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I NUTRITION

Table of Contents

I NUTRITION

- A. Zinc and the immune system 1
- B. Study examines link between low levels of zinc and survival 2
- C. Can vitamin E help people recover from hepatitis B? 3
- D. Extra co-enzyme Q₁₀ for statin-users? 4

II SIDE EFFECTS

- A. Background on glucose — from food to blood sugar 7
- B. Indinavir — effect on sugar and insulin 7
- C. Protease inhibitors and blood sugar problems 8

A. Zinc and the immune system

Background

Nutrients such as copper and zinc are needed by the body in small amounts. Zinc is particularly beneficial for the immune system, where it has the following uses:

- maintaining the health of lymph nodes
- helping T-cells, such as CD4+ and CD8+ cells, fight infections and tumours

Zinc also plays an important role in one of the immune system's major organs — the thymus gland.

The thymus gland

Located in the upper chest, the thymus gland contains T-cells and macrophages. In addition to helping T-cells mature, the thymus gland also makes hormones (called thymic hormones). Although researchers have found several thymic hormones, they don't know the precise function of all of them. Below is a list of some thymic hormones:

- thymosin
- thymosin fraction 5
- thymopoietin
- thymulin
- thymopentin
- thymic humoral factor
- thymosin alpha1

Certainly, some thymic hormones can enhance the functioning of T-cells. Some researchers have used thymic hormones to improve the immune response in subjects with HIV, cancer and hepatitis B and C. Reports on some of these products appear in *TreatmentUpdate* 61, 52, 39 and 17.

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Back to zinc

Since the mid-1980s, researchers have found that HIV positive people are likely to have less-than-normal levels of zinc in their blood. In people with AIDS, the deficiency of zinc is often more severe. Not surprisingly, some researchers thought that supplements of zinc for people with HIV/AIDS (PHAs) would help strengthen their immune systems.

In the time before highly active antiretroviral therapy (HAART), results from one clinical trial suggested that supplements of zinc decreased the risk of life-threatening infections and helped to increase weight and CD4+ cell counts in PHAs — see *TreatmentUpdate 66* for details. All of this information suggests that zinc is very important for the health of PHAs.

Nutrient deficits

The body can experience a shortage of zinc and other nutrients because of the following complications:

- problems absorbing nutrients because of intestinal damage from HIV
- poor eating habits
- diarrhea
- lack of appetite due to infections and/or drug side effects
- nausea and/or vomiting

Zinc and copper absorption

Under normal conditions, the level of zinc in the blood is greater than that of copper. But in cases of cancer and infections, including HIV, levels of copper rise as zinc is moved from the blood to the tissues, where it is needed. In the short term, this change helps the body adapt to fighting tumours and/or infections. Therefore, in the case of long-term (chronic) infections such as HIV, the body's need for zinc increases.

University of Miami researchers Marianna Baum and Gail Shor-Posner have been studying the impact of zinc and other nutrients on the immune systems of PHAs for over a decade. In the following article, we report on results from one of their recently published studies on the effect of zinc on survival in PHAs.

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B. Study examines link between low levels of zinc and survival

Study details

Researchers at the University of Miami recruited 121 HIV positive male subjects in the late 1980s and early 1990s as part of a study on malnutrition and HIV infection. They recently analysed the data, looking at the impact of levels of zinc and copper on survival, and published their results, which we report on in this story.

None of the subjects were injection-drug users. On average, subjects were monitored for about three years. At the start of the study, the profile of subjects was as follows:

- average age – 33 years
- 85% were free from symptoms of HIV infection
- 90% had 200 or more CD4+ cells
- no subject was using anti-HIV therapy

Results — survival and CD4+ cell counts

At the end of the study, researchers analysed their data and divided the subjects into two groups:

- survivors – 84%
- non-survivors – 16%

Note: The 16% (19 subjects) who did not survive died from complications due to HIV infection.

The researchers found that over the course of the study subjects who died were five times more likely than the survivors to have received AZT. Perhaps this was related to the fact that 42% of subjects who died had fewer than 200 CD4+ cells. Having low CD4+ counts would have been an indication for doctors to prescribe AZT. Only 4% of survivors had fewer than 200 CD4+ cells.

Survival – zinc and copper

The researchers found that subjects who had less-than-normal levels of zinc were five times more likely to die than subjects who had normal levels of zinc. As well, those subjects who had more copper in their blood than zinc were eight times more likely to die than subjects with a more balanced level of copper.

In tracking the levels of zinc in the blood of subjects over the course of the study, the researchers concluded that zinc deficiency is more likely to occur in PHAs whose immune systems degrade faster than in other PHAs. Perhaps this accelerated zinc deficiency may be due to malabsorption caused by AIDS-related infections. Reduced zinc levels could in turn lead to further decline of the immune system.

The research team suggests that monitoring levels of zinc and copper in the blood might be a useful part of the health management of PHAs. Because many PHAs in North America use HAART, another study examining the changes in zinc and copper levels in HAART-users may be useful.

Note on supplementation

The body needs both zinc and copper but there is a balance between the two minerals that affects their absorption. Too much zinc causes less copper to be absorbed and too much copper causes less zinc to be absorbed. Nutrition researcher Dr. Lark Lands suggests a daily zinc intake of between 25 mg and 75 mg (“in addition to what is contained in a multivitamin/mineral supplement”). She also recommends a daily dose of between 2 mg and 4 mg copper to balance the dose of zinc. These two minerals should not be taken together at the same time.

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C. Can vitamin E help people recover from hepatitis B?

Background

When someone is first infected with the microbe HBV — hepatitis B virus — it causes inflammation of the liver. Some people can recover from HBV infection, but in people who are not able to recover the virus causes ongoing liver damage, slowly destroying the liver. In some cases, HBV infection eventually leads to liver cancer. Although drugs such as interferon-alpha and 3TC (lamivudine, Epivir) can help some people recover, the majority of people treated with these drugs do not experience a sustained recovery (their recovery is only temporary). Researchers are testing combinations of other drugs to assess their long-term effectiveness.

Meanwhile researchers in Bologna, Italy, have been studying the impact of vitamin E on HBV infection for several years. The researchers chose this nutrient because it may protect the liver from damage associated with HBV infection and it may also enhance the immune system's ability to fight the virus. Preliminary results from experiments on people with HBV by these researchers suggested that 600 mg/day of vitamin E was safe and useful in some people with HBV. We now present their results from a larger study.

Study details

Researchers recruited 32 subjects (8 female, 24 male) who had HBV detected in samples of their liver and blood. As well, all subjects had higher-than-normal levels of the liver enzyme ALT (alanine aminotransferase) for at least six months, suggesting ongoing liver damage. No subject tested positive for HIV or hepatitis C virus. Before entering this study, 23 subjects had received treatment with interferon-alpha for HBV but it did not work. Doctors randomly assigned 15 subjects to receive 300 mg vitamin E twice daily for three months. The remaining 17 subjects received no treatment and served as a control or comparison group. At the end of three months, subjects were monitored for 12 more months.

Results

By the end of the study (month 15), 47% of subjects in the vitamin E group and 0% in the control group had recovered from HBV infection. This difference in recovery between the two groups was statistically significant, that is, not likely due to chance alone.

Four subjects stopped taking vitamin E by the second month of the study because their liver enzyme levels rose to more than 10 times the upper limit of normal. The research team reported no side effects due to vitamin E.

Delayed recovery?

The research team found that in the vitamin E group there appeared to be a “delayed response” to treatment. They noted that levels of HBV continued to decline over time, especially after the third month, when subjects stopped taking vitamin E. The researchers stated that this type of response does not usually occur with the use of anti-HBV drugs such as 3TC. But it has been reported in clinical trials of the immune booster thymosin-alpha1 (Zadaxin) for HBV.

Further studies need to be done by other researchers to confirm these findings in a larger number of subjects. As well, although no subject in this study had HIV, we hope that other research teams will test the impact of vitamin E — with and without anti-HBV drugs — in people who are co-infected with HIV and HBV.

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D. Extra co-enzyme Q₁₀ for statin-users?

Summary

Co-enzyme Q₁₀, or ubiquinone, is a nutrient that is produced in small amounts by the body and is also obtained from food. It plays a key role in helping the body convert food into energy. Co-enzyme Q₁₀ is also an important antioxidant, the need for which appears to increase during HIV infection and in people who use certain lipid-lowering drugs called statins.

What does co-enzyme Q₁₀ do?

Many of the body's functions rely on a series of chemical reactions called oxidation. During these reactions, molecules called free radicals are produced. Free radicals can damage the body in much the same way that rust damages a car. To prevent this damage, the body uses antioxidants such as vitamins C and E as well as co-enzyme Q₁₀. In this report, we will shorten this nutrient's name to Q₁₀.

Power generation

Co-enzyme Q₁₀ plays a critical role inside a cell's power plant, or mitochondria. This nutrient helps to protect the power plant from damage caused by free radicals.

Inside the power plant, sugar or glucose is “burnt” to release energy. Q₁₀ helps to capture the energy so that it can be used to power cells.

Q₁₀ also protects cells and fatty substances, including vitamin E, from free radicals. Q₁₀ can also help to “recharge” or “recycle” vitamin E.

HIV positive people use Q₁₀ for the following reasons:

1. To restore levels of Q₁₀ in the body to normal

At least one study has found that HIV positive people have significantly less Q₁₀ in their bodies than do HIV negative people. Moreover, Q₁₀ levels continue to decline as the immune system degrades. Supplements of Q₁₀ — 200 mg/day — can restore levels of this nutrient to within the normal range.

2. For protection from drug-related toxicity

Drugs such as AZT, ddI, ddC, 3TC, d4T and ABC (abacavir, Ziagen) are called nucleoside analogues (nukes). These drugs can damage the energy-producing parts (mitochondria) of cells. Damaged mitochondria produce less-than-normal amounts of energy. When cells don't have enough energy, they don't work properly and can die. When many cells inside an organ, such as the liver, die, this can cause health problems.

Prolonged use of nukes can lead to lactic acidosis. In this condition, high levels of lactic acid, or lactate, are released into the blood. This can lead to the following symptoms:

- feeling weak or tired
- nausea and/or vomiting
- painful inflammation of the pancreas gland (pancreatitis)
- swollen, fatty liver

Other problems that may be caused by nukes include:

- damage to the nerves in the hands and feet (peripheral neuropathy)
- loss of hearing
- bone loss
- loss of fat
- muscle wasting

These problems may occur, in part, because of damage to mitochondria. Antioxidants such as vitamins C and E can delay or prevent some of these complications. Because Q₁₀ plays such an important

role within mitochondria, it is possible that this nutrient taken with other antioxidants may help prevent some of these nuke-related complications.

3. Protection from some forms of cardiovascular illness

In HIV negative people, results from small studies suggest that Q₁₀ has the potential to do the following:

- help reduce high blood pressure (hypertension)
- help people recover from heart failure
- protect the heart from damage for brief periods when its blood supply is interrupted

In the body, Q₁₀ is often found attached to a form of cholesterol called low-density lipoprotein (LDL). Q₁₀ helps to prevent LDL from being oxidized or damaged by free radicals. As a result, supplements of Q₁₀ may help to reduce the risk of developing cardiovascular disease.

4. Protection from the side effects of lipid-lowering drugs

One common side effect of highly active antiretroviral therapy (HAART) is increased levels of fatty substances or lipids in the blood. Examples of the lipid changes that can occur in HAART-users include the following:

- increased levels of triglycerides
- increased levels of cholesterol
- increased levels of LDL (bad cholesterol)
- decreased levels of HDL (high-density lipoprotein – good cholesterol)

These lipid changes increase the risk of cardiovascular disease in HAART-users. To decrease this risk, doctors may encourage PHAs to make changes to their diet and engage in a programme of regular aerobic exercise. If these steps don't work, then lipid-lowering agents — commonly called statins — can be prescribed. These drugs work by lowering the levels of triglycerides and LDL while raising HDL. Thus, statins can greatly reduce, but do not eliminate, the risk of developing cardiovascular disease. Examples of statins include the following:

- Baycol (cerivastatin)
- Crestor (rosuvastatin)
- Lescol (fluvastatin)
- Lipitor (atorvastatin)
- NK-104 (pitavastatin)
- Mevacor (lovastatin)
- Pravachol (pravastatin)
- Zocor (simvastatin)

These drugs exert their lipid-lowering effect by reducing the body's ability to produce cholesterol. Unfortunately, Q₁₀ production is also affected by statins. Not surprisingly, the body's production of Q₁₀ can fall between 25% and 40% with the use of statins. Reduced production of Q₁₀ means that there is less of this important antioxidant to protect cells from free radicals. It is possible that with less Q₁₀ available, there may be an increased risk of developing certain side effects associated with the use of statins, including the following:

- muscle inflammation, pain and weakness
- fatigue
- liver damage

Some PHAs who use statins also take supplements of Q₁₀ and vitamin E.

Side effects

Most clinical trials of Q₁₀ have used doses ranging from between 30 mg/day to 800 mg/day. At these doses, no serious side effects have been published.

Warning

Warfarin (Coumadin) is a blood-thinning drug that is used to increase the time blood takes to form clots. Q₁₀ taken with warfarin may intensify this effect.

Available forms and usage

The body can make Q₁₀ using the amino-acid tyrosine, B-complex vitamins and vitamin C. Foods that are good sources of Q₁₀ are usually cholesterol-rich and include the following:

- pork
- beef
- chicken
- herring

Bear in mind that it is almost impossible to obtain a high level — 200 mg — of Q₁₀ in one day from food sources alone. This is why some PHAs take supplements of this nutrient. Q₁₀ is sold in capsules, mainly in health food stores. The dose used in clinical trials involving PHAs is 200 mg/day. Because Q₁₀ dissolves in fat, it is best taken with meals to increase absorption. Some Canadian health food stores sell capsules containing a mix of Q₁₀ and flaxseed oil.

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II SIDE EFFECTS

A. Background on glucose — from food to blood sugar

The food we eat gets broken down into three basic groups:

- proteins
- fats
- carbohydrates – starches and sugar

In different parts of the intestine these compounds get broken down or digested even further. Sugar or glucose is absorbed from the intestine into blood. The blood carries glucose around the body. Cells can then pull in glucose from the blood using specialized proteins called glucose transporters. Once inside the cell, glucose can be “burnt” to release energy.

Highs and lows of blood sugar

Because cells are very dependent on glucose for energy, the body tries to maintain blood sugar levels within a normal range using the hormone insulin. When the body doesn't take in enough food, the liver and kidneys try to maintain blood sugar by breaking down stored starch or protein and converting them into glucose. After a meal, blood sugar usually rises and the excess glucose gets stored in fat and muscle cells. This storage is made possible because of the glucose transport proteins, especially one called Glut4.

Problems with insulin

When cells are exposed to insulin they activate the glucose transporters to take in sugar. When this process gets disrupted, that is, when cells become less sensitive to the effect of insulin, a condition called insulin resistance develops. The development of insulin resistance is usually the earliest sign of the beginning of diabetes.

In this issue of *TreatmentUpdate*, we review some of the recent findings on insulin and protease inhibitors by research teams in Canada, France, Israel and the U.S. Although the focus of much of that work is on the protease inhibitor indinavir (Crixivan), readers should note that all protease inhibitors, including

Kaletra (lopinavir), have the potential to cause insulin resistance.

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B. Indinavir — effect on sugar and insulin

Background and summary

The use of highly active antiretroviral therapy (HAART) has led to dramatic improvements in survival among people with HIV/AIDS (PHAs) in North America and Western Europe who can adhere to complex drug regimens. However, HAART often has side effects, perhaps the most notorious of which is the lipodystrophy syndrome. This syndrome includes the following features:

- changes in body shape
- fat wasting
- fat redistribution
- higher-than-normal levels of fatty substances in the blood
- higher-than-normal levels of insulin and sugar in the blood

It is not clear which of these features of lipodystrophy are caused by specific components of HAART, such as protease inhibitors (PIs), nucleoside analogues (nukes) and non-nukes. Some researchers think that HIV infection may also play a role in the lipodystrophy syndrome. To investigate the effect of PIs on the lipodystrophy syndrome, researchers in California conducted a short study of indinavir (Crixivan) in HIV negative subjects. Based on their results, it is clear that even as little as four weeks of exposure to indinavir can increase the risk of people developing diabetes.

Study details

Researchers recruited 10 healthy, HIV negative males whose average age was 42 years. Subjects entered a hospital for five days where they received meals containing a fixed amount of fat, protein and starch/sugar to help maintain body weight and also reduce the effect of diet on changes to insulin, glucose and lipid levels in their blood at the start of the study. At

the end of their hospital stay, subjects began to take 800 mg indinavir every 8 hours for four weeks.

Results — side effects

Commonly reported side effects during the study were as follows:

- dry skin (7 subjects)
- dry mouth (7 subjects)
- nausea (3 subjects)
- muscle aches (3 subjects)
- higher-than-normal levels of the waste product bilirubin in the blood (3 subjects)

Focus on sugar and insulin

Results from several tests done by the researchers on subjects made it clear that all subjects developed problems with the way their bodies dealt with sugar once they started taking indinavir. Specifically, indinavir affected the body's ability to move sugar from the blood into cells where it could be used for energy. Indinavir does this in part by making cells less sensitive to the effect of insulin. These changes increase the risk of indinavir-users developing diabetes — one subject did in fact develop this condition.

Researchers noted that those subjects who had family members with diabetes were more likely to be affected by indinavir's negative impact on blood sugar and insulin.

Fat

Overall, four weeks' exposure to indinavir had little effect on levels of fatty substances in the blood — cholesterol, triglycerides, low-density lipoprotein and high-density lipoprotein. As well, no subject developed changes in body shape. Longer exposure to indinavir may have different results.

This study is a good first step in trying to sort out the possible causes of the lipodystrophy syndrome. Further work needs to be done with other PIs as well as in other populations, such as women, both before and after menopause.

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C. Protease inhibitors and blood sugar problems

In order to find ways to help HAART-users who are experiencing blood sugar/insulin problems, researchers across the globe are studying exactly how

indinavir (Crixivan) and nelfinavir (Viracept) cause these problems. At this time we don't have detailed information on the impact of other protease inhibitors (PIs) and their effect on insulin.

Indinavir

One source of the insulin/sugar problem is that PIs affect the ability of transporter proteins to move sugar (glucose) from the blood into cells. This problem occurs in muscle and fat cells, which are major users of glucose. Laboratory research in France suggests that the drug rosiglitazone (Avandia) helps reverse indinavir's damage to the glucose transporting proteins. Its effectiveness and safety in HAART-users needs to be confirmed in long-term studies.

Nelfinavir

Researchers in Israel have confirmed the negative impact of nelfinavir on the effect of insulin. The drug Rezulin (no longer available in many countries), in laboratory experiments, was able to reduce the level of insulin resistance caused by nelfinavir. Although Rezulin is very similar to other drugs such as rosiglitazone and pioglitazone (Actos) — all three drugs are commonly called glitazones — it is not clear if these other drugs can help nelfinavir-users until results from clinical trials are analysed.

Coming up

Changes to diet and exercise are simple, natural ways of trying to help the body cope with insulin resistance. Sometimes, however, such steps may not be enough, and drugs such as metformin (Glucophage) and the glitazones or older anti-diabetic drugs may be necessary. For results from short trials of metformin in PHAs, see *TreatmentUpdate 111*. There are also several complementary therapies that may be considered for helping to manage blood sugar. Details on some of these other therapies will appear in a future issue of *TreatmentUpdate*.

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Decisions about particular medical treatments should *always* be made in consultation with a qualified medical practitioner knowledgeable about HIV-related illness and the treatments in question.

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