

Bone Loss in Women of Reproductive Age

Part I - Amenorrheic Bone Loss

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Although bone loss is most prevalent in post-menopausal women, some young women are also at high risk. Those with estrogen deficiency and chronic systemic illnesses and those taking medications that result in bone loss are most vulnerable (Table 1). Part I of this article will review amenorrheic bone loss, which often occurs in association with neuroendocrine disorders. Part II will focus on other causes of bone loss in women of reproductive age. Diagnosing bone loss in young women is not only important because of increased fracture risk incurred in the short-term, but also because it results in their entering menopause with reduced bone mass, putting them at much higher risk for fractures later in life.

Amenorrheic Bone Loss

Estrogen deficiency in premenopausal amenorrheic women results in bone loss. In contrast, women with polycystic ovary syndrome, who have amenorrhea, but not reduced levels of gonadal steroids, have been found to have normal or even increased bone mineral density. There are a number of causes of hypoestrogenemic amenorrhea that result in bone loss. Acquired deficiency of the hypothalamic hormone gonadotropin releasing hormone (GnRH) occurs in patients with hyperprolactinemia, functional hypothalamic amenorrhea, anorexia nervosa, and hypothalamic or pituitary lesions. Hyperprolactinemia was the first cause of secondary hypogonadism to be identified as associated with bone loss 1. A 17 percent decrease in cortical and 15 to 30 percent decrease in trabecular bone mineral density have been reported in women with hyperprolactinemia 1-4.

Women with regular menstrual periods despite hyperprolactinemia do not incur bone loss, while their amenorrheic counterparts develop osteopenia despite similar elevations in serum prolactin levels 5. In addition, duration of amenorrhea is strongly associated with diminishing bone density, resulting in lower bone density in women with longer amenorrhea 6. Hypogonadism is, therefore, the likely mechanism of the bone loss in these young women, not the hyperprolactinemia itself. Functional hypothalamic amenorrhea due to excessive exercise, stress or weight loss also causes bone loss in women of reproductive age. Although weight-bearing exercise has been shown to increase bone density at weight-bearing skeletal sites, exercise sufficiently excessive to result in amenorrhea paradoxically results in bone loss. The female athlete triad, defined as amenorrhea, disordered eating behavior, and osteoporosis, has been increasingly recognized as a public health problem, particularly in college athletes.

Table 1. Causes of Bone Loss in Women of Reproductive Age

Estrogen Deficiency	Medications
Acquired GnRH deficiency	GnRH agonists
Hyperprolactinemia	Depot medroxyprogesterone acetate
Functional hypothalamic amenorrhea	Medication-induced
(excessive exercise, stress, weight change)	Chronic glucocorticoid therapy
Anorexia nervosa	Cyclosporine A
Organic sellar or CNS disease	Anti-convulsants
iatrogenic (surgery or radiation)	Heparin
Acquired gonadotropin deficiency	Systemic Illnesses
Organic sellar or CNS disease	Cushing's syndrome
iatrogenic (surgery or radiation)	Growth hormone deficiency
Ovarian failure	Hyperparathyroidism
Oophorectomy	Chronic liver disease
Autoimmune	Celiac sprue
	Inflammatory Bowel Disease
	Cystic Fibrosis

Chemotherapy

Three to 66 percent of female athletes are amenorrheic, depending upon the type, intensity and duration of exercise, and the athlete's nutritional status. Amenorrheic athletes are at significant risk for bone loss. Drinkwater et al. compared amenorrheic athletes to eumenorrheic athletes of similar age, weight, percent body fat, height, age of menarche, sport and training schedule. The mean lumbar spine bone density of the amenorrheic athletes was 14 percent lower than their eumenorrheic colleagues 7. The mean vertebral bone density in the amenorrheic athletes, with a mean age 25 years, was equivalent to that of an average 51-year-old woman. Importantly, this reduced bone density puts these amenorrheic athletes at increased risk for fractures. Warren et al. studied 75 professional ballet dancers, ages 18 to 36 years, and found that the incidence of stress fractures was twice as high among amenorrheic dancers than in those with regular periods 8. In a study of 17 elite

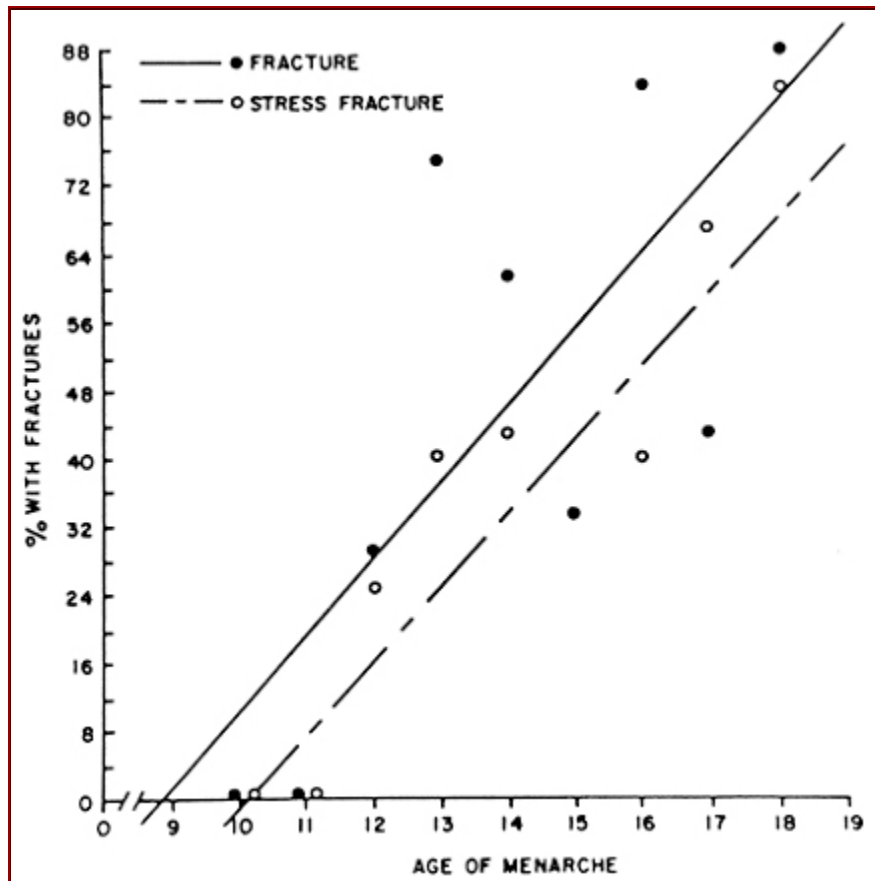


Figure 1. Relationship between age at menarche and the percentage of ballet dancers studied with fractures. Reprinted from the New England Journal of Medicine with permission from the Massachusetts Medical Society [8].

long distance runners, two-thirds of amenorrheic runners were found to have stress fractures, many at multiple sites. In contrast, only one of the eumenorrheic runners experienced a stress fracture 9. Delayed menarche as a result of excessive exercise results in striking vulnerability to stress fractures. Warren et al. demonstrated a linear relationship between age of menarche and prevalence of fractures in a group of ballet dancers. Delay of menarche to age 18 was associated with a nearly 90 percent risk for fractures (Figure 1) 8. Such interference with the normal pattern of gonadal steroidogenesis during puberty, during which approximately 90 percent of peak bone mass is formed, may therefore have particularly severe consequences on bone health.

One-third of women who have functional hypothalamic amenorrhea, such as related to simple weight loss, have vertebral bone densities of 2 standard deviations or more below the mean 10. Similarly, patients with hypothalamic or pituitary dysfunction from organic causes, such as radiation or surgery, with resultant estrogen deficiency due to GnRH or gonadotropin deficiency are also at risk for bone loss.

Anorexia nervosa results in much more severe bone loss than hypothalamic amenorrhea of other causes (Figure 2) 11, likely due to the effects of undernutrition directly on bone and on hormonal factors, such as insulin-like growth factor-I (IGF-I). The mean bone density in women with anorexia nervosa is two

standard deviations below the age-matched mean 12. In fact, bone density in many young women with anorexia nervosa is commonly comparable to that post-menopausal women in their 70's or 80's 10. This bone loss has potentially severe lifetime consequences. Rigotti et al. demonstrated a seven-fold increase in the risk of sustaining a non-spinal fracture compared with age-matched young women 13. Further, although bone density may increase with weight gain and resumption of menses, significant reduction in bone density may persist, increasing the risk for fractures in later life.

Medications that induce estrogen deficiency also result in osteopenia in women of reproductive age. These include GnRH agonists, which may be used to treat severe endometriosis or uterine myomas. GnRH agonist therapy has been shown to result in reduced spinal bone density after six months of therapy. The use of "add-back" norethindrone (10 mg/daily), norethisterone (1.2 mg/daily), or post-menopausal doses of estrogen replacement therapy plus medroxyprogesterone may reduce or prevent bone loss 14. However, these "add-back" regimens may also reduce the effectiveness of the GnRH agonist therapy. Long-term use of depot medroxyprogesterone acetate may also result in bone loss, presumably by causing estrogen deficiency. Cundy et al. compared spinal bone densities in 200 women using depot medroxyprogesterone acetate for contraception with those of 350 healthy controls of reproductive age and found significantly reduced bone density in the depot medroxyprogesterone acetate users. In addition, women who had used the medication for more than 15 years, or who had begun using it before the age of 21, had lower bone densities than women who had used it for a shorter duration¹⁵. These results suggest that duration of use may be important and that there may be a dose-response phenomenon.

Ovarian Failure

The onset of menopause in young women results in similar effects on bone as when the onset is later in life. Significant bone loss has been demonstrated in women with a history of surgical oophorectomy as well as with premature ovarian failure from other causes, including autoimmune disease, chemotherapy or idiopathic. Cann et al. demonstrated a 21 percent reduction in mean spine bone density in women with premature ovarian failure compared with age-matched controls with regular menstrual periods 2. As increasing numbers of young women undergo chemotherapy and survive into older age, this is likely to become an increasingly important public health issue.

Diagnosis

Although bone density testing is not recommended routinely for pre-menopausal women, it should be performed in women at risk for bone loss. In these patients, baseline bone density scans are indicated to assess bone density and risk for fractures. Annual follow-up scans to determine the trend in bone density over time and the effectiveness of therapy are also important. This is true even in women with normal bone densities at baseline, who may have sustained an unmeasured decline from an even higher level. Measurement of AP lumbar spine bone density is often most useful, because most metabolic diseases have a greater effect on trabecular than cortical bone. In addition, spinal bone density measurements have the greatest precision. Therefore, changes in bone density over time can be detected earlier at this site.

Therapy

Estrogen therapy has been shown to be effective in women with premature ovarian failure. One small placebo-controlled study also suggests that estrogen therapy may be effective in normal-weight women with functional hypothalamic amenorrhea 16. However, definitive data are lacking. In contrast, estrogen therapy is ineffective in some forms of amenorrheic bone loss, and is contraindicated in others. For example, in a randomized trial, Klibanski et al. demonstrated that estrogen therapy is largely ineffective in women with bone loss from anorexia nervosa 17. In addition, retrospective studies have shown that women with anorexia nervosa who have used estrogen in the past or are currently using estrogen do not have higher bone densities than those who have never used estrogen. The lack of effectiveness of estrogen in this population may be due to the overriding effects of undernutrition on bone health. In other groups, for example women with histories of breast cancer who have chemotherapy-induced hypoestrogenemic amenorrhea, estrogen therapy is contraindicated, and studies are underway to determine whether other therapies, such as bisphosphonates, are effective.

Bisphosphonates should be used with caution in women of reproductive age and only in those with severe bone loss. It is not known whether they are safe in pregnancy nor whether bisphosphonates secreted into breast milk are detrimental to nursing infants.

In women receiving GnRH agonist therapy, add-back gonadal steroid regimens have been shown to reduce or even prevent bone loss. However, they may reduce the effectiveness of the GnRH agonist therapy in treating conditions such as endometriosis. Intermittent PTH administration has also been shown to be effective in increasing bone density in this population 18. However, it is investigational and, in high doses, causes osteosarcomas in rodents. Therefore, the safety of long-term use or use in young women has not been established.

Conclusion

Measurement of bone density is indicated in young women at risk for bone loss secondary to hypoestrogenemic amenorrhea. This includes patients with functional hypothalamic amenorrhea, anorexia nervosa, hyperprolactinemia, and pituitary or hypothalamic lesions. In addition, a number of medications that induce hypoestrogenemia, including GnRH agonists and depot medroxyprogesterone cause bone loss. Bone loss during puberty can have particularly severe consequences because of its deleterious impact on the development on peak bone density. In addition, women who experience bone loss during their reproductive years enter menopause with reduced bone density and increased fracture risk. Therefore, early intervention, when safe and effective therapies are available, is critical.

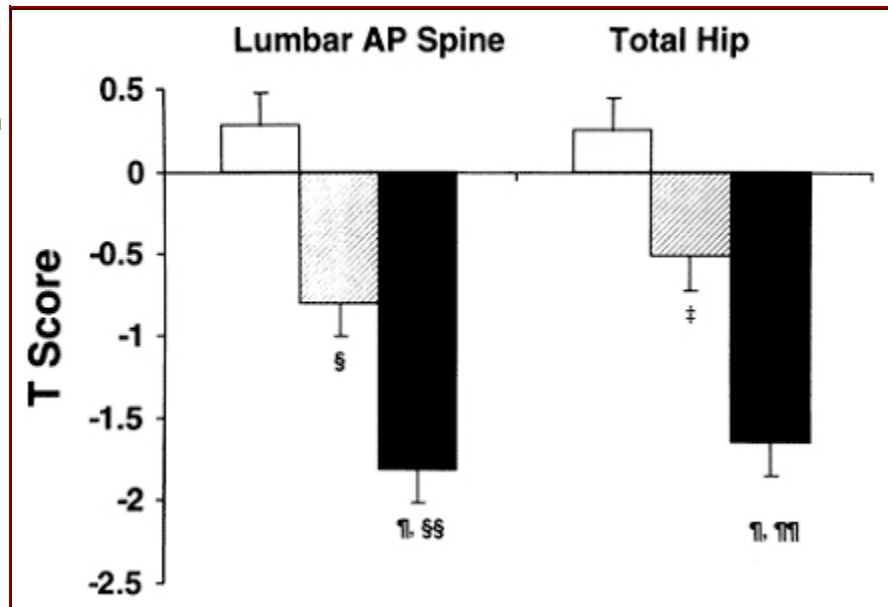


Figure 2. The T scores for lumbar and total hip bone densities in normal controls (white; n = 30) and patients with HA (hatched; n = 19) and AN (black; n = 30). , P < 0.01 vs. controls; §, P < 0.001 vs. controls; , P < 0.0001 vs. controls; §§, P < 0.001 vs. HA; , P < 0.0001 vs. HA. Results are the mean ± SEM. Reprinted from the Journal of Clinical Endocrinology and Metabolism with permission from the Endocrine Society [11].

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*** NEW PULLOUT FEATURE ***

~ PATIENT GUIDE ~

The Neuroendocrine Clinical Center is initiating a new patient education feature which will appear from time to time in this Bulletin. These will consist of a separate pullout section which can be reproduced and handed out to patients who have questions about the topic being addressed. This issue includes "Frequently Asked Questions About Transsphenoidal Surgery For Pituitary Adenomas: A Patient Guide". Authored by Brooke Swearingen, M.D., the

renowned expert pituitary surgeon at Massachusetts General Hospital, it answers the 15 most commonly asked questions by patients requiring transsphenoidal surgery for pituitary adenomas.

Frequently Asked Questions About [Transsphenoidal Surgery](#) For Pituitary Adenomas
A Patient Guide
by [Brooke Swearingen, M.D.](#)

Cushing's Disease after Successful Transsphenoidal Surgery - What to Expect and How to Manage
by: **Wesley P. Fairfield, M.D.**

Pituitary corticotrope adenomas overproduce adrenocorticotropin hormone (ACTH) resulting in Cushing's disease and account for 10-15% of all pituitary adenomas. Transsphenoidal surgery (TSS) is recognized as the primary therapy for the majority of patients diagnosed with Cushing's disease. Over 90% of patients who have microadenomas (tumor size < 10 mm) or no visible tumor on MRI are cured with TSS, if performed by an expert pituitary surgeon, and over 90% of these patients remain disease free at 10 years. Much is written about the challenges encountered in diagnosing and treating Cushing's disease. This article will focus instead on what endocrinologists and patients can expect after Cushing's disease has been cured surgically.

The normal regulation of cortisol secretion by the adrenal cortex involves a negative feedback cycle between the adrenal glands and the pituitary gland and hypothalamus. Corticotropin releasing hormone (CRH) is synthesized in the hypothalamic paraventricular nucleus and stimulates the release of ACTH from pituitary corticotrope cells. ACTH then stimulates the adrenal cortex to produce cortisol, an essential regulator of body composition and modulator of many different metabolic pathways. Cortisol indirectly regulates its own production by inhibiting hypothalamic CRH and pituitary ACTH production (see **Figure A**).

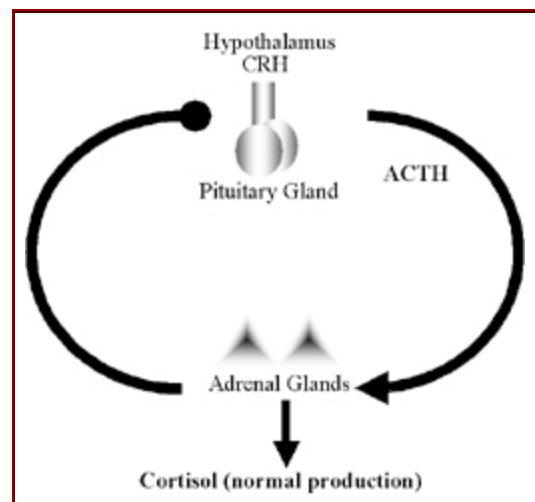


Figure A.

Excess production of cortisol by the adrenal glands results in the characteristic clinical features of Cushing's disease including increased central fat deposition, muscle fatigability and weakness, facial plethora, thinning of the skin with easy bruising and violaceous stretch marks, high blood pressure, glucose intolerance, osteopenia, menstrual irregularity, impotence and neuropsychiatric disturbances.

In Cushing's disease, the primary abnormality results from ACTH overproduction by pituitary tumor cells. Production of CRH and ACTH by the normal cells is profoundly suppressed by long-standing exposure to high cortisol levels (see **Figure B**). In a patient cured of Cushing's by TSS, the source of ACTH is removed. Cortisol levels plummet within 24-48 hours, as evidenced by very low morning blood cortisol levels and low 24 hour urinary free cortisol levels. Post-operatively, the suppressed normal corticotropes are unable to produce ACTH for some time, resulting in temporary adrenal insufficiency (see **Figure C**). Rarely, patients cured of their Cushing's disease may not develop adrenal insufficiency for 1-2 weeks post-operatively, exhibiting delayed evidence of cure.

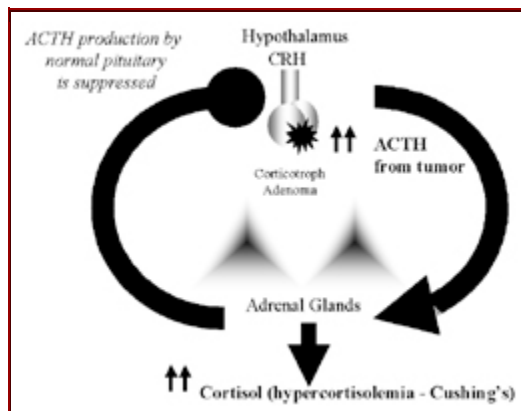


Figure B.

After surgery for Cushing's disease, patients collect 24-hour urine samples and have morning blood samples drawn for cortisol. Low levels, at or near the detection limit of the assay, suggest cure. In order to prevent patients from becoming symptomatic from steroid withdrawal, replacement is often given. Dexamethasone is used perioperatively because it does not cross-react with urine and blood measurements of cortisol. The ideal dose and taper depend on clinical features, including the severity of endogenous cortisol production preoperatively. The goal of post-operative steroid replacement is to titrate the patient down to a physiologic dose as possible to allow recovery from Cushing's, but without causing severe steroid withdrawal symptoms.

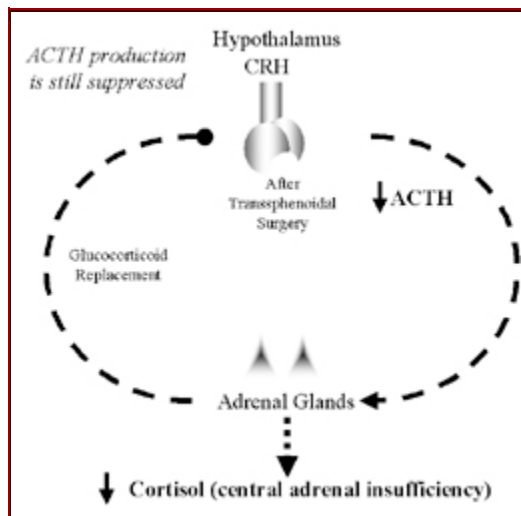


Figure C.

After post-operative blood and urine testing is complete, patients are switched to a glucocorticoid with an intermediate half-life such as prednisone. The dose of prednisone replacement post-operatively can be guided by the degree of hypercortisolemia observed pre-operatively. A typical dose initiated approximately 5 days after surgery (following completion of testing for cure) for a patient with moderate pre-operative elevations in urine free cortisol might consist of 7.5-10 mg of prednisone daily. Doses of prednisone ³7.5 mg can be split with 2/3 to 3/4 of the dose administered in the morning, and 1/4 to 1/3 of the dose in the mid-afternoon.

Post-operative relative adrenal insufficiency is often accompanied by lightheadedness, dizziness, nausea, vomiting, abdominal pain, fatigue and weight loss. Given that patients with Cushing's disease are accustomed to very high levels of cortisol, even a relative reduction in cortisol levels can result in symptoms of adrenal withdrawal. It is important to emphasize to the patient cured of Cushing's disease the importance of daily glucocorticoid replacement and the potential clinical consequences of untreated adrenal insufficiency. Because adrenal mineralocorticoid secretion is typically preserved in these patients, fludrocortisone is not required. Patients should be advised to wear a medical alert bracelet until their hypothalamic-pituitary-adrenal (HPA) axis recovers. In addition, they should be advised to double their steroid dose during illness, to receive parenteral glucocorticoids if unable to use orally, and to inform all health care providers that they are taking steroids. It often takes 6 months to 2 years for patients cured of their Cushing's to demonstrate an intact HPA axis and discontinue glucocorticoid replacement therapy. In

some cases, central adrenal insufficiency may be a permanent complication from surgery and lifelong replacement may be needed. The clinical features of Cushing's begin to improve as soon as the replacement dose is below the level of preoperative endogenous cortisol production.

After surgery, frequent contacts with the patient are advisable to optimize downward titration of glucocorticoid replacement. Patients are evaluated 4-6 weeks post-operatively for a more thorough assessment of pituitary function. As with all post-TSS patients, it is important to determine whether they have developed deficiency in adrenal, thyroid, sex steroid, or growth hormone production. Monitoring for diabetes insipidus and the Syndrome of Inappropriate Anti-Diuretic Hormone secretion is also necessary. Patients usually return several times the first 6 months and at least every 6 months thereafter in order to monitor for recurrent hypercortisolemia.

Tapering prednisone over the ensuing months can be one of the most challenging aspects in the management of Cushing's disease. This is related to the fact that there is no lab test which can determine whether the replacement dose is correct. Each reduction in the amount of prednisone may result in increases in fatigue and lethargy. It is important for patients to anticipate that they will most likely experience an extended period of time (from several weeks to several months) during which they may feel less well before starting to feel better. Once the dose is in the physiologic range (such as 4-5 mg of prednisone), the goal is to reduce it further, often on alternate days, to allow recovery of the HPA axis. Therapy with ≥ 5 mg or more of prednisone (or equivalent) daily may ameliorate symptoms but remains supraphysiologic for most patients and can delay recovery of the normal HPA axis.

When patients reach physiologic replacement (doses equivalent to prednisone 5 mg daily or less), additional testing may be performed to assess whether the HPA axis has returned to normal (**see Figure D**). A cortisol level greater than 18 mcg/dl in the morning or after Cortrosyn administration is generally accepted as evidence that pituitary control of the adrenal glands has recovered, provided the patient is not on medication which increases cortisol binding globulin, such as estrogen. Glucocorticoid replacement can then be discontinued. Patients need to be counseled that the typical recovery period is approximately one year, and that a healthy diet and exercise program are important. Those patients on medical therapy for hypertension or diabetes mellitus should be monitored carefully, as dose reductions may be needed whenever steroid doses are tapered. The recovery from Cushing's can be remarkable, with many patients returning to their pre-Cushing's physical and psychological health within 1-2 years.

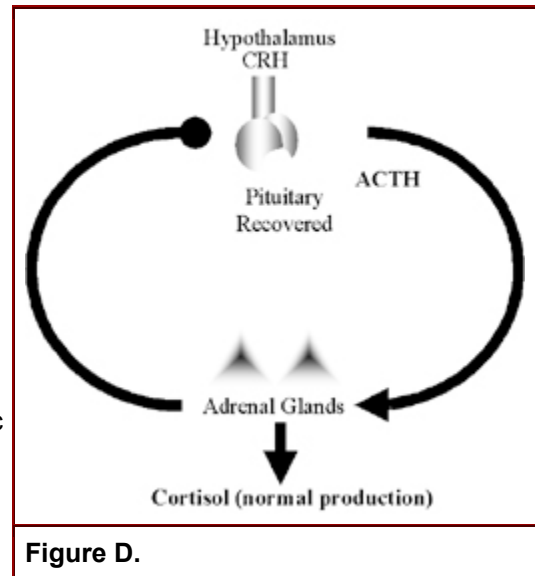


Figure D.

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