

CUSHING'S SYNDROME
AND CUSHING'S DISEASE
YOUR QUESTIONS ANSWERED



Contents

What are Cushing's syndrome and Cushing's disease?	1
What causes Cushing's syndrome and Cushing's disease?	2
What are the symptoms of Cushing's syndrome?	2
How is Cushing's syndrome diagnosed?	3
What tests are needed specifically to diagnose Cushing's disease?	4
What can I do to help myself manage Cushing's syndrome?	5
What are the treatment options for Cushing's disease?	6
How can I expect to feel after treatment for Cushing's disease?	8
Cushing's disease FAQs	9
For further information	12
Glossary	

What are Cushing's syndrome and Cushing's disease?

Cushing's syndrome is a rare condition that occurs when there is excess cortisol in the body. Cortisol is a hormone normally made by the adrenal glands and is necessary for life. It allows us to respond to stressful situations such as illness or injury, and has effects on almost all body tissues. It is produced in varying amounts over the course of the day, most in the early morning, with very little at night.

Cushing's syndrome refers to the condition caused by excess cortisol in the body, regardless of the cause. When Cushing's syndrome is caused by a pituitary tumor, it is called Cushing's disease.

Cushing's syndrome is more often found in women than in men and often occurs between the ages of 20 and 40.

Cushing's syndrome is caused by the production of too much cortisol.



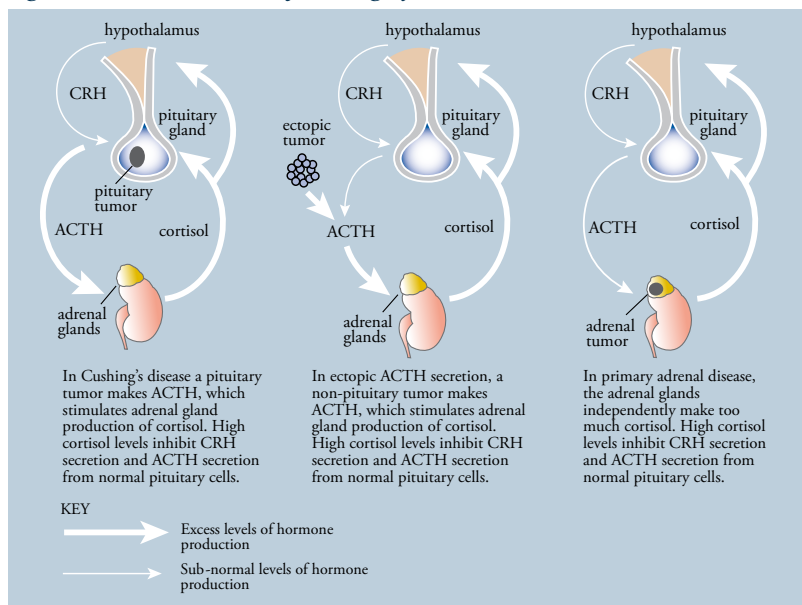
Funding was provided by the Ipsen Group; Novo Nordisk, Inc; Pfizer; and Eli Lilly through unrestricted educational grants

What causes Cushing's syndrome and Cushing's disease?

Cushing's syndrome can be caused by cortisol-like medications (called glucocorticoids) or by a tumor. Sometimes, there is a tumor of the adrenal gland(s) that makes too much cortisol. Cushing's syndrome may also be caused by a tumor in the pituitary gland (a small gland under the brain that produces hormones that in turn regulate the body's other hormone glands). Some pituitary tumors produce a hormone called adrenocorticotropic hormone (ACTH), which stimulates the adrenal glands and causes them to make too much cortisol. This is termed Cushing's disease. ACTH-producing tumors can also originate elsewhere in the body and these are referred to as ectopic tumors. See Figure 1 for an illustration of the differences between these three situations.

It is important to note that pituitary tumors are almost never cancerous.

Figure 1. The various causes of Cushing's syndrome



What are the symptoms of Cushing's syndrome?

The main signs and symptoms are shown in Table 1. Not all people with the condition have all these signs and symptoms. Some people have few or mild symptoms – perhaps just weight gain and irregular menstrual periods. Other people with a more severe form of the disease may have nearly all the symptoms. The most common symptoms in adults are weight gain (especially in the trunk, and often not accompanied by weight gain in the arms and legs), high blood pressure (hypertension), and changes in memory, mood and concentration. Additional problems such as muscle weakness arise because of loss of protein in body tissues.

Table 1. Signs and symptoms of Cushing's syndrome

COMMON FEATURES	LESS COMMON FEATURES
Weight gain	Insomnia
Hypertension	Recurrent infection
Poor short-term memory	Thin skin and stretch marks
Irritability	Easy bruising
Excess hair growth (women)	Depression
Red, ruddy face	Weak bones
Extra fat around neck	Acne
Round face	Balding (women)
Fatigue	Hip and shoulder weakness
Poor concentration	Swelling of feet/legs
Menstrual irregularity	Diabetes

How is Cushing's syndrome diagnosed?

Because not all people with Cushing's syndrome have all signs and symptoms, and because many of the features of Cushing's syndrome, such as weight gain and high blood pressure, are common in the general population, it can be difficult to make the diagnosis of Cushing's syndrome based on the symptoms alone. As a result, doctors use laboratory tests to help diagnose Cushing's syndrome and, if that diagnosis is made, go on to determine whether it is caused by Cushing's disease (i.e., from a pituitary tumor). These first diagnostic tests determine if too much cortisol is being made spontaneously or if the normal control of hormones isn't working properly.

The most commonly used tests measure the amount of cortisol in the saliva or urine. It is also possible to check whether there is over-production of cortisol by giving a medication called dexamethasone that mimics cortisol. This is called a dexamethasone suppression test. If the body is regulating cortisol correctly, the cortisol levels will decrease, but this will not happen in someone with Cushing's syndrome.

These tests are not always able to definitively diagnose Cushing's syndrome because other illnesses or problems can cause excess cortisol or abnormal control of cortisol production. These conditions that mimic Cushing's syndrome are called 'pseudo-Cushing's states' and include the conditions shown in Table 2. Because of the overlap in symptoms and laboratory test results between Cushing's syndrome and pseudo-Cushing's states, doctors may have to do a number of tests and may treat pseudo-Cushing's states – such as depression – to see if the high cortisol levels become normal during treatment. If they do not, and especially if the physical features get worse, it is more likely that the person has true Cushing's syndrome.

Table 2. Pseudo-Cushing's states

Strenuous exercise	Sleep apnea	Psychiatric disorders
Pregnancy	Pain	Stress
Uncontrolled diabetes	Alcoholism	Extreme obesity

What tests are needed specifically to diagnose Cushing's disease?

Patients with adrenal causes of Cushing's syndrome have low blood ACTH levels and patients with the other causes of Cushing's syndrome have normal or high levels. A doctor can measure the level of ACTH in the blood; measuring the ACTH levels helps to determine if the tumor is in the adrenal gland(s) or elsewhere in the body.

The best test to distinguish an ACTH-producing tumor in the pituitary from one in another part of the body is a procedure called inferior petrosal sinus sampling, or IPSS. This test involves inserting small plastic tubes into both the right- and left-sided veins in the groin (or neck) and threading them up to the veins near the pituitary gland. Blood is then taken from these locations and also from a vein not close to the pituitary gland.

During the procedure, a medication that increases ACTH levels from the pituitary is injected. By comparing the levels of ACTH produced close to the pituitary gland in response to the medication with those produced by other parts of the body, the presence or absence of a pituitary tumor can be determined.

There are other tests used for the diagnosis of Cushing's disease, such as the dexamethasone suppression and corticotropin-releasing hormone (CRH) stimulation tests. However, these are not as reliable as IPSS to distinguish between the causes. A doctor may want to do multiple tests to confirm the results.

It is also possible to visualize the pituitary gland using a process called magnetic resonance imaging (MRI). This involves an injection of a contrast agent that will help the tumor to show up on the MRI scan (Figure 2).

Figure 2. Use of Magnetic Resonance Imaging (MRI) to Visualize the Pituitary Gland



If this test shows a definite tumor and the CRH and dexamethasone test results are compatible with Cushing's disease, IPSS may not be needed. However, up to 10% of healthy people have an abnormal area on their pituitary consistent with a tumor. Therefore, the presence of an abnormality alone is not diagnostic of Cushing's disease. Also, in about 50% of patients with Cushing's disease, the tumor is too small to be seen. Thus the absence of a tumor on a MRI scan does not necessarily exclude Cushing's disease.

What can I do to help myself manage Cushing's syndrome?

- Look after your general health, eat well, and exercise regularly. However, because bones may weaken, avoid high impact exercise or sports that involve falls, to reduce the chance of a broken bone.
- Ask your doctor if you are getting enough calcium and vitamin D in your diet. These may help strengthen the bones.
- Give up smoking. This decreases the chance of having problems with surgery.
- Don't drink too much alcohol.
- Make sure you take the full course of any medicines that your doctor may give you.
- Do go back and see your doctor if any of your symptoms worsen.
- The tests involved to make the diagnosis are unfamiliar and may seem complicated. Make sure you understand how to do and time the tests (swabs for salivary cortisol, urine collections, and medications for suppression testing). If you have questions, ASK!
- After pituitary surgery, if you feel sick or suffer flu-like symptoms, do contact your doctor.

A doctor can diagnose whether too much ACTH is causing Cushing's syndrome by measuring its level in the blood.

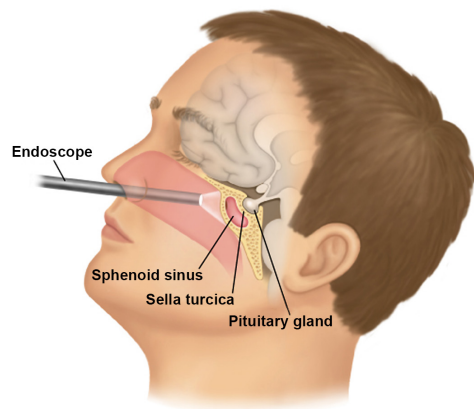


What are the treatment options for Cushing's disease?

The best way to cure the tumor is by surgically removing it, but there are other ways to control the tumor and effects of excess cortisol. In addition, there are other complementary approaches that may be used to treat some of the symptoms. For example, diabetes, depression and high blood pressure will be treated with the usual medicines used for these conditions. Also, doctors may prescribe calcium or vitamin D supplements, or other medicine to prevent thinning of the bone.

Removal of the pituitary tumor by surgery is recommended for those who have a tumor that is not extending into areas outside of the pituitary gland, and who are well enough to have anesthesia. This approach, known as transsphenoidal surgery, is usually carried out by going through the nose or underneath the upper lip and then through the sphenoid sinus to reach the tumor (Figure 3). This route is less traumatic for the patient than having to get to the pituitary through the upper skull and allows quicker recovery.

Figure 3. Transsphenoidal Surgical Approach



Removing only the tumor leaves the rest of the pituitary gland intact so that it will eventually function normally. This is successful for 70–90% of people when performed by the best pituitary surgeons. The success rates reflect the experience of the surgeon performing the operation. However, the tumor can return in up to 15% of patients, probably because of incomplete tumor removal at the first surgery.

Other options for treatment include radiation therapy to the entire pituitary gland or targeted radiation therapy (called radiosurgery), when the tumor is seen on MRI. This may be used as the only treatment or it may be given if

pituitary surgery is not completely successful. One important side effect of radiation therapy is that it can damage the pituitary gland and affect other pituitary cells that make other hormones. As a result, up to 50% of patients who undergo radiation therapy will need to take other hormone replacement within 10 years of the treatment. Radiation therapy and radiosurgery can take up to 10 years to have full effect. In the meantime patients take medicine to reduce adrenal gland production of cortisol. These medications include ketoconazole, metyrapone and/or occasionally mitotane. Gastrointestinal complaints such as nausea, lack of interest in eating, and diarrhea can occur with each of these. Ketoconazole can damage the liver, so blood tests are done to monitor liver function. Metyrapone can cause excess hair growth in women and high blood pressure in both men and women. At high doses, mitotane can cause problems with coordination and thinking and it also can cause birth defects or abortion. Neither ketoconazole nor mitotane should be given to a woman who would like to have children in the near future.

Removal of both adrenal glands eliminates the ability of the body to produce cortisol, and so the effects of excess cortisol resolve. Since adrenal hormones are necessary for life, patients must then take a cortisol-like hormone and the hormone fludrocortisone, which controls salt and water balance, every day for the rest of their life. Since removing the adrenal glands does not treat the underlying pituitary tumor, the pituitary needs to be monitored with periodic MRI scans to observe for possible tumor enlargement.

There are now new medications that can be used to treat Cushing's syndrome. One of these, pasireotide, may act to both stop tumor growth and lower ACTH production. Since it does not kill the tumor, it has to be given indefinitely. One of the important side effects of pasireotide is that it can raise blood sugar levels; therefore, blood sugar levels must be carefully monitored. Pasireotide is FDA-approved for the treatment of Cushing's disease. It is given by injection twice daily and normalizes urine cortisol levels in about 20% of patients.

Cabergoline, another medical treatment, is given by mouth about twice a week, and normalizes urine cortisol levels in about 40% of patients. Its main side effect is fatigue.

Another recently introduced medication, mifepristone, does not affect the tumor itself but blocks the effects of cortisol in the entire body, and improves the complications associated with excess cortisol. It is approved for the treatment of high blood sugar caused by Cushing's syndrome. Because there is no anti-tumor effect, the tumor itself has to be carefully followed, and there are other important side effects of the treatment as well. These drugs are best administered by a pituitary or neuro-endocrinologist skilled in their use.

How can I expect to feel after treatment for Cushing's disease?

Most people will start to feel gradually better after surgery and the hospital stay may be quite short if there are no complications. It can take some time to feel completely back to normal, to lose weight, to regain strength, and to recover from depression or loss of memory. It is important to remember that the high cortisol levels physically change the body and brain, and that these changes may reverse quite slowly. This is a normal feature of the recovery period and patience is definitely a virtue here.

After successful pituitary surgery, cortisol levels are very low. This can continue for 3–18 months after surgery. These low levels of cortisol can cause nausea, vomiting, diarrhea, aches and pains, and a flu-like feeling. These feelings are common in the first days and weeks after surgery as the body adjusts to the lower cortisol levels. Doctors give people a cortisol-like medicine (glucocorticoid) until recovery of the pituitary and adrenal glands is either well under way or complete, and this medication may be required for months. Hydrocortisone or prednisone is usually used for this purpose.

Doctors monitor the recovery of the pituitary and adrenal glands by measuring morning cortisol values, or by testing the ability of the adrenal glands to secrete cortisol in response to an injected medication similar to ACTH.

Until the pituitary and adrenal glands recover, the body does not respond normally to stress – such as illness – by increasing cortisol production. As a result people who suffer with 'flu', fever or nausea may have to double the oral dose of the glucocorticoid when they are sick. However, this increased dosage should only be used for 1–3 days. On occasion, people can suffer vomiting or severe diarrhea that prevents them from absorbing the glucocorticoids taken by mouth. In this situation, it may be necessary to receive injections of dexamethasone or another glucocorticoid, and seek emergency medical care. For this reason, patients should wear a MedicAlert bracelet until glucocorticoid replacement is stopped.

If it is necessary to have a prolonged increase in hydrocortisone or other glucocorticoid, a doctor should evaluate this need, and a 'tapering' regimen may be needed to reduce the dose back to the daily requirement.

People who have had their adrenal glands removed will have to take a glucocorticoid (like cortisone) and a mineralocorticoid (like fludrocortisone) for the rest of their lives. There may be a concern that the pituitary tumor will enlarge, so MRI imaging of the pituitary gland may be done after this surgery. People whose adrenal glands have been removed may have initial symptoms that are similar to those after pituitary surgery, and they should

take extra glucocorticoid during illness as described above, and wear a MedicAlert bracelet.

It is important to note that, if you are taking replacement cortisol, there may be a number of occasions when you need additional replacement. This can include stressful situations, such as surgical procedures – whether or not related to Cushing's syndrome – dental procedures, and so on. You should discuss your specific condition with your endocrinologist and ensure you know what situations to look out for and what action to take.

Cushing's disease FAQs

1. I have been told I might have Cushing's syndrome and have been referred to an endocrinologist. Why is this?

An endocrinologist is a physician who specializes in hormone disorders. Cushing's syndrome and disease are fairly rare, the diagnostic procedure is complex, and the best results can be expected when these are treated by a specialist endocrinologist, often together with a neurosurgeon.

2. I have been told I need pituitary surgery. What does this involve?

The most common way to remove pituitary tumors is through the transsphenoidal approach. This involves entering the pituitary gland by going through the nose or underneath the upper lip, and approaching the pituitary gland through the sphenoid sinus. Using a microscope or endoscope, the surgeon will explore the pituitary gland, hopefully find the tumor, and remove it.

3. What are the risks of this surgery?

Since these tumors are very small, it can be difficult to find them, and the normal pituitary gland can be damaged during the procedure. If this happens (about 10–20% of the time), other hormone function can be lost. Since the pituitary gland controls the production of thyroid hormone, estrogen in women and testosterone in men, and growth hormone – in addition to ACTH – replacement therapy for these other hormones might be required. Also, if the posterior part of the pituitary is damaged, anti-diuretic hormone can be lost. This hormone is responsible for water reabsorption by the kidneys, and without it patients urinate frequently and in large amounts ("diabetes insipidus"), leading to dehydration. This hormone can be replaced with a daily dose of a nasal spray or pill. These hormone functions of the pituitary can be replaced with medication.

4. Are there other risks associated with this surgery?

Since the pituitary gland is bordered by the optic nerves and carotid arteries, there is a very small risk that these structures could be damaged (less than 1%). If this were to happen, the patient could suffer visual loss or a stroke. The pituitary is separated from the spinal fluid by a thin membrane. If this membrane is damaged during the surgery, a spinal fluid leak can result. If spinal fluid leakage occurs and is undetected, a serious infection, meningitis, can result. Most surgeons take a small piece of fat from the abdominal wall to use as a plug to prevent this leakage from occurring. The risk of this happening is about 1%. Since the pituitary gland is involved in water and sodium balance, this can be affected transiently by the surgery as well, and your endocrinologist will monitor your sodium levels for a few weeks after the surgery. All of these risks are minimized in the hands of an experienced surgeon.

5. How will I feel after the surgery?

Direct effects of the surgery include nasal congestion and possibly headache. These symptoms will resolve after 1–2 weeks. If the operation is successful, however, the cortisol levels will drop dramatically. Patients can experience symptoms of cortisol withdrawal, which can include profound fatigue, joint aches and mild nausea. This can sometimes last for weeks or months after the surgery. If the operation is successful, the patient will have to take cortisol replacement until the remaining normal pituitary gland recovers.

6. How will I know if my treatment has been successful?

Your endocrinologist will test your blood, urine, and/or salivary cortisol levels a few days after the surgery. Usually success can be determined within a few weeks of the operation.

7. Will I feel better?

Almost all of the symptoms of Cushing's disease are reversible. When the cortisol levels drop, the obesity improves and appetite normalizes. Muscles and bones become stronger. These improvements occur slowly and may take months to achieve a normal state. Diabetes and hypertension improve, often very soon after surgery. The psychological effects can be very troublesome and can persist for months, even if cured.

8. What if the treatment is not successful?

There are a number of options if the initial transsphenoidal operation is unsuccessful. Sometimes, a second operation is recommended if no tumor was found during the initial operation. Alternatively, radiation therapy of the pituitary gland can be considered. This is effective in about half the patients within a few years, but medical control of cortisol levels is required while awaiting the beneficial effects of radiation. Alternatively, the adrenal glands themselves can be removed. This stops the body from making any cortisol, and so the symptoms of Cushing's disease resolve, although the pituitary tumor itself remains untreated. Removal of the adrenals may lead to a more rapid growth of the remaining pituitary tumor, which will require careful monitoring with MRI imaging. Finally, there are now new medical options to treat the disease. Administration of the drug cabergoline, initially used to treat prolactin-producing tumors, is effective in some cases of Cushing's disease. Two new drugs, pasireotide and mifepristone, have recently been approved by the FDA. Pasireotide acts directly on the pituitary tumor to stop its growth and lower cortisol production. Mifepristone acts to block the peripheral effects of cortisol and so improves the symptoms of the disease. Choosing between these options requires a careful discussion between the patient, endocrinologist, and surgeon.

9. My surgery was unsuccessful and my endocrinologist has suggested treatment with cabergoline. What will this do?

Cabergoline acts directly on the tumor to reduce ACTH production and tumor growth. It successfully normalizes urine cortisol for 12 months in about 40% of patients. Some patients who have a response in the first one or two months will “relapse”, meaning that the drug may not successfully control cortisol levels long-term. Because of this, the response should be monitored monthly. The overall effect on tumor size has not been well described, although some patients have had reduction in tumor size.

10. My surgery was unsuccessful and my endocrinologist has suggested treatment with pasireotide. What will this do?

Pasireotide acts directly on the tumor to reduce ACTH production and tumor growth. It successfully normalizes urine cortisol for 12 months in about 20% of patients, and may work best in patients whose urine cortisol levels are less than two-times normal when treatment is started. At the highest dose tested, it is associated with a decrease in tumor size in some patients. A common side effect is the development of high blood sugar levels requiring treatment (or additional treatment) for diabetes.

11. My surgery was unsuccessful and my endocrinologist has suggested treatment with mifepristone. What will this do?

Mifepristone is approved by the FDA for the treatment of high blood sugar levels caused by Cushing’s syndrome. It blocks cortisol action throughout the body. As a result, its effects cannot be judged by cortisol levels, which may not change. Because it is used to lower blood sugar levels, those levels should be monitored and medications adjusted. Its ability to normalize other features of Cushing’s syndrome is not clear, and additional treatment may be needed to fully treat the signs and symptoms of Cushing’s syndrome.

For further information

The Pituitary Society
 8700 Beverly Blvd., Room 2051
 Los Angeles, CA 90048
 310-988-9486
www.pituitarysociety.org

Glossary

<i>ACTH</i>	Adrenocorticotrophic hormone. This hormone is produced by the pituitary gland and flows through the blood to the adrenal glands to tell them to produce more cortisol.
<i>Adrenal glands</i>	Glands situated just above each of the kidneys and which produce various essential hormones including cortisol and aldosterone.
<i>Adrenalectomy</i>	Surgical removal of the adrenal glands.
<i>Cortisol</i>	One of the hormones produced by the adrenal glands. It is particularly important in times of stress and illness.
<i>CRH</i>	Corticotropin-releasing hormone normally made by the hypothalamus to stimulate ACTH production. In synthetic form, used to test for pituitary-dependent Cushing’s disease.
<i>Cushing’s disease</i>	Cushing’s syndrome when caused by a tumor of the pituitary gland.
<i>Cushing’s syndrome</i>	Caused by overproduction of cortisol for any reason.
<i>Ectopic ACTH</i>	Production of ACTH from a site other than the pituitary gland.
<i>Endocrinologist</i>	A doctor who specializes in treating hormone illnesses.
<i>Florinef</i>	A medication, also known as fludrocortisone, that controls salt and water balance.
<i>Glucocorticoid</i>	A medicine that has effects similar to those of cortisol, for example, hydrocortisone, prednisone and dexamethasone. After successful surgery, cortisol levels are low and a glucocorticoid is given to replace cortisol until the pituitary and adrenal glands resume normal function (in the case of Cushing’s disease) or as life-long replacement (if the adrenal glands are removed).
<i>Hydrocortisone</i>	The drug name of cortisol when it is made into a tablet or injection.
<i>MRI scan</i>	Magnetic resonance imaging – a type of scan that uses a strong magnetic field and radio waves (no X-rays) to produce a detailed view of the brain and pituitary.
<i>Pituitary gland</i>	A small gland that is situated under the brain and which controls hormone production in many other parts of the body.
<i>Radiosurgery</i>	Precisely targeted radiation aimed directly at the tumor, usually given in a single dose.
<i>Radiotherapy</i>	Radiation treatment, usually used after surgery, which prevents regrowth of the tumor. Radiotherapy has a long-acting effect and may cause reduction of some of the other pituitary hormones over time, thus requiring them to be replaced.
<i>Transsphenoidal surgery</i>	Surgery that involves approaching the pituitary gland via the nose or upper lip and the sphenoid sinus, thus avoiding the need to go through the upper skull.



Written by Lynnette Nieman, M.D. and Brooke Swearingen, M.D.
on behalf of the Pituitary Society.
Series Editor David L. Kleinberg, M.D.


produced and published
by CMM Global
www.cmmglobal.com