG synthesis both begin with the mitochondrial molecule Acetyl-CoA
- Low cholesterol is dangerous and increases risk of the following:
 - Male Infertility⁶
 - Female Infertility⁷
 - Depression⁸
 - Suicide⁹
 - Aggressive behavior (many violent criminals are shown to have low cholesterol)¹⁰
 - Poor Memory¹¹
 - Autism and Asperger's Disorder¹²
 - Alzheimer's Disease¹³

Keep in mind that the majority of people with a cholesterol problem in developed countries have high cholesterol, which indicates their cellular pathways are already over-saturated from excess fructose and other refined carbohydrates. And the problem of excess cholesterol gets plenty of attention from doctors, drug companies and media campaigns. Yet there are many who are suffering from low cholesterol and are getting poor treatment. This is due to ignorance on the part of doctors and clinicians and a misunderstanding of basic human biochemistry. Since choline is critical for neurological health, digestion, methylation, and more, anything that puts choline levels at risk also puts our health at risk. Low cholesterol and low TGs may not be an issue if it weren't for the detrimental effect it has on choline levels and cell wall function.

Estrogen and Choline Deficiency

Given the connection between low lipids and choline deficiency, it would be tempting to think that as long as someone has enough cholesterol and TG that they will be protected from choline deficiency. Unfortunately this is not the case. Having adequate lipids does indeed help support healthy choline levels, but it does not guarantee a person will avoid choline deficiency. The truth is that choline deficiency can come from more than one source. Both sex hormone levels and genetic SNPs may lead to a choline deficiency by influencing the PEMT enzyme – the enzyme responsible for synthesis of choline inside the body. Recent research now confirms how hormones and genetic polymorphisms play a major role in choline deficiency.

The body can make choline only one way; that is by methylating a molecule of phosphatidylethanolamine (PE) into a molecule of phosphatidylcholine (PC). The body's only method for accomplishing this is via the enzyme PEMT (phosphatidylethanolamine N-methyltransferase) which is found in the liver, brain, muscle, fat and other tissues.^{14,15} As with other well-known methylation enzymes like MTHFR and COMT, the PEMT enzyme can have genetic SNPs that slow it down. When this enzyme slows down the body cannot make choline in high amounts and choline deficiency is more likely. But there is more to the story of PEMT than just polymorphisms. In addition to being slowed by SNPs, PEMT is also dependent upon the hormone estrogen for activation.^{14,16} What this means is that the PEMT enzyme, the body's only method of synthesizing choline, has not one but two Achilles heels.

As mentioned above, the sex hormone estrogen is intimately linked with the production of choline. Women have a biological advantage here as the premenopausal female body has much higher levels of estrogen than does the male body. When a woman becomes pregnant this advantage is taken to an extreme, as pregnancy increases estrogen levels over 30 times normal.¹⁷ A successful pregnancy requires high amounts of nutrients delivered to the growing

baby, esp. choline. Since the mother's body is building a human being from scratch, there is an added burden on her biology to provide enough nutrition to her growing baby. Viewed from this perspective, the high estrogen levels during pregnancy can be seen to act like a biochemical insurance policy. Since the PEMT enzyme requires estrogen to function, pregnancy allows a woman to make extra choline for her developing child. Furthermore, the nervous system is the first system to form in utero and is a tissue that requires high levels of choline for proper development.^{18, 3} Choline plays such an important role in cell membranes, myelin sheaths, and nervous system tissue that the high estrogen levels during pregnancy help make sure the growing brain and nervous system is nourished. It is a genius system that assures the health and survival of the child.

Even though Nature has conferred an advantage to females by providing them with higher estrogen levels, esp. during pregnancy, this alone cannot protect against a lack of choline in the diet. All the estrogen in the world will not save a woman from choline deficiency if the gene responsible for producing choline is slowed down by a polymorphism. Genetic research has shown that the gene responsible for synthesizing choline, the PEMT gene, is susceptible to common polymorphisms which alter its function by slowing it down. In a recent study looking at a population in North Carolina, men and women of various ages were placed on a choline-deficient diet. They were followed closely for up to 42 days on a low choline diet consisting of less than 50mg choline per day. Throughout the study, the participants' liver function was continuously assessed for any sign of fatty liver and damage. After eating a choline deficient diet for just six weeks, 63% of participants developed liver dysfunction and choline blood levels dropped 30% in every single participant, including premenopausal females.¹⁹ During this six week trial of low dietary choline the odds of developing liver dysfunction were 77% for men, 80% for postmenopausal women and just 44% for premenopausal women.¹⁹ Based on what has been discussed so far about estrogen and choline, it makes sense that men and postmenopausal women would be more susceptible to developing fatty liver since they don't have high estrogen levels. And based on the fact that estrogen levels drive choline production, premenopausal women should have been protected from fatty liver since they make higher amounts of choline - but that was not the case.

With dietary choline restricted to just 50 mg/day, approximately half of the premenopausal group also suffered liver dysfunction, suggesting that a choline deficient diet can even harm women with higher estrogen levels. In addition, blood tests revealed that premenopausal female experienced a 30% loss of choline on a low choline diet right along with everyone else. Despite the fact that higher estrogen levels allow fertile women to make more choline, many were not able to make enough to avoid problems. A PEMT gene polymorphism is the only mechanism that can explain how women with high estrogen levels are still susceptible to choline deficiency when placed on a low choline diet.

Just like many individuals in the population, some of the premenopausal women inherited one or two copies of the PEMT gene which slows down the production of choline. This study showed that fatty liver occurred in 80% of the premenopausal women with two copies of PEMT and in 43% with only one copy of PEMT.²⁰ What this means is that a premenopausal woman with two copies of the slowed PEMT gene has exactly the same risk of fatty liver as a postmenopausal woman. It is as if inheriting two copies of the PEMT gene effectively shuts off all estrogen-related choline production in the body. If a woman only has a single copy of the slowed PEMT gene, she will still have a roughly 50% chance of liver dysfunction on a low choline diet. Thus a single copy of the gene is only slightly better than two copies, as at least some estrogen-related choline production is preserved.

If having a PEMT gene can put one at risk for choline-related diseases like fatty liver, then it is important to know how common these genes are in population. We know that 74% of all women in the study had a SNP in the PEMT that made their PEMT enzyme unresponsive to estrogen.²¹ This means that only 26% of women can make enough choline on a low choline diet; and that ability depends on whether the woman is still fertile or has entered menopause. In this way genetics can take away the biological advantage that high estrogen levels usually offer to premenopausal females. Women with these PEMT genes will be at risk for choline deficiency and liver damage just like all men and post-menopausal women – two groups who don't have enough estrogen to make choline regardless of their genes. Due to all the interference from the PEMT gene, dietary choline levels must be optimized for the vast majority of our population.

Summary of PEMT and Choline Deficiency:

- In humans, choline is only made by the PEMT enzyme
- Estrogen is required for the PEMT enzyme to activate and function normally
- Men and postmenopausal women have an elevated risk of choline deficiency due to low estrogen levels.
- The PEMT enzyme is commonly slowed down by polymorphisms, making it unresponsive to estrogen levels
 - 74% of women have at least one copy of a slowed PEMT
 - Homozygous carriers of PEMT have much higher risk of choline deficiency
- Men, postmenopausal women, and premenopausal women with PEMT SNPs need to increase choline intake in the diet to offset elevated risk of liver dysfunction

The take away here is that studies have recently shown that because of common genetic polymorphisms, choline deficiency is a widespread problem. Normally the hormone estrogen allows the body to make choline from scratch. However, genetic variation in the PEMT enzyme, estrogen levels and gender differences prevent most people from making adequate choline. Realistically then the only group in our population who is protected from choline deficiency are premenopausal females without a single copy of the slowed PEMT gene. Every single male, every single postmenopausal woman, and 74% of premenopausal woman all require daily intake of approx. 500 mg of choline to prevent fatty liver, organ damage, and the associated health problems.¹⁹ If the body is already depleted, then levels that simply prevent deficiency won't be enough to replete the body. In these cases, higher daily doses of at least 1 gram or more are needed to replenish the tissues. Choline it seems must be absorbed from the diet in just about everyone except for the few young women who have a normal PEMT gene and can synthesize choline regardless of dietary intake.

Gut Dysbiosis and Choline Deficiency

In addition to the problems discussed above, there are yet other issues that may arise to cause a choline deficiency. So far we have touched on how low TG and cholesterol, low sex hormones, and genetic polymorphisms may cause a choline deficiency. But a digestive system issue can be the source of a choline deficiency all by itself. Even if someone has healthy lipid levels, excellent estrogen levels, and a normally functioning PEMT enzyme, they may still develop a choline deficiency due to gut-based problems. In other words, without a healthy gut all bets are off!

The body depends on healthy bacteria in the gut in order to absorb important vitamins and nutrients from the diet. To illustrate this point, we shall heed the words of Dr. Robert Rakowski, DC, a brilliant clinician, chiropractor and natural medicine doctor. He states that "good bugs eat toxins and poop vitamins; bad bugs eat vitamins and poop toxins." While that may seem like an oversimplification, it is absolutely true. In essence the gut is all about balance. When the gut is healthy, yeasts and other harmful organisms are held in check by the healthy bacteria. When the gut is healthy the bacteria in our colon assist us by providing nutrients needed for health. However, when the gut is stressed with antibiotics, surgeries, heavy metals, chronic illnesses, food sensitivities, etc. the good bacteria die off in large numbers. This allows the opportunistic yeasts and harmful bacteria to grow wild. These become the "parasitic" micro-organisms that can disrupt choline levels and cause a deficiency.

The main issue with choline deficiency and the gut has to do with the digestive process itself. It is not often appreciated that when we just swallow something it does not guarantee it will be

absorbed into the body. Actually absorbing what we eat is a complex process and is often compromised in the general population. Remember from earlier discussions that choline is the most important nutrient for building a healthy cell wall. Due to the fact that bacteria also have cell walls, parasitic bacteria may steal choline from our diet and use it for their own cell walls before it becomes available for the body. If this happens once and while, the consequences would be small. But due to the fact that many people have poor gut bacteria, this process of pathogenic bacteria stealing nutrition from the host is a major threat to human health. Or stated another way, poor gut health can rob you of choline and ultimately kill you. Figure 1.3 illustrates the pathways involved in choline-robbing bacteria, toxin production, and cardiovascular disease.

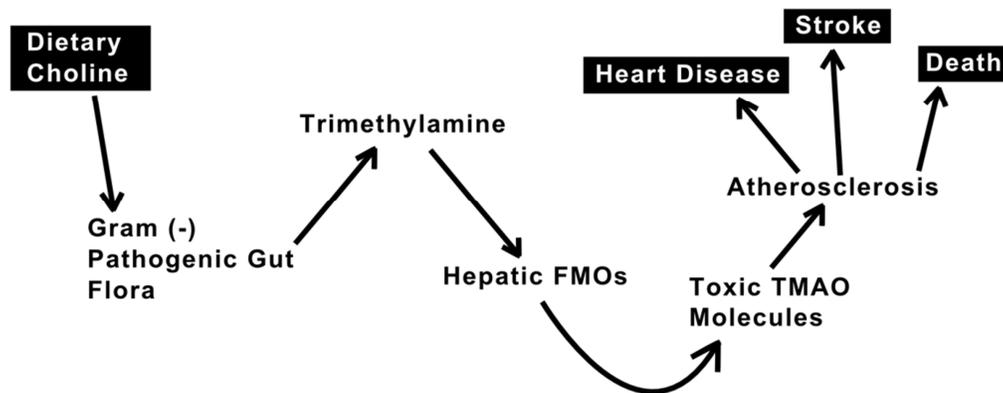


Figure 1.3 – Pathways showing conversion of dietary choline into trimethylamine by pathogenic gut bacteria. Hepatic enzymes convert trimethylamine into TMAO which is a known cause of atherosclerosis and the increased mortality and morbidity associated with cardiovascular disease. TMAO – trimethylamine-N-oxide; FMO - hepatic flavin monooxygenases.

To lend support to the idea that gut health influences choline levels, we turn to research. Recent studies prove that the microbes in our gut can cause obesity, inflammatory bowel disease, and other chronic health problems.^{22,23} The microbes that live in the gut also have a huge impact on our choline levels. For example many gram-negative gut bacteria that live in our colon consume choline from our diet and break it down into a toxin called trimethylamine (TMA).²⁴ They steal the choline we eat and pump out TMA which is absorbed by the liver where it gets converted into trimethylamine n-oxide (TMAO), another toxic molecule. TMAO then circulates in the bloodstream where it is a known contributor to atherosclerosis, heart disease and stroke.²⁵ In this way, pathogenic gut bacteria can act as a parasite, stealing nutrition while simultaneously poisoning the host. This disturbing fact is yet more evidence that the key to health resides in the digestive tract.

Obviously if these bacteria are eating our nutrients before we are, it is going to affect how much nutrition we get from our diet. But that isn't all these bad bugs can do to harm us. When these same pathogenic bacteria enter the bloodstream through a leaky gut, other problems arise. Almost immediately, these bacteria are destroyed by the immune system but the fragments of the once-living bacteria are numerous. So numerous in fact that the "dead body" fragments of the bacteria which the immune system killed are a problem unto themselves. These dead bacteria pieces are called Lipopolysaccharides (LPS) and they are also related to inflammation and disease. The LPS toxins from these bacteria can lead to insulin resistance, diabetes, and even life-threatening illnesses like sepsis.^{24,26,27} And all this from eating a piece of steak or a lobster tail! In essence, the bad bugs get us twice. First they steal our nutrients before we get a chance to use them. This can lead to choline deficiency since there is less choline for us to digest. Secondly they hurt us by irritating our immune system and creating systemic inflammation, esp. in the brain. This can cause a loss of choline since inflammation increases homocysteine levels and choline is the most important methyl donor next to folate.

But don't give up your healthy animal-based diet just yet, for we can change our gut bacteria and prevent this problem altogether. In other words, the "who" or "what" that lives in our gut is a major player in our health and we have a great deal of control over that. If we have bad bacteria in our gut from poor diet, stress, anti-biotic therapy or any number of other common problems, we then become susceptible to disease even if we are taking the right vitamins. Without healthy gut bacteria, eating vitamins may actually trigger inflammation and cause metabolic disease.²⁸ This may explain why in some studies, eating choline-rich foods was associated with an increase in health problems. If the gut isn't taken care of and supported first, piling on supplements may not create the benefit that was intended – it may actually do harm. To prevent this we look to modulating the gut flora with probiotic administration. Probiotics not only help the gut, but they help prevent cardiovascular disease and diabetes by changing how we absorb our nutrition. We now know that probiotics prevent bad bacteria from stealing our choline and converting it into the disease-causing toxin TMAO.^{29, 30} Probiotics not only make the gut function better, they prevent dangerous, systemic, inflammatory responses to nutrient-dense, animal-based food like choline. It is a fact that eating high choline diets can increase levels of TMAO and cause cardiovascular disease. But don't blame choline for a problem that resides in the gut.

Choline Deficiency and Fatty Liver

It is not surprising that rates of fatty liver are rising when we consider the extremely high prevalence of processed sugar, low-nutrient diets in our society. While this type of food is designed to be both addictive and profitable, it has left us with high rates of preventable

disease. In fact, studies are now suggesting that at least 30% of the US population is currently suffering from fatty liver disease.²⁸ This grave statistic hints at the widespread glycemic excess and choline deficiency in our modern diets. Our ancestors ate fresher, less processed, and more nutritious food that provided their bodies with higher levels of choline and other nutrients. Modern carbohydrate-based diets are devoid of nutrients but high in calories, which puts phenomenal pressure on the liver. Post-prandial excess from high glycemic loads will force the liver to convert glucose molecules into free fatty acids and then TGs. As TG levels increase inside the liver and muscle cell, there is a simultaneous loss of PC levels in those cells which leads to destruction of liver and muscle tissue.¹⁹ If the liver cannot export TGs into circulation, it will be forced to hold on to the TG and store them inside the liver. When this process goes on too long, fatty liver disease develops.

Any dietary, lifestyle, or genetic challenge that causes choline deficiency will put the body at elevated risk of fatty liver disease. It is widely known that choline deficiency leads to fatty liver disease both in rodents and in humans.^{31,32} This is due to the fact that phosphatidylcholine is required in order for the liver to form VLDL molecules and send fat and TGs into the circulation.³³ The liver can make TGs indefinitely but since TGs are hydrophobic (will not mix into water), they cannot enter the bloodstream without the phosphatidylcholine and other phospholipids necessary to form VLDL molecules.² These phospholipids allow TG to be soluble in water much like detergent helps oils dissolve into water, through the process of mycelization. Without choline, the liver simply cannot remove the TGs and they begin to accumulate inside the liver, starting the process of fatty liver disease.

Even though fatty liver is a major health problem and can damage the body, the body is still acting intelligently. This phenomenon of fatty liver is a perfect example of how the body always acts to protect the bloodstream at the expense of other tissues like the liver. First, the body has an incentive to convert glucose to TG to prevent tissue damage from hyperglycemia. Converting excess blood sugar into fat protects the rest of the body from excess inflammation and supplies long term energy storage for survival. Secondly, studies have now shown that TG accumulation in the liver may actually be protective since free fatty acids are more damaging to cells than TGs.³⁴ And third, if the liver were to allow TGs to enter the bloodstream unbound to a VLDL molecule it would be very dangerous as they would clump together, form clots, and cause stroke or embolisms! Remember that the blood stream is a watery connective tissue, and fats that don't dissolve in water would be life threatening if they entered the bloodstream. Oil and water do not mix, nor do triglycerides and blood. The body is smart enough to store fat in the liver rather than allow an embolism or stroke to occur. And for that we should all be thankful.

Summary

Choline is a fundamental part of every individual cell and therefore plays a key role in supporting the triad of health. Since low phospholipids, low hormones, genetic polymorphisms, and imbalanced gut flora all conspire to cause choline deficiency, it should be clear that choline deficiency is a widespread problem getting too little attention. And given the relationship of methylation problems and chronic disease, choline should be viewed as a first-line approach for supporting healthy methylation. Based on the best evidence available, choline deficiency is a common condition and millions of patients are likely affected. Therefore supporting choline levels through the biochemical pathways discussed above should be incorporated more into clinical practice.

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