The prevalence of obesity has doubled since the year 1980. The latest study reveals that for the first time, obese Americans outnumber those who are merely overweight.

The war against obesity is an obvious failure. Overlooked are a plethora of research findings indicating substantial fat-loss effects in response to the proper use of bioidentical hormones, certain prescription drugs, and nutrients, along with lifestyle changes.

The reason these proven weight-loss strategies have not caught on is that when used in isolation, they often fail to meet the expectations of a typical obese or overweight individual.

In this eye-opening report, Life Extension® discusses how to interpret blood test results to prescribe an armada of medications, natural hormones, and lifestyle alterations that can safely induce substantial and sustainable weight loss.
Our Bloated Bloodstreams

Overeating is associated with bloating of the gastrointestinal tract (stomach and intestines). Forgotten is what happens after excess fats and sugars leave the digestive system and enter the bloodstream.

People in modern societies have succumbed to a pathological propensity of ingesting excess calories throughout the day (and sometime night). The result of successive meal intakes is that our bloodstreams are chronically bloated with fats and sugars. Constant exposure to excess fats and sugars results in insulin resistance, oxidative stress, vascular inflammation, and platelet activation, all of which sharply increase heart attack, stroke, and diabetes risks. Chronically bloated bloodstreams also contribute to unwanted weight gain and preclude the shedding of surplus fat pounds.

The term postprandial is defined as "after eating a meal." A growing number of medical studies discuss the role of postprandial lipemia (too much fat remaining in the blood after a meal) and postprandial hyperglycemia (too much after-meal glucose) as culprits in today's obesity epidemic. As long as our meals contain enough of the wrong fats, a transient increase in postprandial lipemia will likely occur. Even when simple carbohydrates are avoided, insulin resistance causes many aging people to suffer higher-than-desirable blood glucose and correspondingly elevated triglyceride levels.

Unless definitive actions are taken, most people will spend most of the day in a postprandial state, i.e., their bloodstreams will be chronically overloaded with sugars and fats. One might think that dieting (food restriction) alone would resolve postprandial metabolic disorders. The problem is that there are fundamental age-related impediments that often require pharmaceutical intervention to circumvent.

Dietary Sugars or Fats—There May be Little Difference

Postprandial metabolic disorders can be caused by chronically eating the wrong kinds of fats or simple carbohydrates. For overweight individuals, it may not matter which food groups they choose to restrict. That is because as the blood becomes saturated with fats or sugars, enzymatic conversions of fat to glucose and vice versa results in chronic postprandial overload that can sabotage the best-laid weight-loss plan.

Most of us are familiar with how delayed or excess insulin secretion (postprandial hyperinsulinemia) contributes to weight gain. Consuming soluble fibers before each meal can help normalize insulin responses and the release of dietary carbohydrates into the bloodstream. Correcting the postprandial disorders afflicting overweight and obese individuals, however, often requires more aggressive intervention.

Please know that patients with normal fasting glucose and triglyceride blood levels can nonetheless suffer from excess postprandial fat (triglyceride) and sugar (glucose), meaning their bloodstreams remain bloated two to eight hours after eating.

Temporarily Suppressing Fat and Carbohydrate Enzymes

In recognizing postprandial disorders as an underlying cause of weight gain and impediment to successful fat loss, we will review studies showing benefits when lipase, alpha-glucosidase, or alpha-amylase enzymes are inhibited in the digestive tract.

For some patients, drugs or nutrients that inhibit these enzymes will cause gastrointestinal discomforts. The objective of suggesting these enzyme inhibitors on a 60-90-day trial basis is to provide the patient with an opportunity to restore a healthier metabolic profile, provide immediate fat-loss effects (especially in the abdomen), and forcibly educate the patient about the life-long dietary patterns they should endeavor to follow.

The temporary use of compounds that inhibit fat and sugar absorption is designed to "break" the "food addiction" cycle that causes so many people to be overweight or obese. For example, if one's diet consists of more than 30% calories from fat, a lipase inhibitor drug (orlistat) will induce unpleasant gastrointestinal side effects and provide strong motivation for the patient to make healthier food choices.
**Treating Postprandial Disorders**

It is difficult to initiate weight loss in the presence of a bloodstream that is chronically overloaded with glucose and lipids. While each patient will express individual variability, implementing a treatment regimen to reduce the postprandial burden will facilitate an improvement in metabolic parameters that helps reduce body fat, while lowering markers of vascular disease risk.

Patients of course should be encouraged to initiate diets low in saturated and omega-6 fats, while consuming complex whole-food carbohydrates and soluble and insoluble fibers, along with foods that naturally contain omega-3 fatty acids. While following a Mediterranean-type diet is considered ideal, overweight patients in the real world will most often require additional interventions to ameliorate postprandial disorders that have developed over a period of years or decades.

The four steps for reversing postprandial overload are:

1. Reduce calorie intake, especially saturated fats, omega-6 fats, and simple sugars.
2. Block acute glucose absorption to reduce excess insulin response.
3. Inhibit lipase, alpha-amylase, and alpha-glucosidase enzymes to reduce amount of absorbed fat and carbohydrate calories.
4. Modulate hormones and enzyme systems in the liver, blood, and adipose tissues to induce healthy metabolism and removal of excess fats-glucose from the bloodstream (postprandial overload) and stored triglycerides from abdominal adipocytes.

**Inhibiting the Alpha-Glucosidase Enzyme**

The metabolic syndrome is strongly associated with insulin resistance and has been recognized as a cluster of risk factors for cardiovascular diseases that appear outwardly in the form of visceral obesity.

Postprandial hyperglycemia is one characteristic feature of insulin resistance. Excess blood glucose rapidly converts into triglycerides and other lipids and impairs fat clearance with the result being postprandial lipemia. Excessive postprandial absorption of glucose has been associated with greater cardiovascular disease risk than the fasting plasma glucose level.

Aggressive actions to suppress postprandial hyperglycemia are thus an important first step in reducing excess body fat and protecting against vascular disease.

Before carbohydrates are absorbed from food, they must be broken down into smaller sugar particles like glucose by enzymes in the small intestine. One of the
enzymes involved in breaking down carbohydrates is called \textit{alpha-glucosidase}. By inhibiting this enzyme, simple carbohydrates (like sucrose) are not broken down as efficiently and glucose absorption is delayed. \textit{Alpha-glucosidase inhibitors} are available as prescription drugs (such as \textit{acarbose}) or dietary supplements (such as the InSea2\textsuperscript{TM} compound contained in the new \textit{Enhanced Irvingia} formula). They function by decreasing the breakdown of simple carbohydrates in the intestine, resulting in a slower and lower rise in blood glucose throughout the day, especially after meals.

\textit{Alpha-glucosidase inhibitors} are sometimes used in the treatment of type 2 diabetes, but their use has also been studied in non-diabetic individuals. A multicenter, placebo-controlled randomized trial revealed that the alpha-glucosidase inhibitor drug \textit{acarbose} improved postprandial hyperglycemia and reduced the risk of development of type 2 diabetes in patients with impaired glucose tolerance. In this study, acarbose treatment was also found to slow the progression of intima-media thickness of the carotid arteries, a surrogate marker for atherosclerosis, and reduce the incidence of cardiovascular diseases and newly diagnosed hypertension. This study also showed that acarbose produced small reductions in body mass index and waist circumference.

A meta-analysis of seven long-term studies has also shown that intervention with acarbose prevents heart attack and cardiovascular diseases in type 2 diabetic patients. This analysis showed improvements in glucose control, triglyceride levels, body weight, and systolic blood pressure in response to acarbose treatment.

How Effective Are \textit{Alpha-Glucosidase Inhibitors}?

An overview of the published literature on \textit{alpha-glucosidase inhibitors} reveals the following:

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reducing Postprandial Hyperglycemia</td>
<td>Very Effective</td>
</tr>
<tr>
<td>Improving Cardiac Risk Factors</td>
<td>Very Effective</td>
</tr>
<tr>
<td>Preventing Heart Attack</td>
<td>Very Effective</td>
</tr>
<tr>
<td>Inducing Body Fat Loss</td>
<td>Minimally Effective</td>
</tr>
</tbody>
</table>

It is regrettable that the medical establishment has largely ignored the multiple benefits demonstrated by \textit{alpha-glucosidase inhibitors} in published clinical trials. One study showed a 91\% reduction in acute heart attack incidence in response to acarbose therapy in patients with impaired glucose tolerance.\textsuperscript{22} A meta-analysis showed a 36\% decreased incidence of type 2 diabetes in patients taking acarbose.\textsuperscript{23}

You would think these kinds of studies would make headline news, but pharmaceutical companies have not promoted these findings the way they do for statin drugs. One reason may be that the public can access low-cost \textit{alpha-glucosidase inhibitors} as over-the-counter dietary supplements.

The weight loss shown in response to \textit{alpha-glucosidase inhibitors} is considerably less than
what one might expect. While one report showed 15.4-pound weight loss over five months in single case study, most clinical studies show weight loss of only a few pounds.\textsuperscript{23} Based on these reports, alpha-glucosidase inhibitors (like acarbose) should not be used as standalone methods for inducing weight loss. Alpha-glucosidase inhibitors have been documented to effectively ameliorate postprandial conditions\textsuperscript{24,25} and would appear to be an important initial constituent in a comprehensive weight-loss program.

When one observes how effective alpha-glucosidase inhibitors are at reducing blood glucose levels, yet only minimally effective at inducing weight loss, it becomes apparent that a multi-pronged approach (as will be described herein) is required to successfully combat obesity.

**Additional Benefits Using Alpha-Amylase Inhibitors**

Carbohydrates contribute to the synthesis of fats in our bodies. Since postprandial hyperglycemia leads to an increase in fat storage, the use of substances that interfere with glucose breakdown and absorption are important components of a weight-loss program.

As just discussed, alpha-glucosidase inhibitors interfere with the breakdown of simple carbohydrates into glucose. Alpha-amylase inhibitors, on the other hand, interfere with the breakdown of large carbohydrate molecules like starch into linked glucose polymers. These simple sugars are then broken down to glucose by the alpha-glucosidase enzyme.

The best-documented alpha-amylase inhibitor consists of an extract from the white kidney bean (Phaseolus vulgaris). In a placebo-controlled study, those taking standardized white kidney bean extract lost 3.8 pounds over an eight-week period. More importantly, they lost 1.5 inches of abdominal fat and their triglycerides plummeted 26 points (milligrams per deciliter, or mg/dL), indicating a reduction of the deleterious postprandial syndrome.\textsuperscript{26}

There would appear to be an even greater benefit in combating postprandial hyperglycemia-lipemia by taking both an alpha-glucosidase and an alpha-amylase inhibitor. Such combinations are now available in dietary supplement form. Alternatively, one can be prescribed 50 mg three times a day of the drug acarbose, while a standardized white kidney bean extract supplement can be taken before each carbohydrate-containing meal. Specific dosing suggestions will appear in the summary on pages 60 and 61.

Any patient with a fasting triglyceride blood level over 80 mg/dL should be suspected as suffering some degree of postprandial lipemia. As is too often observed, overweight patients usually present with fasting triglyceride readings well over 150 mg/dL, which indicates postprandial hyperglycemia and lipemia as underlying causes of their weight gain. Inhibiting carbohydrate absorption will help reduce triglyceride and glucose blood levels.

Please remember that alpha-glucosidase and alpha-amylase enzyme inhibition is only one step in the comprehensive weight-loss program we are presenting.

**Inhibiting the Lipase Enzyme**

A regrettable consequence of normal aging is that people no longer have the metabolic capacity to consume the same number of calories they did in their youth. Part of this loss of metabolic capacity relates to the aging patient’s increasing inability to rapidly utilize and then purge dietary fats from their bloodstream.

Excess calorie intakes manifest outwardly as unwanted fat deposition. The vascular and inflammatory damage inflicted by chronic overeating, however, can be as deadly as when a smoker diagnosed with emphysema continues to smoke. For some smokers, no matter how many respiratory and vascular diseases they contract, they continue their tobacco habit until the very day it kills them.

We fear “food addiction” may be an even greater problem for aging humans based on startling studies that began appearing only a few years ago. These studies show heart attack and stroke risks to be substantially higher in patients with only modestly elevated after-meal (postprandial) triglyceride levels.\textsuperscript{27} Coupled with data revealing how obesity is related to chronically elevated blood fat levels (lipemia), it is critical to take aggressive steps to reduce the amount of fats that linger in patients’ bloodstream.
The sidebar appearing on the following page provides a number of proven methods to reduce postprandial lipemia. For overweight and obese patients seeking to lose substantial body fat, however, we are recommending a 60-90-day regimen using a lipase inhibitor drug called orlistat.

Orlistat reduces dietary fat absorption by 30% and has been around for about 10 years. It functions by blocking an enzyme (lipase) that breaks down dietary fat in the intestinal tract, thus impeding its absorption into the bloodstream.

Clinical studies demonstrate significant weight loss in response to using this drug. In the real world, however, orlistat has been associated with gastrointestinal discomforts including fat-laden diarrhea and fat seepage into patients' underwear, causing patients to discontinue its use.

We at Life Extension are concerned with potential side effects that could manifest in response to long-term use of a drug like orlistat. We are more frightened, however, about the inability of obese individuals to lose enough weight to regain youthful metabolic function. We therefore recommend that patients commit to taking orlistat for 60-90 days. It will dramatically reduce postprandial lipemia.

If patients consume too many fat calories, they will likely suffer digestive discomforts that should force them to adopt healthier eating patterns that they should follow for the rest of their lives. We also believe that the visual appearance of fat in an obese patient's feces, combined with the knowledge that absorption of this fat results in deadly postprandial lipemia and continued weight gain will motivate life-long reduced fat ingestion.

One might think that if overweight and obese individuals took 120 mg of orlistat before each meal (which would reduce absorption of dietary fats by 30%), significant weight loss would universally occur. The harsh reality is that study subjects had to reduce their dietary fat intake and take orlistat. This documents the futility of relying on modest dieting alone to significantly reduce body fat. It reveals that people are consuming far more calories than they should be, resulting in chronically bloated bloodstreams that preclude successful weight loss.

How Orlistat Works

Orlistat is an inhibitor of pancreatic and gastric lipase. It decreases the intestinal absorption of ingested dietary triglycerides by 30%.

By reducing postprandial lipemia, orlistat enhances weight loss, lessens insulin resistance, and improves cardiovascular risk factors in patients with metabolic syndrome, with and without type 2 diabetes.

In studies of obese subjects, orlistat treatment improves insulin and glucose blood levels while significantly decreasing C-reactive protein, a marker of chronic inflammation. Orlistat treatment favorably influences other blood markers (such as leptin and adiponectin) that are involved with obesity.

In a one-year trial of overweight women, a group with metabolic syndrome treated with orlistat (120 mg three times a day) and lifestyle modification lost 20.5 lbs compared with only 0.44 lbs weight loss in the placebo control group. A group of overweight women without metabolic syndrome achieving the same dose of orlistat + lifestyle modification lost 20.2 lbs more than the control group with metabolic syndrome.

In a three-month open-label trial of overweight patients without type 2 diabetes treated with orlistat (120 mg three times a day), men lost 17.4 lbs and women lost 12.3 lbs. In overweight patients with type 2 diabetes mellitus, men lost 18.7 lbs and women lost 12.5 lbs. In overweight patients without type 2 diabetes mellitus, the level of insulin resistance as measured by HOMA-IR (a validated modeling instrument for insulin resistance), decreased by 28% with orlistat treatment. For overweight patients with type 2 diabetes mellitus, insulin resistance decreased by 41%. Leptin levels decreased by 51% in men with type 2 diabetes and 29% in women with type 2 diabetes mellitus. Leptin levels dropped by 49% in overweight
men and 28% in overweight women without type 2 diabetes mellitus.4 A reduction in leptin blood levels is considered a favorable response as it indicates a reduction in the “leptin resistance” phenomenon that so often precludes weight loss.

Not all studies, however, demonstrate this much weight loss in response to orlistat. Poor compliance is always a factor in the variability that exists among studies of the same compound. Another reason for these discrepancies is that orlistat users are warned to avoid excess ingestion of dietary fats, and are likely to switch to consuming more simple carbohydrates. Overweight individuals often suffer metabolic disturbances, meaning that ingested sugars readily convert to stored (triglyceride) fats on the body. This is why taking carbohydrate-blocking agents (alpha-glucosidase and alpha-amylase inhibitors) in conjunction with orlistat for the first 60-90 days may be necessary to induce some of the immediate reduction of fat pounds that overweight and obese individuals expect.

A concern with taking a lipase-inhibiting drug like orlistat is reduced absorption of fat-soluble vitamins. Since orlistat only reduces fat absorption by 30%, a patient taking supplemental vitamin A, D, E, and K should be able to maintain more than sufficient levels of these nutrients.

The body has a significant capacity to store vitamin A, so we would not expect a problem with this nutrient. Vitamin D is also stored rather well by the body, but an obese patient might consider taking 10,000 IU each day of vitamin D for one week prior to initiating orlistat to build up sufficient levels. Obese individuals require more vitamin D than lean people. This nutrient also has functions that may help facilitate weight loss.22-24 Vitamin D can be measured with a blood test that measures 25-hydroxyvitamin D. Optimal blood levels are greater than 50-60 ng/mL of 25-hydroxyvitamin D. Patients should be able to maintain these levels by supplementing with 5,000 to 10,000 IU of vitamin D3 at the time of the day that is most removed from their last orlistat dose.

Vitamin K, an important fat-soluble vitamin, is not stored by the body as well as vitamins A and D. The ideal form of vitamin K2 is menaquinone-7, which remains in the body several days after ingestion. The minimum suggested daily dose of menaquinone-7 vitamin K2 is 90 mcg, and can be taken in supplements that also provide vitamin K1 and the menaquinone-4 form of vitamin K2. Like vitamin D3, vitamin K should be taken at the time of the day that is most removed from the patient’s last orlistat dose. (Those taking the anticoagulant drug Coumadin® (warfarin) should consider using low dose (45 mcg of menaquinone-7 a day) only under the close supervision of the physician prescribing warfarin.)

Ingesting optimal amounts of omega-3 fats is critical in reducing postprandial lipemia.35,36 Patients should consume at least 1,400 mg of eicosapentaenoic acid (EPA) and 1,000 mg of docosahexaenoic acid (DHA) in a fish oil supplement. Those with triglyceride levels above 99 mg/dL of blood often require more EPA/DHA. Omega-3 fish oil supplements should be taken with vitamins D and K, at the time of the day that is most removed from the patient’s last orlistat dose.

Fat-soluble carotenoids such as zeaxanthin, lutein, and beta-carotene, along with alpha and gamma tocopherol should also be taken at the time of day (usually at bedtime) that is most removed from the patient’s last orlistat dose. Fat-soluble nutrients contained in a multi-vitamin can be taken with orlistat, just make sure your patient takes most of their fat-soluble nutrients at a time most removed from their last orlistat dose.
In conjunction with the medications, dietary alterations, supplements, and lifestyle changes discussed in this article, the use of orlistat for a 60-90-day initiation period should provide some immediate weight loss, while enabling the re-establishment of a more youthful metabolic profile in the body whereby postprandial lipemia, insulin resistance, and other metabolic abnormalities are suppressed.

Orlistat is available by prescription in 120 mg capsules as Xenical®, or over-the-counter under the trade name alli® in 60 mg capsules. The suggested dose for the 60-day initiation period is 120 mg before each meal (three times a day). Considering the relatively high cost of over-the-counter alli®, patients with insurance coverage might save money by using prescription-strength orlistat.

**Restoring Youthful Metabolic Parameters From the Inside**

At this point, the patient has erected a multi-pronged barrier to impede the excess absorption of unwanted calories. These include:

1. Reducing their intake of simple carbohydrates, saturated fats, omega-6 fats, and trans fats.
2. Impeding glucose absorption by inhibiting the alpha-glucosidase and alpha-amylase enzymes.
3. Suppressing the insulin spike by slowing carbohydrate absorption with soluble fiber taken before each meal.
4. Inhibiting fat absorption by taking the lipase inhibitor orlistat.

For many people, sticking to the above program for the time period we suggest should provide optimal fat-loss benefits. As discussed already, we prefer that patients not use orlistat for more than 60-90 days because it may interfere with the absorption of fat-soluble nutrients like vitamins D, E, and K. It will also impede absorption of critical omega-3 fatty acids. Certain patients, however, who are successfully benefiting from orlistat may continue it longer.

The 60-90-day program we have suggested thus far will dramatically reverse many of the metabolic imbalances that are underlying causes of excess fat accumulation and increased vascular disease risk. Overweight and obese patients expect to see a rapid reduction in body weight and abdominal inches. The 60-90-day program outlined so far will help facilitate immediate fat-loss results and provide substantial patient incentive to follow a reduced-calorie regimen that involves Mediterranean diet-type food choices along with plenty of dietary fiber.

Overweight and obese individuals demonstrate chronically elevated fat levels in their blood long after meals are ingested. This postprandial lipemia is a significant risk factor for degenerative disease and can sabotage efforts to reverse type 2 diabetes, metabolic syndrome, and obesity.

Saturated fats, like those found in butter, shortening, and fried foods, are especially potent inducers of excess postprandial lipoproteins. Because postprandial disorders cause fats to linger longer, avoiding unhealthy fats is doubly important. Minimizing these fats is advisable for other reasons, such as reducing LDL, blood pressure, inflammation, and cancer risk. While avoiding saturated fats will not eliminate postprandial lipids and lipoproteins, it will help reduce them. A polyunsaturated omega-6 fatty acid derived from safflower also raises postprandial lipid and lipoprotein levels, just as saturated fats do.

Although the immediate cause of persistent and increased postprandial lipoproteins is an unhealthy fat-containing meal, two varieties of fat reduce postprandial lipoproteins:

- Monounsaturated oils, like olive oil, modestly reduce postprandial lipoproteins. Monounsaturated oils may thus be a preferable form of oil for cooking and everyday use.
- Polyunsaturated omega-3 fatty acids reduce postprandial lipoproteins dramatically. It is not uncommon to see omega-3 supplementation significantly reduce abnormal postprandial patterns. Sources of omega-3 fatty acids include fish oil, flaxseed oil, and walnuts.

If undesirable saturated fats lead to increased postprandial lipoprotein particles, does a low-fat diet reduce postprandial lipoproteins? Paradoxically, it does not. All too often, low-fat diets can evolve into diets rich in processed carbohydrates, which cause postprandial lipid and lipoprotein particles to multiply out of control. Diets that are rich in monounsaturated fats, omega-3 fats, fiber, and lean proteins, and low in saturated fats and processed carbohydrates, are effective tools in reducing postprandial lipoproteins.

The following strategies can reduce triglycerides dramatically, and help reduce or eliminate elevated postprandial fats:

- **Weight loss** can greatly reduce triglycerides and postprandial lipids and lipoproteins, particularly when it is accomplished with a diet that is low in fiber-poor, refined carbohydrates and high in fiber, lean protein, and monounsaturated fats. Cutting out processed
carbohydrates (such as breads, crackers, breakfast cereals, bagels, and pretzels made with refined, processed white flour) alone can yield a 30% reduction in postprandial lipoproteins. Increasing intake of yogurt, cottage cheese, and other low-fat dairy products, raw almonds and walnuts, and fish, chicken, turkey, and other sources of lean protein will also yield substantial reductions in postprandial lipoprotein particles. Weight loss restores the insulin responsiveness lost in metabolic syndrome, which also reduces postprandial lipids and lipoproteins.

- **Omega-3 fatty acids** in fish oil exert powerful effects in reducing postprandial lipoproteins. Ingesting just 1,200 mg of EPA/DHA from fish oil can easily lower postprandial fat remnants by 50%, and higher doses can produce even greater reductions. When fasting triglycerides are higher than 80-99 mg/dL, higher doses of fish oil may be indicated to fight excess postprandial lipids and lipoproteins. Omega-3 fatty acids decrease the liver’s production of artery-damaging very low-density lipoprotein (VLDL) by 30% or more. Fish oil can safely augment the cholesterol-lowering effects of statin drugs such as Lipitor®, yielding dramatic improvement in triglycerides, VLDL, and postprandial lipoproteins.

- **Soy protein** (20 grams per day) from tofu, soy milk, soy protein powder, and other sources can lower LDL by 10-20 mg/dL and reduce postprandial lipoproteins by 10%. We suggest that soy be used as part of a healthy diet in which soy is substituted for unhealthy fats found in meat.

- **Green tea** contains catechins (flavonoids) that can decrease postprandial lipids and lipoproteins by up to 30%. Approximately 600-700 mg of green tea catechins are required to achieve this effect, the equivalent of 6-12 servings of brewed tea. Nutritional supplements provide green tea catechins at this dose. Green tea’s effectiveness in accelerating weight loss may in part relate to its ability to reduce postprandial lipids and lipoproteins. For green tea to be effective, it should be taken immediately before meals to help block the absorption of fats and sugars. Use decaffeinated green tea extract supplements if caffeine bothers you. A new green tea phytosome (described on page 30 of this issue) has demonstrated remarkable weight loss and triglyceride-lowering effects at a dose of only 300 mg a day.

- **Vigorous exercise** can reduce postprandial lipoproteins by 30%.

- **Niacin** in doses of 2,000 to 3,000 mg a day will significantly lower triglycerides, and provide beneficial changes in HDL while changing LDL particles to a less atherogenic form. Niacin can cause a skin “flushing” side effect that can be mitigated by taking niacin with aspirin and a meal. Some people cannot tolerate this flushing effect on a daily basis and choose other options to lower triglycerides.

- **Diabetes treatment** (with insulin or oral hypoglycemic drugs) significantly reduces postprandial lipoprotein levels. The thiazolidinedione drug Actos® may be especially effective for its postprandial lipid-suppressing effects. The drug metformin also reduces fasting and postprandial triglycerides by 25%. (Caution: Like other thiazolidinediones, Actos® can cause fluid retention, which may lead to or exacerbate heart failure. Actos® should be discontinued if any deterioration in cardiac status occurs.)

- **Statin drugs** such as generic simvastatin, Crestor®, and Lipitor® not only lower cholesterol, but can reduce postprandial lipoproteins by 30-80%.

- **Fibrates** (cholesterol-lowering drugs such as Lopid® and Lofibra®) can reduce postprandial lipids and lipoproteins by 70%. They can be a useful second-line strategy if fish oil, weight loss, and nutritional efforts fail to do the job. Clearly, choosing the right foods and supplements should be the patient’s first choice in controlling a postprandial disorder. Fish oil is safe, inexpensive, and easy to take, yet it provides an extraordinary array of benefits, including reduced risk of sudden cardiac death, stroke, and depression. Weight loss, exercise, soy protein, and green tea can all increase the patient’s likelihood of success.
The long-term objective is to restore a more youthful metabolic pattern that will last a lifetime. This most often requires hormonal balancing and enzymatic modulation at the cellular level. For men, replacing free testosterone lost to normal aging is usually required. Women deficient in estrogen are encouraged to restore estrogen to more desirable ranges. Both sexes should maintain TSH (thyroid-stimulating hormone) and T3 (tri-iodothyronine) thyroid hormone levels in the optimal ranges described later in this article.

Normal aging results in reduced insulin signaling throughout the body that disrupts healthy glucose metabolism. The prescription drug metformin helps correct several mechanisms involved in glucose impairment by increasing insulin sensitivity, enhancing peripheral glucose uptake in energy-producing cells, decreasing intestinal absorption of glucose, and suppressing excess glucose synthesis from the liver. Metformin also increases a satiety hormone called ghrelin-like peptide 1, thus helping to induce a long-term appetite-suppressing effect that will better enable patients to adjust to a life-long reduced-calorie diet.

**Effects of Sex Hormones on Adipose Tissues**

Sex hormones are involved in the metabolism, accumulation, and distribution of body fat. Adipocytes (fat cells) have receptors to bind testosterone, estrogen, and progesterone, thus enabling these sex hormones to exert a direct action.

Sex steroid hormones carry out their function in adipose tissues by both genomic and non-genomic mechanisms. In the genomic mechanism, the sex steroid hormone binds to its receptor on the adipocyte and can regulate the transcription of genes involved in obesity. Leptin is a hormone secreted from adipocytes that regulates appetite and induces beneficial triglyceride breakdown in adipocytes. Lipoprotein lipase is an enzyme that breaks down circulating triglycerides into free fatty acids that are readily stored in adipocytes (fat cells). Both leptin and lipoprotein lipase exert control over adipose (fat) tissues and are genomically regulated by sex hormones.

In the non-genomic mechanism, sex hormones can activate certain hormone-sensitive lipases, ultimately leading to lipolysis (fat breakdown). In the presence of certain sex hormones, a normal distribution of body fat exists. On the other hand, with an imbalance of certain sex hormones (as occurs with aging), there is a tendency towards an increase in abdominal obesity: a major risk factor for cardiovascular disease, type 2 diabetes, and cancer.

Since sex hormones regulate the amount and distribution of adipose tissues, they are key elements of a comprehensive program to eliminate obesity. When properly prescribed, bioidentical hormone replacement therapy in postmenopausal women and older men often reduces the degree of abdominal obesity.
Testosterone Prevents Triglycerides From Accumulating in the Male Abdomen

In men, a testosterone deficit is often accompanied by visceral obesity. When deficient men are supplemented with testosterone, the result is a region-specific decrease in the visceral (abdominal) adipose tissue mass. This suggests that testosterone is exerting its effects by inhibiting lipid uptake and/or enhancing lipid mobilization from adipocytes, particularly abdominal fatty tissues.

To assess the effect of testosterone on fat mass, a study was done using labeled triglyceride fatty acids and measuring their incorporation into adipose tissues in two different regions of the body. The study subjects were all abdominally obese and divided into three groups. Group one received topical natural testosterone cream, the second group received a testosterone metabolite called dihydrotestosterone, while the third group was given a placebo cream. After two months, the testosterone group exhibited a 34% reduction in triglyceride uptake and increased turnover rate of triglycerides in abdominal adipose tissue.

Interestingly, the uptake of labeled triglyceride at baseline was 20% greater in abdominal fat compared with upper leg fat, which helps explain why so many men suffer expanding waistlines as they age, especially in the presence of less than optimal testosterone. This study shows that testosterone replacement diminished triglyceride uptake by fat cells in the abdomen, while simultaneously promoting a more rapid release of abdominal triglyceride stores.

The underlying mechanism proposed by the study’s authors was a significant 47% decrease in lipoprotein lipase activity in the abdominal region. As discussed earlier, lipoprotein lipase is involved in the deposition of triglycerides in adipocytes, thus causing fat cells (and people) to become bloated.

Triglyceride is the predominant form of fat that floats adipocytes. Excess fat in the bloodstream after eating (postprandial lipemia) is often described as postprandial hypertriglyceridemia. Interestingly, testosterone supplementation can reduce blood triglyceride levels by increasing their breakdown in the liver (via increased hepatic lipase activity). Testosterone also improves insulin sensitivity and can facilitate a reduction in postprandial hyperglycemia. Several additional mechanisms have been identified that enable testosterone to reduce triglyceride levels in abdominal adipocytes (fat cells) of men.

A number of studies document a reduction in belly fat after men with low testosterone are supplemented with testosterone. If a blood test reveals less-than-optimal testosterone level (below 20 pg/mL), consider prescribing the patient a topical testosterone cream after first ruling out prostate cancer using a PSA (prostate-specific antigen) blood test and digital rectal exam. (Refer to the sidebar on the next page for prescribing information.)

Some men will convert (aromatize) too much of their testosterone to estrogen. Optimal estradiol levels in men range from 20 to 30 pg/mL of blood. Excess estradiol can be easily suppressed by prescribing an aromatase-inhibiting drug like Arimidex in the dose of 0.5 mg two times a week.

Make sure that estradiol levels are not lowered below 20 pg/mL of blood as this may disable testosterone’s ability to induce abdominal fat loss. Some studies suggest that the decrease in abdominal lipoprotein lipase that occurs in response to testosterone replacement therapy may have to do with the conversion of some of the testosterone to estrogen. These studies are contradicted when observing abdominally obese men whose blood tests reveal low free testosterone and excess estradiol. These overweight men often present with enlarged breasts (gynecomastia) induced by this excess estradiol. Since much of the excess estradiol in these aging men is a result of the aromatization of testosterone to estradiol in abdominal adipocytes, it is difficult to comprehend that testosterone’s benefit in reducing belly fat is reliant on significant aromatization to estradiol.

These subtle nuances, which vary considerably amongst individuals, are why regular blood testing to ensure optimal free testosterone and estrogen levels is so important.
The use of topical testosterone creams has skyrocketed over the past decade in response to a plethora of positive research findings and endorsements from prominent physician-scientists. While balancing sex hormones in women is challenging, it is quite easy to achieve optimal hormone balance in aging men. What follows is a simple protocol to optimize a male patient’s free testosterone levels:

1. Have the patient’s blood tested for free testosterone, estradiol, and PSA, along with complete blood counts and blood chemistries. These blood tests are all included in the comprehensive Male Blood Test Panel that most Life Extension® members have performed annually.

2. If these blood test results reveal free testosterone below 20-25 pg/mL, consider prescribing natural testosterone cream.

3. To enable the patient to obtain natural testosterone cream at the lowest price, consider writing a prescription for compounded natural testosterone cream. A sample prescription for a two-month supply of natural testosterone cream appears in the next column.

4. The approximate testosterone dose is based on the blood test results and body mass. After 45-60 days, have the patient’s blood retested in order to prescribe a more precise testosterone dose. Each patient may vary slightly based on their rate of absorption and internal metabolism. These blood tests also help rule out prostate cancer and guard against excess red blood cell production and excess estradiol conversion, as well as ensure that liver enzymes are in normal ranges. Digital rectal exams can help to further rule out existing prostate cancer.

5. If your patient’s estradiol level is over 30 pg/mL, consider prescribing a very low-dose aromatase-inhibiting drug such as 0.5 mg of Arimidex® twice a week. This will usually bring estradiol into the optimal range of 20-30 pg/mL. Do not reduce estradiol below 20 pg/mL as this may interfere with the ability of testosterone to induce abdominal fat loss. Life Extension® members will often have their blood drawn ahead of time so their doctor can properly prescribe testosterone during their first visit. Your patients can also order the Male Panel Blood Test that includes all these blood tests and more by calling 1-800-208-3444.

Compounded testosterone cream can be obtained for as little as $40 for a 60-day supply, as opposed to around $450 for a 60-day supply of conventional testosterone gels.

Low Estrogen Promotes Weight Gain in Women

Menopause causes a large decrease in estrogens and progesterone with a corresponding increase in total and abdominal obesity. Several studies show a reduction in abdominal obesity in women in response to estrogen replacement therapy.64,83

Analogous to the way testosterone reduces male abdominal fat mass, estrogen in females reduces lipoprotein lipase activity in abdominal adipocytes. Lipoprotein lipase converts circulating triglycerides into free fatty acids that are readily stored in adipocytes (fat cells).

The control of lipoprotein lipase is very complex and involves several hormones. In women, cortisol,94-96 testosterone,97,98 and insulin99 promote lipid accumulation in adipocytes by increasing lipoprotein lipase activity, whereas growth hormone and estrogen decrease lipoprotein lipase (and thus facilitate abdominal weight loss).12,98,100,101

Conventional estrogen drugs list side effects that include weight gain. One reason for this is that until recently, the most commonly prescribed estrogen drugs were Premarin® and Prempro®, which are horse urine-derived compounds that are not identical to the estrogen naturally produced in a woman’s body. The dose of these drugs was seldom individualized, meaning that women often received too much (or too little) estrogen to meet their particular needs.

With the advent of bioidentical estrogen drugs that are individually dosed, women whose blood tests reveal low estrogen can precisely restore estrogen levels to a range that may induce a reduction in abdominal fat mass, along with other benefits.
Natural estrogen compounds are available by prescription from compounding pharmacists. These types of estrogen are bioidentical—this term means that the hormones are chemically the same as the natural estrogen produced in a woman's body. The types of estrogens commonly used in bioidentical hormone replacement therapy are estradiol and estriol.

Bioidentical estrogen drugs are prepared using different percentages of estriol and estradiol compounded into a topical cream. The most popular compounded bioidentical estrogen used today is bi-estrogen or bi-est. It is prescribed as a topical cream that may consist of 80% estriol and 20% estradiol, or a percentage ratio individualized to the patient's need. Based on a woman's estradiol blood test reading, and the body composition changes that occur, the dose of estradiol and estriol in bi-est may be increased or decreased.

An individualized approach to bioidentical hormone restoration is best. A woman will need to carefully monitor and assess her individual responses and report them to her prescribing physician so that adjustments can be made to her hormone regimen. In general, experts in the field of bioidentical hormone restoration suggest that most women feel their best when estradiol blood levels are in the range of 90-250 pg/mL, a range of estradiol that is common during the majority of the menstrual cycle for most healthy young women.

In addition to natural estrogen, natural progesterone is an important hormone for women. Natural progesterone cream or ointment is available as a compounded prescription or OTC (over-the-counter) product. The benefit of using a topical product over an oral form is that the topical form avoids the 'first pass' effect of metabolism through the liver, and therefore the dosage is lower (than oral forms).

Progestins such as Provera® are not natural progesterone. Provera® is a type of chemical that bears some similarity to natural progesterone but is chemically distinct. Natural progesterone is believed to be a safer option for women seeking hormone restoration.

There are studies showing increased risks of certain cancers in response to estrogen drug therapy and higher estrogen levels. Many of these studies used Premarin® or Prempro®, drugs that many women today avoid because of the lethal risks that were revealed. In response to concerns about estrogen and cancer, Life Extension® compiled an article titled "Is Fear of Cancer a Reason to Be Deprived of Hormones?" This article discusses healthy dietary and lifestyle alterations that have been shown to substantially reduce the risk of estrogen-induced cancers. Anyone contemplating estrogen replacement therapy should review this article at www.lef.org/estrogen

Refer to the sidebar on the page 57 for specific information prescribing bioidentical female hormones and blood levels to strive for.

Some obese women have elevated testosterone levels. Studies show that certain subgroups of obese women (for example, obese women suffering from polycystic ovary syndrome [PCOS], characterized by excess visceral body fat, insulin resistance, and high levels of testosterone) can improve metabolic profiles, reduce visceral fat accumulation, and reduce testosterone levels with a combination of metformin and low-dose flutamide, a specific anti-androgen drug available by prescription. For example, a study in 40 obese women suffering from elevated testosterone levels...
and insulin resistance treated with metformin (850 mg twice daily) and flutamide (250 mg twice daily) showed decreased visceral fat, total cholesterol, and low-density lipoprotein (LDL), and reduced excess testosterone concentrations. If a blood test reveals excess free testosterone in the presence of excess visceral fat in a woman, consider prescribing 250 mg of flutamide twice daily with concomitant metformin treatment in addition to a low-calorie diet and physical exercise.

**Weight Loss Might Not be Possible if Thyroid Hormone Levels Are Insufficient**

The thyroid gland secretes hormones involved in cellular energy expenditure. When a person restricts their calorie intake (i.e., goes on a diet), there is often a decrease in metabolically active thyroid hormone that causes the body’s fat-burning processes to slow down.

One reason people put on weight as they grow older is because aging impairs their ability to efficiently utilize carbohydrates and fats. One cause of impaired carbohydrate and lipid metabolism is sub-clinical thyroid deficiency. Some physicians believe that most people over 40 have a sub-clinical thyroid deficiency that contributes to their unwanted weight gain. 

To give you an idea of how profoundly the thyroid gland dictates body weight, consider that when the thyroid produces too much thyroid hormone, the most common clinical symptom is significant weight loss. The name for the disease caused by an overactive thyroid gland is hyperthyroidism, and in 76–83% of cases, a patient’s first complaint to their physician is about how much weight they have been losing.

In the 1960s and 1970s, the connection between hypothyroidism and weight gain caused some people to assume they could speed up their metabolism and lose weight by using supplemental thyroid hormones. This led to an abuse of thyroid hormone as people created an artificial state of excess thyroid hormone (a condition medically known as hyperthyroidism). Hyperthyroidism can cause weight loss as well as irregular heartbeats, sweating, and tremors. Although people taking supplemental thyroid hormones in these studies may have lost weight, they were losing lean muscle mass in addition to undesirable body fat.

Today our understanding of the relationship between thyroid hormone and weight loss is more complete. It works like this: when calorie intake is drastically lowered, the activity of an enzyme called 5'-monodeiodinase is reduced; 5'-monodeiodinase is necessary to convert the thyroid hormone T4 into T3. When 5'-monodeiodinase level are reduced, the levels of T3 drop. T3 is the stronger form of thyroid hormone.

Decreased T3 levels can be directly replaced. Some older clinical studies testing this theory were promising. However, later studies showed that direct T3 supplementation by dieters was connected with muscle wasting. During fasting, administration of large doses of T3 caused even more severe muscle wasting. During fasting, administration of large doses of T3 caused even more severe muscle wasting.

More recent studies suggest that using very low doses of replacement thyroid hormone during dieting, once the body has switched over from carbohydrate burning to fat burning, may not be associated with muscle breakdown.

**How to Prescribe Thyroid Hormones**

While there are studies showing that thyroid supplementation promotes weight loss in some people, it should only be used when there is evidence of a thyroid hormone imbalance, either in the form of decreased secretion from the thyroid gland or decreased conversion of T4 to the metabolically active T3 in the peripheral tissues. It is important to remember that many people’s metabolic rate decreases in response to dieting, as their body attempts to slow the metabolic rate to conserve body mass.

That means a person with normal thyroid status before dieting may become thyroid-deficient because of the reduced intake of calories. This may occur when drugs like metformin or natural products are used to suppress appetite. For optimal fat-loss effects, a person may be prescribed small doses of Cytomel® (a prescription form of T3) if their T3 levels are not in the upper one-third range of normal, or if consuming fewer calories results in a reduction of T3 levels.
How To Prescribe Bioidentical Estrogen Drugs to Aging Females

Most practitioners use the level of estradiol in women’s blood, along with an assessment of the patient’s symptoms to prescribe the initial dose of bioidentical estrogen. The estradiol blood level must be considered in context to the other hormones such as progesterone. Looking at the estradiol blood level alone as a target is somewhat effective but not entirely comprehensive.

Here is an example of how estradiol reading is commonly used as an approximation. In menopause, a woman typically has an estradiol blood level of 0-19 pg/mL. If with compounded bi-est (estradiol and estradiol) cream, the blood estradiol level goes up to 100 pg/mL, for example, then you know that the bi-est is being absorbed and has increased your patient’s estradiol level. You may then assume that the other estrogens also went up, and if the patient reports her menopausal symptoms have resolved, she is losing abdominal fat mass, and is happy, most practitioners would stop there and continue the patient on the dosage she has been using and do periodic follow-up.

If, however, the patient is still having symptoms, you can increase the bi-est dose or order additional tests such as the total estrogen blood test and/or estrone or a urinary estrogen test to get a better handle on the other estrogens and proceed from there. A typical starting dose for bi-est topical cream prescription might read as:

```
Your Doctor’s Name
Your Doctor’s Address
Your Doctor’s Phone Number
Patient’s Name
Age
Address

Bi-est: 0.5 mg estradiol/20 mg estradiol per mL
Apply 1 mL topically every day

Refill times (Signature)
```

The dose can be increased when severe symptoms of estrogen deficiency are present.

Any women with an intact uterus must also be prescribed natural progesterone (not synthetic progestin drugs like Provera®) in a dose that achieves a youthful balance. Natural progesterone produces many benefits when properly balanced with estrogen. A typical twice-daily dose is one-quarter teaspoon of a 2.5% OTC natural progesterone cream applied to a different part of the body twice each day. Progesterone can help the skin appear younger, and many women apply it on certain days to their facial skin. It can also be applied to the breasts and inner thighs. Suggested dosing is as follows:

- Premenstrual and perimenopausal women: 1/4 tsp. twice daily starting on day 12 of the menstrual cycle continuing up to day 28.
- Menopausal women: 1/4 tsp. twice daily for 21 days followed by 7 days off.

The dose can be adjusted up or down depending on the symptoms and response.

A typical dose for prescription natural progesterone cream is:

```
Your Doctor’s Name
Your Doctor’s Address
Your Doctor’s Phone Number
Patient’s Name
Age
Address

PROGESTERONE cream 50 mg/mL
Directions: Apply 1 mL (pump) topically twice daily or at bedtime days 1-25
Dispense: 1 or 2 month supply

Refill times (Signature)
```

A blood level target to strive for in aging women might be:

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Target Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol</td>
<td>90-250 pg/mL</td>
</tr>
<tr>
<td>Progesterone</td>
<td>2.0-6.0 ng/mL</td>
</tr>
<tr>
<td>Free testosterone</td>
<td>1.0-2.2 pg/mL</td>
</tr>
</tbody>
</table>

Remember that too much free testosterone in an aging woman induces abdominal weight gain, as does a deficiency of estradiol. Progesterone may be weight neutral, though some complementary practitioners claim it helps facilitate weight loss. Some doctors seek to increase progesterone levels up to 15 ng/mL.

The objective is to achieve a more youthful sex hormone balance not only to induce abdominal fat loss, but also to improve the patient’s overall state of health and well-being. The use of estrogen drugs is contraindicated in women with existing estrogen-receptor positive cancer.

There are several blood tests used to assess thyroid function. If any of these tests indicate a thyroid deficiency, consider prescribing the appropriate dose of the drug Cytomel® (T3) or Armour® desiccated thyroid to bring your patient’s level into the normal range.

If a blood test shows an increase in thyroid-stimulating hormone (TSH), this means that the pituitary gland is over-secreting a hormone to stimulate thyroid function because of an apparent thyroid deficiency. The normal range for TSH can be as wide as 0.2–5.5 mIU/mL. However, if TSH levels are above 2.0, this indicates the patient may be hypothyroid and could benefit from Cytomel® or Armour® drug therapy. Remember, the higher the TSH blood level, the more likely the patient is to be thyroid-deficient.
T4 (or free thyroxine) tests the biologically available hormone being secreted by the thyroid gland. If T4 is deficient, most doctors prescribe Synthroid™, which is a synthetic T4 hormone. We recommend Cytomel® (T3) or Armour® desiccated thyroid, however, instead of Synthroid™ (T4) because T3 is the metabolically active form of thyroid that aids in thermogenesis (body fat burning). When evaluating T4 blood test results, optimal levels for males seeking to lose weight should be in a range of 8.5–10.5 mcg/dL. Females under age 60 seeking to lose weight should be in the range of 9–11 mcg/dL. Women older than 60 years should be in the range of 8.5–10.7 mcg/dL. If there is too much T4, this is a sign of hyperthyroidism that should receive immediate medical treatment.

Measuring the amount of T3 is one way of ascertaining how much metabolically active thyroid hormone is available to the tissues. The normal free T3 range is 2.3–4.2 pg/mL, but for losing weight, you might want a range of 3.4–4.2 pg/mL. If the patient’s blood levels are below this, then Cytomel® drug therapy should be considered. Some patients are started with 12.5 mcg of Cytomel® twice a day. The dose can be increased if blood T3 levels do not return to a normal range or if symptoms of thyroid deficiency persist. If T3 levels are above normal, this can indicate an overdose of drugs like Synthroid® or Cytomel, or hyperthyroidism.

It should be emphasized that thyroid hormone by itself does not induce fat loss. Human clinical studies show that when thyroid hormone is given in the absence of thyroid insufficiency, muscle tissue is depleted. The purpose of testing a patient’s thyroid hormone status is to ensure they are in the optimal range (upper one-third of the normal reference range for T3).

### Suppressing Obesity-Inducing Inflammatory Factors

In recent years, C-reactive protein (CRP) has emerged as a reliable marker of many age-related diseases that have a hidden inflammatory component, such as heart disease and cancer. However, scientists are now realizing that CRP may also play a more direct role in disease by contributing to the growing obesity epidemic.

In a recent breakthrough, scientists from the University of Pittsburgh have discovered that CRP interacts directly with a key hormone in the body called leptin, which signals satiety as well as promotes the breakdown of fat. By binding to leptin, the researchers conclude that CRP blocks its ability to pass through the blood-brain barrier to reach the hypothalamus and turn off chronic hunger signals, effectively interfering with leptin’s ability to regulate body weight. These exciting results reveal the importance of controlling CRP levels as part of a successful weight-management strategy.

Indeed, studies using the dietary supplement *Irvingia gabonensis* have shown a dramatic reduction in weight accompanied by a marked decline in CRP levels. Medications such as orlistat, metformin, and the carbohydrate enzyme-inhibiting agents can also reduce CRP. There are several nutritional approaches that offer a safe and effective means of reducing CRP levels:

- A combination of vitamins C and E can help to fight inflammation. A recent placebo-controlled study in 19 overweight subjects found that this antioxidant combination reduced CRP levels by 32% compared with an increase of 50% in the placebo group.
- The Mediterranean diet is an effective approach to reducing inflammation. Consuming a diet rich in omega-3 fatty acids has been shown to reduce CRP levels. For example, the Greek ATTICA Study of over 3,000 men and women yielded a 20% reduction of CRP in participants who most closely adhered to a traditional Mediterranean diet.
- Increasing soluble fiber intake has been used successfully for reducing inflammation, achieving up to 28% reduction in CRP levels in overweight individuals. Beta-glucans are an excellent form of soluble dietary fiber that help lower CRP levels.
- Niacin at a dose of 1,000 mg (which should be used with medical supervision) has been shown to reduce CRP levels by 15%.
Vitamin D is also gaining recognition as a crucial modulator of inflammation. A University of London study demonstrated a dramatic reduction in CRP levels of 23% following vitamin D supplementation. Researchers have found that vitamin K status and intake also affect levels of CRP. In an analysis of the Framingham Offspring Study of 1,381 subjects with a mean body mass index of 28.1 (classified as overweight), higher levels of vitamin K status and intake (measured both by vitamin K plasma concentration and intake of the vitamin) were associated with lower levels of CRP. Curcumin, the active ingredient in the curry spice, turmeric, has been used for centuries as a topical anti-inflammatory agent in India. Experimental studies confirm its anti-inflammatory ability, showing that it reverses the threat that elevated CRP levels pose to human endothelial cells. Flavonoid antioxidants found in tea extracts, red wine, and cocoa can also reduce inflammation. In experimental studies, resveratrol and quercetin, found in red wine, have been shown to suppress the expression of CRP in a dose-dependent manner. Dark chocolate, which contains another class of flavonoids called cocoa polyphenols, reduces inflammation too. In a study of 4,849 subjects, researchers found that CRP levels were up to 17% lower in those who consumed up to 20 grams of dark chocolate every three days compared with non-consumers, signaling the benefits of cocoa polyphenols for reducing CRP levels. In addition, a human study of purified theaflavin extracts (found in black tea) produced a dramatic reduction in disease-causing mediators of inflammation, including CRP.

Restoring Insulin Sensitivity and Further Reducing Postprandial Triglycerides

Metformin is an oral hypoglycemic drug that helps lower blood sugar levels in people with type 2 diabetes. It is a member of a class of antidiabetic agents originally derived from a plant called French lilac (Galega officinalis), which has been known for centuries to improve symptoms of diabetes. But, as with so many other substances (both supplements and prescription drugs), metformin has some unexpected and beneficial side effects when it comes to weight loss. Recognizing that metformin-treated diabetics often lose weight, and believing that the drug might reduce patients’ food intake, researchers at the St. Louis University Medical Center explored possible mechanisms for this effect in 1998. Twelve obese women with type 2 diabetes who were on no medication were randomly assigned to receive oral metformin (850 or 1,700 mg) or placebo at 8:00 a.m. for three days. After a six-hour fast on the third day, subjects were given a “meal test” at 2:00 p.m., at which they were offered sandwich canapés. Just before, the meal subjects rated their hunger on a standard scale, and researchers then recorded the number of sandwiches the subjects ate in three consecutive 10-minute periods. Subjects who had taken metformin at either dose had significantly decreased calorie intake compared with placebo recipients, with the higher dose producing the most marked effect. Metformin-treated subjects also rated their hunger as lower, with the 1,700 mg/day dose producing the greatest decrease.

The researchers then went on to study 48 similar obese diabetic women who had not lost weight using diet alone. These subjects were given a 1,200-calorie diet and then were started on metformin (850 mg) or placebo twice daily for 24 weeks. The metformin-treated patients lost weight continuously throughout the treatment period, with a mean maximum weight loss that was 17.6 pounds greater than the placebo group. Not surprisingly, the metformin recipients also had lower fasting blood glucose levels as well as lower levels of the hemoglobin A1C molecule that is a marker of chronic blood sugar levels. The authors of this study concluded that "metformin decreases calorie intake in a dose-dependent manner and leads to a reduction in bodyweight in non-insulin dependent diabetic patients with obesity."
Metformin's health benefits now appear to extend beyond simple weight loss—other studies are showing that it can beneficially affect a variety of other parameters that are disturbed by obesity. A group of Turkish researchers, for example, writing in Internal Medicine in 2008, demonstrated that, in addition to weight loss, metformin-treated obese subjects had highly significant decreases in hypertension, disruptions of lipid profiles, and fasting blood sugar levels compared with placebo-treated subjects. These researchers ended their report with the statement that "metformin treatment should be initiated in patients with excess weight in their fifties." While that may be a bit over-enthusiastic, it does highlight the excitement that is being generated by this drug.

A Mexican research group has made similar findings with greater precision. They treated 60 obese patients with the metabolic syndrome (a constellation of findings related to obesity and its consequences), giving them metformin 850 mg/day or placebo, along with dietary counseling for all patients. They followed the patients for one year, tracking vital indicators of obesity-related cardiovascular health such as BMI, waist circumference, blood pressure, lipid profiles, blood sugar, and markers of the oxidant stress and inflammation that are cardinal features of the metabolic syndrome. Both groups lost weight and had improved blood pressures during the study, but patients taking metformin also had reductions in total cholesterol, markers of oxidation and CRP, a critical marker of inflammation related to vascular health. Perhaps most impressively, treated patients also had significant reductions in their intima-media thickness (IMT), which is a direct measure of blood vessel health reflecting the vessels' actual reaction to metabolic risk factors. Not surprisingly these researchers concluded that "metformin has a considerable beneficial effect on nitroxidation, endothelial function and IMT in patients with metabolic syndrome."

Metformin has been used by healthy anti-aging enthusiasts since the early 1990s. Its ability to reduce glucose and insulin levels have led some to postulate that metformin may mimic some of the beneficial effects of caloric restriction. There are relatively few contraindications for prescribing metformin. Our only concern vis-à-vis this comprehensive weight-loss protocol we are proposing are hyper-responders to the alpha-glucosidase and alpha-amylase inhibitors who also overly respond to metformin. There is a theoretical risk of inducing a state of hypoglycemia when all three agents are combined. In the real world setting, however, most overweight and obese patients will already suffer from some degree of glucose impairment and should benefit greatly from all three of these treatment

A lot of ground has been covered in this article, but we will tie it all together succinctly here.

Overweight and obese patients are likely to suffer from postprandial disorders that preclude sustainable fat loss. Young healthy humans can often ingest high-calorie meals without accumulating surplus body fat. Their young bodies respond with an immediate surge of insulin that precisely converts ingested calories to energy with minimal fat storage. They have abundant functioning insulin receptors capable of optimally regulating how they metabolize their food. Hormones that regulate fat storage are primed to keep their young bodies slender.

Normal aging severely disrupts these healthy metabolic patterns, necessitating aggressive medical interventions to reverse. Blood test results help enlighten you and the overweight patient to the degree of metabolic disturbance that may manifest on a blood test report showing fasting triglycerides far above 60-80 mg/dL and fasting glucose hovering around 100 mg/dL.

What has become accepted as "normal" blood test findings (within the "reference range") are really an indicator of how widespread metabolic disorders have become in modern societies. An overweight or obese patient with fasting glucose around 100 mg/dL almost always has dangerously high fasting insulin levels. While this surplus insulin may temporarily keep glucose
at barely acceptable levels, insulin resistance disrupts normal metabolic processes and contributes to excess storage of body fat. For long-term weight loss to occur, it is critical to enhance insulin sensitivity and purge the excess levels of fats (mainly triglycerides) and glucose that chronically saturate the patient’s bloodstream.

We therefore recommend the following interventions for the first 60-90 days (or longer in certain patients):

1. **Orlistat** in the dose of 120 mg should be taken three times a day before each meal to inhibit the *lipase* enzyme. This will result in a rapid reduction of triglycerides and chronic inflammatory markers with a partial reversal of insulin resistance syndrome.

2. After two days, the drug **acarbose** in the dose of 50 mg taken three times a day before meals should be introduced to inhibit the *alpha-glucosidase* enzyme. Those who prefer taking a natural dietary supplement in lieu of acarbose can try 125 mg of InSea2™ (a combination of brown seaweed polyphenols and bladderwrack) before carbohydrate-containing meals to suppress *alpha-glucosidase*. Suppressing *alpha-glucosidase* significantly improves metabolic parameters involved in unwanted weight gain. This dose of InSea2™ is included in the new *Enhanced Irvingia* formula.

3. After another two days, the patient should initiate **alpha-amylase** inhibition using a standardized *white kidney bean extract* (*Phaseolus vulgaris*) in the dose of 445 mg before carbohydrate-containing meals. Suppressing *alpha-amylase* significantly improves metabolic parameters involved in unwanted weight gain. This dose of *Phaseolus vulgaris* is also included in the new *Enhanced Irvingia* formula.

4. All patients should supplement their meals with at least five grams of **soluble fiber** powder such as beta-glucans from oat or barley, psyllium, guar gum, and/or pectin to further reduce the rapid absorption of sugars into the bloodstream (and the subsequent insulin spike). Patients who don’t want to mix powders can derive some benefit by taking four capsules (2,000 mg) of a highly purified glucomannan called PGX® with each meal. These fibers also help reduce blood lipid levels.

5. Patients presenting with any indications of metabolic syndrome, pre-diabetes, or frank type 2 diabetes should be considered for **metformin** therapy. Initial dose should be 250 mg with the two largest meals of the day. The dose may be increased to 850 mg taken with each meal (up to 2,550 mg/day). Metformin functions via multiple mechanisms to improve a patient’s metabolic profile while helping to suppress appetite.

6. **Men** with free **testosterone** levels below optimal ranges of 20-25 pg/mL of blood should be prescribed a **compounded testosterone cream** with the objective of increasing their free testosterone to optimal levels (20-25 pg/mL of blood). Low testosterone predisposes men to abdominal obesity. Men with existing prostate cancer should not be prescribed testosterone. Estradiol levels in men should be maintained in the range of 20-30 pg/mL of blood.

7. **Women** with **estradiol** levels below 90 pg/mL of blood should be prescribed a compounded **bioidentical estriol/estradiol cream** to increase their estradiol blood reading to over 90 pg/mL of blood. Women deficient in estrogen are predisposed to abdominal fat accumulation. Women with existing estrogen receptor positive cancers should not be prescribed estrogen drugs. All women with an intact uterus should be prescribed natural progesterone and most women will benefit by restoring progesterone blood levels to the youthful range. Women with excess free testosterone should be prescribed metformin and flutamide as discussed on pages 54 and 55 of this article.

8. **Thyroid** status can be assessed with blood tests and patients’ free T3 level should be kept in the upper one-third range of normal, but should never be increased to above the upper range of normal.

Ensuring compliance is critical if your patients are to achieve meaningful weight loss. We urge that you refer your patients to **The Nine Pillars of Successful Weight Loss** (next article and located at www.lef.org/pillar). The information provides patients with guidance on dietary, nutrient, and lifestyle changes they should implement to enhance the fat-reducing benefits of the various medications discussed in this article.
modalities. A safe starting dose of metformin would be 250 mg twice a day before a meal. If glucose levels are not overly suppressed, the metformin dose can be increased to as high as 850 mg two or even three times a day before meals.

An undesirable side effect of metformin for men is that it can reduce testosterone levels. As you read earlier in this article, low testosterone predisposes aging men to abdominal obesity. This may be why metformin has not always produced significant weight loss in clinical studies. Men who are prescribed testosterone replacement therapy can readily overcome this side effect if blood tests reveal that the prescribed dose of testosterone is not increasing free testosterone blood levels to the optimal 20-25 pg/mL range. All the prescribing doctor has to do is slightly increase the testosterone dose to overcome the testosterone-reducing effect of the metformin.

**Optimal Blood Ranges to Facilitate Weight Loss**

There are a variety of blood tests that can direct what drugs, hormones, and nutrients you prescribe to correct underlying hormonal and metabolic disorders and facilitate weight loss.

An obese individual will often exhibit dangerously high levels of C-reactive protein. Not only is this inflammatory marker associated with increased vascular disease, dementia, and cancer risk, but it can preclude weight loss by binding to leptin and creating a state of leptin resistance. Leptin is a satiety hormone that also helps promote the breakdown of triglycerides in adipocytes. Most of the drugs suggested in this protocol will induce a significant reduction in C-reactive protein blood levels. For men, ideal C-reactive protein is below 0.55 mg/L. Women should be below 1.55 mg/L of blood.

We have learned to accept any reading of fasting glucose under 100 mg/dL of blood as acceptable. The reality is that any increase of fasting glucose over 85 mg/dL incrementally increases heart attack risk and probably contributes to unwanted fat accumulation. Ideal fasting glucose is probably in the range of 72-74 mg/dL, but it will be challenging to achieve these levels in overweight and obese individuals even when all the medications suggested in this protocol are concomitantly prescribed.

The standard reference range for fasting triglycerides extends up to 149 mg/dL of blood, but any number above 80 mg/dL is probably too high. To protect against vascular disease, triglyceride levels should be suppressed far below 100 mg/dL. To treat the postprandial lipemia that has been identified as a probable cause of obesity, suppressing triglyceride levels below 60 mg/dL of blood would be ideal, though you will be challenged to achieve these levels in most aging overweight patients. Scientists have identified a phenomenon known as postprandial hypertriglycerideremia, in which triglyceride levels remain high after a meal; this represents a significant independent risk factor for vascular disease. Don’t hesitate to test your patient’s blood two to three hours after they have ingested a typical meal. A patient with acceptable fasting triglycerides might demonstrate higher than desirable (greater than 133 mg/dL) postprandial triglycerides. The medications and nutrients suggested in this protocol should sharply reduce triglyceride levels and thus help purge the bloodstream of chronic postprandial lipemia that contributes to their surplus body fat stores.

The reference range for thyroid hormone tests can cause those with less than optimal thyroid hormone levels to be diagnosed as “normal.” Make sure your patient’s TSH is below 2.00 mU/mL of blood and free T3 is in the upper one-third of the standard reference range.

For most aging men, a free testosterone blood reading of 20-25 pg/mL is optimal, while estradiol levels should be kept at 20-30 pg/mL of blood.

The optimal blood level of estradiol in aging women varies considerably amongst individuals. An estradiol target to attain using bioidentical estrogens is 90-250 pg/mL. If this range helps facilitate abdominal fat loss, then it may be ideal for that particular patient. Make sure any female patient prescribed estrogen reviews the cancer risk-reduction program that can be accessed by logging on to www.lef.org/estrogen. Remember that in female patients, excess free testosterone can cause abdominal obesity.
Managing “Unrealistic” Weight-Loss Expectations

Clinical studies document that overweight and obese subjects have unrealistic expectations about the rapidity and amount of body fat loss that will occur in response to weight-loss drugs.154 For many patients, if immediate fat-loss results do not occur, they will abandon the program, even when being repeatedly told that weight loss will be a gradual process. Regrettably, the desire for major cosmetic weight loss and the lack of understanding of the medical benefits derived from modest body fat reduction can conspire to derail the best-laid scientific protocols.

A key element to short- and long-term success is to educate the patient while encouraging continuous compliance. The next article titled “The Nine Pillars to Successful Weight Loss” (also available at www.lef.org/pillar) should be printed out and given to patients to help them understand what they need to do to allow a comprehensive program like this to work for them.

Addressing psychological issues such as emotional eating are important patient considerations. Drugs like Wellbutrin® and Adderall® have been shown to induce weight loss, but can cause psychological disturbances.155-157 Likewise, the drug sibutramine (Meridia®) has demonstrated potent weight-loss properties,158,159 but we are concerned about the long-term effects of artificially interfering with normal neurotransmitter reuptake. Sibutramine reduces the reuptake of serotonin (by 54%), norepinephrine (by 73%), and dopamine (by 16%), thereby increasing the levels of these transmitters in the brain and helping to enhance early satiety.160

As is explained in The Nine Pillars of Successful Weight Loss, patients with emotional eating issues may benefit from a specially formulated tryptophan supplement designed to deliver greater amounts of tryptophan into the brain for conversion to serotonin.

Summary: Is All of This Too Complicated?

After reading this multi-pronged approach to optimally induce immediate and sustainable weight loss in your patients, you may wonder if it is too complicated and expensive.

Fortunately, Life Extension® now offers comprehensive blood tests at the lowest prices ever. Many of the drugs can be obtained in very low-cost generic or compounded form. There are also nutritional supplements that can be substituted for some of the medications. So the cost of implementing this program is affordable to most patients.

As far as the complexities of this protocol, please remember that approximately 2.2 million Americans die each year.161,162 When tallying up the data, including higher rates of suicides and accidents in obese individuals, it becomes rapidly apparent that the metabolic dysfunction displayed outwardly in the form of excess body fat is by far the leading killer. Be it stroke, heart attack, dementia, or cancer, the more overweight a patient is, the greater the likelihood they will be stricken by these lethal diseases.

If this multi-pronged protocol induces the kind of sustainable weight loss and reduction in metabolic disorders that the published studies indicate it will, you may want to recommend it for all of your overweight or obese patients. It seems more logical to prioritize even modest reductions in body weight as opposed to dealing with the plethora of obesity-related diseases that inevitably develop.

Up until now, there was little that physicians could do to induce significant fat loss in their aging patients. For the past 50 years, a wide variety of methods have been attempted to overcome the worsening obesity epidemic, yet there are more overweight Americans now than ever before. Until a magic bullet is discovered, the only way to achieve optimal weight control in your patients may be to follow most, if not all, of the suggestions you have just read.

In addition, please refer your patients to the Nine Pillars of Successful Weight Loss (www.lef.org/pillar) to provide them with guidance on dietary and lifestyle changes they should implement to enhance the fat-reducing benefits of the various medications discussed in this article.

If you have any questions on the scientific content of this article, please call a Life Extension Health Advisor at 1-800-226-2370.
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