

# Cushing's syndrome: causes and symptoms



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The human body is an advanced piece of machinery which possesses many organs and systems that regulate the numerous processes that keep every part functioning to sustain normal life or Homeostasis. In the event that any of these numerous processes occur unchecked with absolutely no controlling limits it results in a physiological disorder, syndrome or disease; each of these syndromes has characteristic effects on the human anatomy which can be manifested physically of which some can be controlled or cured.

Cushing's syndrome, which is a hormonal disorder caused by the prolonged exposure of body tissues to high levels of the hormone cortisol and is frequently referred to as hypercortisolism.

Cushing's syndrome is relatively rare and most commonly affects adults aged 20 to 50 years, people who are obese and have type 2 diabetes, along with poorly controlled blood glucose also called blood sugar and high blood pressure, have an increased risk of developing the disorder. Cortisol is a very important hormone as its job is to help the body respond to stress. Most people suffering from depression, alcoholism, malnutrition, or panic disorders also have increased cortisol levels.

## **Causes**

### Physiological

The cause of Cushing's syndrome is divided into two groups based upon whether the problem is being caused by a defective pituitary gland, which is a small gland located on the ventral side of the brain or by the adrenal glands which are located on the superior poles of the kidneys. Cushing's syndrome is caused when the body's tissues are exposed to high volumes of the

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hormone cortisol for extremely long durations of time. Many individuals have developed Cushing's syndrome as a result of use or consumption of products that contain glucocorticoids. Glucocorticoids are steroid hormones that are structurally similar naturally produced to cortisol e. g. prednisone, which is contained in most asthma, rheumatoid arthritis, lupus and other inflammatory disease medications. Glucocorticoids also have properties which also allow them to be used to suppress the immune system after organ or tissue transplants to keep the body from rejecting the new organ or tissue.

Some people develop Cushing's syndrome as a result of their bodies' inability to produce adequate amounts of the hormone cortisol. The normal production of cortisol follows an exact and precise chain of events. In the hypothalamus, a part of the brain the size of a small sugar cube, it releases corticotrophin releasing hormone (CRH) to the pituitary gland. Corticotrophin causes the pituitary gland to secrete adrenocorticotropin hormone (ACTH), which in return stimulates the adrenal glands. When the adrenals, which are located just above the superior lobes of the kidneys, receive the ACTH, they respond by releasing cortisol into the bloodstream.

Cortisol is very important to the body because it is required to perform vital tasks in the body which include helping to maintain blood pressure and cardiovascular function, reduction of the immune system's inflammatory response, the balancing of the effects of insulin, which breaks down glucose for energy and the regulation of the metabolism of proteins, carbohydrates and fats. Cortisol is very important to the for its role in many processes but its most important role is to help the body cope with stress and it is for this

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reason well trained athletes and pregnant women have high levels of the hormone circulating within their blood. In most cases individuals suffering from alcoholism, malnutrition and or panic disorders may also have increased cortisol levels. Under normal circumstances, when the cortisol levels are near normal levels the hypothalamus and pituitary release less CRH and ACTH. This ensures that the level of cortisol in the blood released by the adrenals is the exact balance to meet the body's normal requirements.

There are four common types of Cushing's syndrome and each is caused by different factors e. g. pituitary adenomas, adrenal tumors, ectopic ACTH syndrome and Familial Cushing's syndrome. Of the four different types of Cushing's syndrome, cases of familial Cushing's syndrome occurs more frequently. Most cases of familial Cushing's syndrome are not inherited genetically, however some cases are the result of gene which causes the development of tumors on one or more glands of the endocrine system which releases hormones into the bloodstream. There are some exceptions e. g. with primary pigmented micronodular adrenal disease, which is developed in children or young adults which develop small cortisol producing tumors on the adrenal glands. There are occurrences where multiple endocrine neoplasia type 1 (MEN), where hormone secreting tumors develop on the parathyroid glands, pancreas and pituitary.

In Cushing's syndrome caused by adrenal tumors, an abnormality of the adrenal glands causes the Cushing's syndrome. The adrenal tumor develops four to five times more in females than in males and begins at approximately at age forty. Most cases of adrenal tumors involve noncancerous tissues of

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the adrenal glands and are called adrenal adenomas and are responsible for the release of additional cortisol into the blood. In the case of adrenocortical carcinomas, the cancerous form of adrenal tumors, the cancer cells release additional volumes of several types of adrenal androgens or male hormones which may include cortisol. The adrenocortical carcinomas are usually responsible for very high hormone levels and rapid development of symptoms.

In Ectopic ACTH syndrome which is another cause of Cushing's syndrome, in some cases it is benign and in most caused by cancerous tumors that develop on the external surface of the pituitary and is capable of producing adrenocorticotrophic hormone. Lung tumors are known to be associated with increased risks of development of ectopic ACTH as it was present in more than half of all occurrences and is known to be more prevalent males than in females. The most prolific form of adrenocorticotrophic hormone producing tumors is minute cell lung cancer and accounts for approximately thirteen percent of all lung cancer cases and carcinoid tumors, which are small, slow growing tumors that develop from hormone producing cells in various parts of the body. There are other less common types of tumors which possess the ability to produce adrenocorticotrophic hormone e. g. thymomas, medullary carcinomas of the thyroid and pancreatic islet cell tumors.

In most cases of Cushing's syndrome seventy percent are caused by the development of pituitary adenomas and these statistics excluded instances where it is caused by glucocorticoid use. This type of benign, or noncancerous tumor of the pituitary gland is responsible for the secretion of additional adrenocorticotrophic hormone into the bloodstream. In most

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instances persons afflicted by this disorder have a single adenoma and is referred to as Cushing's disease and it is known to affect women five more than men.

### Biochemical Diagnosis of Cushing's syndrome

To diagnose Cushing's syndrome several factors are taken into consideration; a person's medical history, physical examinations and laboratory tests. In diagnosing Cushing's syndrome the most commonly used tests are the 24-hour urinary free cortisol test, measurement of midnight plasma cortisol or late night salivary cortisol and low dose dexamethasone suppression test. In some instances an additional test dexamethasone corticotrophin releasing hormone test may be needed to differentiate Cushing's syndrome from causes of excess.

The 24 hour urinary cortisol level test consists of the collection of several urine samples over a 24 hour period and these samples are tested for cortisol. If the cortisol levels are higher than fifty to one hundred micrograms a day for an adult, this suggests that the individual has Cushing's syndrome. From laboratory to laboratory the normal upper limit varies depending on which technique is used.

The second test that may be used to diagnose Cushing's syndrome is Midnight plasma cortisol and late-night salivary cortisol measurements. This test measures cortisol concentrations in the blood. In normal individuals Cortisol production is normally restricted at night, but in Cushing's syndrome, this restriction does not occur. If cortisol level in the individual is more than 50 nano-moles per liter (nmol/L), then the individual may have

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Cushing's syndrome. This test usually requires a 48-hour hospital stay to avoid falsely elevated cortisol levels due to stress.

Another utilized in the diagnosis of Cushing's is the Low-dose dexamethasone suppression test (LDDST). In this test, the individual is given a low dose of dexamethasone, which is a synthetic glucocorticoid, orally every 6 hours for 2 days. Urine samples are collected before dexamethasone is administered and several times on each day of the test. The modified Low-dose dexamethasone suppression test uses a onetime overnight dose. Cortisol and other glucocorticoids signal the pituitary to release less ACTH, so the normal response after taking dexamethasone is a drop in blood and urine cortisol levels. If cortisol levels do not drop, Cushing's syndrome is suspected. In some instances Low-dose dexamethasone suppression test may not show a drop in cortisol levels in people with depression, alcoholism, high estrogen levels, acute illness, or stress, which will falsely indicate Cushing's syndrome. In some instances, drugs such as phenytoin and phenobarbital may cause cortisol levels to drop, falsely indicating that Cushing's is not present in people who actually have the syndrome and it is for this reason, physicians usually advise their patients to stop taking these drugs at least 1 week before the test.

The last test used to diagnose Cushing's syndrome is the Dexamethasone-corticotrophin-releasing hormone (Crh) test. There are some exclusion to the rule as some individuals have high cortisol levels but do not develop the progressive effects of Cushing's syndrome, such as muscle weakness, fractures, and thinning of the skin. These people may have pseudo-Cushing's syndrome, which is a condition sometimes found in people who have

depression or anxiety disorders, persons who drink alcohol excessively, have poorly controlled diabetes, or are severely obese. Pseudo-Cushing's does not have the same long-term effects on health as Cushing's syndrome and does not require treatment directed at the endocrine glands. The dexamethasone-CRH test is used to rapidly distinguish pseudo-Cushing from mild cases of Cushing's syndrome. This test combines the Low-dose dexamethasone suppression test and a CRH stimulation test. In the CRH stimulation test, an injection of CRH causes the pituitary gland to secrete ACTH. Pretreatment with dexamethasone prevents CRH from causing an increase in cortisol in people with pseudo-Cushing. Elevations of cortisol during this test suggest usually Cushing's syndrome.

#### Tests to Find the Cause of Cushing's Syndrome

Once a positive diagnosis of Cushing's syndrome has been obtained, other tests are performed to locate the cause of the abnormality that leads to excess cortisol production. The choice of test depends, in part, on the preference of the endocrinologist or the center where the test is performed.

A CRH test is performed, without pretreatment with dexamethasone, this helps separate people with pituitary adenomas from those with ectopic ACTH syndrome or adrenal tumors. As a result of the CRH injection, people with pituitary adenomas usually experience a rise in blood levels of ACTH and cortisol because CRH acts directly on the pituitary. This response is rarely seen in people with ectopic ACTH syndrome and practically never in those with adrenal tumors.



A high-dose dexamethasone suppression test (hDDST) may also be used as well. The A high-dose dexamethasone suppression test is the same as the LDDST, except it uses higher doses of dexamethasone. This test helps separate persons with excess ACTH due to pituitary adenomas from those with ectopic ACTH-producing tumors. A high dose of dexamethasone suppresses cortisol levels in people with pituitary adenomas but not in those with ectopic ACTH-producing tumors.

Another test that may be used is radiological imaging of the endocrine glands. This test utilizes the use of computerized tomography (CT) and magnetic resonance imaging (MRI) to reveal the size and shape of the pituitary and adrenal glands to determine if a tumor is present. Imaging tools are used to locate the tumor after a positive diagnosis of Cushing's syndrome. Imaging is not used to make the diagnosis of Cushing's syndrome since benign tumors are commonly found in the pituitary and adrenal glands.