

ABSTRACTS

Insulin

Insulin sensitivity and sodium excretion in normotensive offspring and hypertensive patients.

Insulin resistance and hyperinsulinemia have been suggested to precede and promote hypertension, possibly by impairing sodium balance. We examined insulin sensitivity and the influence of acute hyperinsulinemia on sodium excretion after acute sodium loading in hypertension-prone individuals. Insulin sensitivity and sodium excretion in response to a 1,000-mL isotonic saline bolus were examined in 24 strictly normotensive offspring of at least 1 hypertensive parent, 19 controls without a family history of hypertension, and 8 untreated, young hypertensive patients. After the saline bolus, urinary sodium excretion was measured at baseline and during a 2-hour euglycemic, hyperinsulinemic clamp, and insulin sensitivity was determined. Insulin, pressor hormones, and atrial natriuretic peptide (ANP), were measured by radioimmunoassay (RIA) or high-performance liquid chromatography (HPLC). Results are given as means \pm SEM. Offspring and controls were well matched in age (23.7 \pm 0.5; 24.6 \pm 0.5 years, respectively), blood pressure (113.0 \pm 2.9/68.5 \pm 1.9; 110.6 \pm 2.5/71.7 \pm 2.2 mm Hg, respectively), bone mass index (BMI), plasma glucose, and lipid parameters. Insulin sensitivity index did not significantly differ between offspring and controls (0.102 \pm 0.012; 0.112 \pm 0.018 micromol/min/kg/body weight [BW]/pmol, respectively), but was markedly reduced in hypertensives (0.045 \pm 0.006, $P < .001$). In response to sodium loading, natriuresis increased significantly ($P < .05$) in both offspring and controls to a similar extent, despite the presence of hyperinsulinemia, but failed to increase in hypertensives. In normotensive offspring of hypertensive patients who have not yet developed any features of the metabolic syndrome, insulin sensitivity is not impaired. Acute hyperinsulinemia impairs the ability to excrete an acute sodium load in hypertensive patients, but not in offspring of hypertensives with normal insulin sensitivity.

Metabolism. 2001 Aug;50(8):929-35

Impaired glucose tolerance and cardiovascular disease: the possible role of post-prandial hyperglycemia.

There is increasing evidence that the post-prandial state is an important contributing factor in the development of atherosclerosis. In subjects with impaired glucose tolerance, whereas fasting glycemia is in reference range, the post-prandial phase is characterized by a rapid and large increase in blood glucose levels. The possibility that this post-prandial "hyperglycemic spike" may be relevant to the development of cardiovascular disease in these subjects has received recently much attention. The oral glucose tolerance test, although highly non-physiological, has been used largely as model of the post-prandial state, and epidemiological studies have shown that impaired oral glucose tolerance is associated with an increased risk of cardiovascular disease, because the glycemia level after 2 hours of the glucose challenge is a direct and independent risk factor. Most of the cardiovascular risk factors are modified in the post-prandial phase and are directly affected by an acute increase of glycemia. The mechanisms through which acute hyperglycemia exerts its effects may be identified in the production of free radicals, which favours the development of an endothelial dysfunction, a prothrombotic and proinflammatory condition. Future studies may evaluate whether correcting the post-prandial hyperglycemia in the impaired glucose tolerance state can form part of the strategy for the prevention and management of cardiovascular diseases in these subjects.

Am Heart J. 2004 May;147(5):803-7

Glucomannan: properties and therapeutic applications.

Glucomannan is a dietary fiber employed quite frequently in the western countries since two decades now, as its ingestion plays an important role in human health. However, eastern people have used this fiber for more than a thousand years. This dietary fiber is the main polysaccharide obtain from the tubers of the *Amorphophallus konjac* plant, a member of the family Araceae found in east Asia. The chemical structure of glucomannan consists, mainly, in mannose and glucose in the ratio 8:5 linked by beta (1-->4) glycosidic bonds. This soluble fiber has an extraordinarily high waterholding capacity, forming highly viscous solutions when dissolved in water. It has the highest molecular weight and viscosity of any known dietary fiber. It has been demonstrated that this product is highly effective in the treatment of obesity due to the satiety sensation that it produces; as a remedy for constipation, because it increases the faeces volume; as hypocholesterolemic agent, interfering in the transport of cholesterol and of bile acids and as hypoglycemic and hypoinsulinemic agent, probably, by delaying gastric emptying and slowing glucose delivery to the intestinal mucosa. To the beneficial properties of this fiber, several disadvantages can be added as the production of flatulence, abdominal pain, esophageal obstruction, lower gastrointestinal obstruction or even the possible modification of the bioavailability of other drugs. This paper reviews the main characteristics of glucomannan, as well as its properties, physiologic effects and therapeutic uses.

Nutr Hosp. 2004 Jan-Feb;19(1):45-50

Inhibition of insulin secretion as a new drug target in the treatment of metabolic disorders.

The pattern of insulin release is crucial for regulation of glucose and lipid haemostasis. Deficient insulin release causes hyperglycemia and diabetes, whereas excessive insulin release can give rise to serious metabolic disorders, such as nesidioblastosis (Persistent Hyperinsulinemic Hypoglycemia of Infancy, PHHI) and might also be closely associated with development of type 2 diabetes and obesity. Type 2 diabetes is characterized by fasting hyperinsulinemia, insulin resistance and impaired insulin release, i.e. reduced first phase insulin release and decreased insulin pulse mass. The beta cell function of patients with type 2 diabetes slowly declines and will ultimately result in beta cell failure and increasing degrees of hyperglycemia. Type 2 diabetes, in combination with obesity and cardiovascular disorders, forms the metabolic syndrome. It has been possible to improve beta cell function and viability in preclinical models of type 1 and type 2 diabetes by reducing insulin secretion to induce beta cell rest. Clinical studies have furthermore indicated that inhibitors of insulin release will be of benefit in treatment or prevention of diabetes and obesity. Pancreatic beta cells secrete insulin in response to increased metabolism and by stimulation of different receptors. The energy status of the beta cell controls insulin release via regulation of open probability of the ATP sensitive potassium (K(ATP)) channels to affect membrane potential and the intracellular calcium concentration [Ca(2+)](i). Other membrane bound receptors and ion channels and intracellular targets that modulate [Ca(2+)](i) will affect insulin release. Thus, insulin release is regulated by e.g. somatostatin receptors, GLP-1 receptors, muscarinic receptors, cholecystokinin receptors and adrenergic receptors. Although the relationship between hyperinsulinemia and certain metabolic diseases has been known for decades, only a few inhibitors of insulin release have been characterized in vitro and in vivo. These include the K (ATP) channel openers diazoxide and NN414 and the somatostatin receptor agonist octreotide.

Curr Med Chem. 2004 Jun;11(12):1595-615

Changes in sex hormone-binding globulin and testosterone during weight loss and weight maintenance in abdominally obese men with the metabolic syndrome.

BACKGROUND: Mild hypoandrogenism in men, usually defined by low levels of testosterone, is a peculiar feature of abdominal obesity that independently predicts the development of insulin resistance and diabetes mellitus. Little is known about the short- and long-term effects of weight loss on sex steroids in abdominally obese men, however. **OBJECTIVES:** We assessed the effect of rapid weight loss and sustained weight maintenance on the plasma concentrations of testosterone and other sex hormones in 58 abdominally obese men (age, 46.3 +/- 7.5 years; body mass index, 36.1 +/- 3.8 kg/m²; waist girth, 121 +/- 10 cm) with the metabolic syndrome. **RESULTS:** The men lost on average 16.3 +/- 4.5 kg during a 9-week very low-calorie diet (VLCD) and maintained 14.3 +/- 9.1 kg weight loss after a 12-month maintenance period (vs. baseline, p < 0.001). Sex hormone-binding globulin (SHBG) increased from 27.6 +/- 11.9 to 48.1 +/- 23.5 nmol/l during the VLCD but decreased to 32.6 +/- 12.9 nmol/l during weight maintenance, which was still higher than at baseline (p < 0.001). Free testosterone (fT) increased from 185 +/- 66 to 208 +/- 70 pmol/l (p = 0.002) during the VLCD and remained high after 1 year of weight maintenance (212 +/- 84 pmol/l, p = 0.002). Total testosterone levels followed a pattern intermediate between fT and SHBG. Plasma estradiol and dehydroepiandrosterone sulphate concentrations changed only transiently or not at all. **CONCLUSIONS:** Rapid weight loss with successful weight maintenance in abdominally obese men with the metabolic syndrome brings about a sustained increase in fT levels. The dramatic increase in SHBG attenuated initially during weight maintenance but remained elevated. These findings may be important with regard to prevention of progressive metabolic decompensation and cardiovascular disease associated with obesity and the metabolic syndrome.

Diabetes Obes Metab . 2004 May;6(3):208-15

ABSTRACTS

Thyroid

Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study.

BACKGROUND: Overt hypothyroidism has been found to be associated with cardiovascular disease. Whether subclinical hypothyroidism and thyroid autoimmunity are also risk factors for cardiovascular disease is controversial. **OBJECTIVE:** To investigate whether subclinical hypothyroidism and thyroid autoimmunity are associated with aortic atherosclerosis and myocardial infarction in postmenopausal women. **DESIGN:** Population-based cross-sectional study. **SETTING:** A district of Rotterdam, The Netherlands. **PARTICIPANTS:** Random sample of 1149 women (mean age \pm SD, 69.0 \pm 7.5 years) participating in the Rotterdam Study. **MEASUREMENTS:** Data on thyroid status, aortic atherosclerosis, and history of myocardial infarction were obtained at baseline. Subclinical hypothyroidism was defined as an elevated thyroid-stimulating hormone level (>4.0 mU/L) and a normal serum free thyroxine level (11 to 25 pmol/L [0.9 to 1.9 ng/dL]). In tests for antibodies to thyroid peroxidase, a serum level greater than 10 IU/mL was considered a positive result. **RESULTS:** Subclinical hypothyroidism was present in 10.8% of participants and was associated with a greater age-adjusted prevalence of aortic atherosclerosis (odds ratio, 1.7 [95% CI, 1.1 to 2.6]) and myocardial infarction (odds ratio, 2.3 [CI, 1.3 to 4.0]). Additional adjustment for body mass index, total and high-density lipoprotein cholesterol level, blood pressure, and smoking status, as well as exclusion of women who took beta-blockers, did not affect these estimates. Associations were slightly stronger in women who had subclinical hypothyroidism and antibodies to thyroid peroxidase (odds ratio for aortic atherosclerosis, 1.9 [CI, 1.1 to 3.6]; odds ratio for myocardial infarction, 3.1 [CI, 1.5 to 6.3]). No association was found between thyroid autoimmunity itself and cardiovascular disease. The population attributable risk percentage for subclinical hypothyroidism associated with myocardial infarction was within the range of that for known major risk factors for cardiovascular disease. **CONCLUSION:** Subclinical hypothyroidism is a strong indicator of risk for atherosclerosis and myocardial infarction in elderly women.

Ann Intern Med. 2000 Feb 15;132(4):270-8

Epidemiology and prevention of clinical and subclinical hypothyroidism.

Iodine deficiency is the most common cause of hypothyroidism worldwide. In persons living in iodine-replete areas, causes are congenital, spontaneous because of chronic autoimmune disease (atrophic autoimmune thyroiditis or goitrous autoimmune thyroiditis [Hashimoto's thyroiditis]), or iatrogenic because of goitrogens, drugs, or destructive treatment for thyrotoxicosis. Screening for congenital hypothyroidism exists and its use prevents mental retardation. The prevalence of spontaneous hypothyroidism is between 1% and 2% and is more common in older women and 10 times more common in women than in men. A significant proportion of subjects have asymptomatic chronic autoimmune thyroiditis and 8% of women (10% of women over 55 years of age) and 3% of men have subclinical hypothyroidism. Approximately one third of patients with newly diagnosed overt hypothyroidism have received destructive therapy for hyperthyroidism and indefinite surveillance is required. There is not much that can be done to prevent the occurrence of spontaneous autoimmune hypothyroidism, but if identified early, something can be done to prevent progression to overt disease. Controversy exists as to whether healthy adults would benefit from screening for autoimmune thyroid disease because a significant proportion of subjects tested will have evidence of mild thyroid failure. Case finding in women at menopause or visiting a primary care physician with nonspecific symptoms appears justified.

Thyroid. 2002 Oct;12(10):839-47

Effect of subclinical hypothyroidism and obesity on whole-body and regional bone mineral content.

OBJECTIVE: The present investigation was aimed to evaluate the effect of subclinical hypothyroidism and obesity on bone mineral content (BMC) in different body segments. **METHODS:** Thirty-two premenopausal women (age: 37 \pm 9.9 years), with a wide range in body mass index (BMI), were studied. Subclinical hypothyroidism was defined by a basal TSH \geq 4 microU/l and/or a TRH-stimulated peak \geq 30 microU/l. For each subject, weight, height, BMI (weight/height²) and the waist/hip ratio were measured. Total BMC, total bone mineral density (BMD), leg BMC, leg BMD, trunk BMC, trunk BMD, arm BMC and arm BMD were determined using dual-energy X-ray absorptiometry. Thyroid function (basal and TRH-stimulated TSH, free T₃ and free T₄) were determined from fasting blood samples for all subjects. **RESULTS:** Anova was conducted within all the groups to observe the effect of thyroid status and/or obesity on BMC and BMD. There was no statistical difference for age. Total BMC was affected by obesity ($p < 0.05$) but not by thyroid status, BMD of the legs was significantly influenced both by thyroid function and obesity ($p < 0.01$); total BMD was affected by hypothyroid status ($p < 0.05$). A direct relationship between leg BMD and TSH was demonstrated. **CONCLUSION:** Subclinical thyroid hypofunction and obesity seem to affect BMD differently in the body segments. An influence of gravitational force seems necessary in order to make evident the effect of subclinical hypothyroidism on bone. A condition of subclinical hypothyroidism should be considered when evaluating subjects for osteoporosis, since a BMD measured at the femoral neck may induce underestimation of initial osteoporosis.

Horm Res. 2002;57(3-4):79-84

The Colorado thyroid disease prevalence study.

CONTEXT: The prevalence of abnormal thyroid function in the United States and the significance of thyroid dysfunction remain controversial. Systemic effects of abnormal thyroid function have not been fully delineated, particularly in cases of mild thyroid failure. Also, the relationship between traditional hypothyroid symptoms and biochemical thyroid function is unclear.

OBJECTIVE: To determine the prevalence of abnormal thyroid function and the relationship between (1) abnormal thyroid function and lipid levels and (2) abnormal thyroid function and symptoms using modern and sensitive thyroid tests. DESIGN: Cross-sectional study. PARTICIPANTS: Participants in a statewide health fair in Colorado, 1995 (N = 25 862). MAIN OUTCOME MEASURES: Serum thyrotropin (thyroid-stimulating hormone [TSH]) and total thyroxine (T4) concentrations, serum lipid levels, and responses to a hypothyroid symptoms questionnaire. RESULTS: The prevalence of elevated TSH levels (normal range, 0.3-5.1 mIU/L) in this population was 9.5%, and the prevalence of decreased TSH levels was 2.2%. Forty percent of patients taking thyroid medications had abnormal TSH levels. Lipid levels increased in a graded fashion as thyroid function declined. Also, the mean total cholesterol and low-density lipoprotein cholesterol levels of subjects with TSH values between 5.1 and 10 mIU/L were significantly greater than the corresponding mean lipid levels in euthyroid subjects. Symptoms were reported more often in hypothyroid vs euthyroid individuals, but individual symptom sensitivities were low. CONCLUSIONS: The prevalence of abnormal biochemical thyroid function reported here is substantial and confirms previous reports in smaller populations. Among patients taking thyroid medication, only 60% were within the normal range of TSH. Modest elevations of TSH corresponded to changes in lipid levels that may affect cardiovascular health. Individual symptoms were not very sensitive, but patients who report multiple thyroid symptoms warrant serum thyroid testing. These results confirm that thyroid dysfunction is common, may often go undetected, and may be associated with adverse health outcomes that can be avoided by serum TSH measurement.

Arch Intern Med. 2000 Feb 28;160(4):526-34

TSH-controlled L-thyroxine therapy reduces cholesterol levels and clinical symptoms in subclinical hypothyroidism: a double blind, placebo-controlled trial (Basel Thyroid Study).

This study evaluated the effect of physiological, TSH-guided, L-thyroxine treatment on serum lipids and clinical symptoms in patients with subclinical hypothyroidism. Sixty-six women with proven subclinical hypothyroidism (TSH, 11.7 +/- 0.8 mIU/liter) were randomly assigned to receive L-thyroxine or placebo for 48 wk. Individual L-thyroxine replacement (mean dose, 85.5 +/- 4.3 microg/d) was performed based on blinded TSH monitoring, resulting in euthyroid TSH levels (3.1 +/- 0.3 mIU/liter). Lipid concentrations and clinical scores were measured before and after treatment. Sixty-three of 66 patients completed the study. In the L-thyroxine group (n = 31) total cholesterol and low density lipoprotein cholesterol were significantly reduced [-0.24 mmol/liter, 3.8% (P = 0.015) and -0.33 mmol/liter, 8.2% (P = 0.004), respectively]. Low density lipoprotein cholesterol decrease was more pronounced in patients with TSH levels greater than 12 mIU/liter or elevated low density lipoprotein cholesterol levels at baseline. A significant decrease in apolipoprotein B-100 concentrations was observed (P = 0.037), whereas high density lipoprotein cholesterol, triglycerides, apolipoprotein AI, and lipoprotein(a) levels remained unchanged. Two clinical scores assessing symptoms and signs of hypothyroidism (Billewicz and Zulewski scores) improved significantly (P = 0.02). This is the first double blind study to show that physiological L-thyroxine replacement in patients with subclinical hypothyroidism has a beneficial effect on low density lipoprotein cholesterol levels and clinical symptoms of hypothyroidism. An important risk reduction of cardiovascular mortality of 9-31% can be estimated from the observed improvement in low density lipoprotein cholesterol.

J Clin Endocrinol Metab. 2001 Oct;86(10):4860-6

ABSTRACTS

Migraine

A correlation between migraine, histamine and immunoglobulin e.

Although migraine affects about 15% of population and many studies have been performed to find the mechanism and a successful management, the physiopathology of migraine is still largely unknown. The possibility of an immunoglobulin E (IgE)-mediated allergic mechanism and the role of histamine remain controversial. The aim of the present study was to evaluate serum total IgE and histamine levels in migraine patients and the influence of allergy on them. Seventy patients (18-58 years) with migraine without aura were divided into two groups according to their history of allergy (60% with and 40% without allergy). Serum samples were collected during fasting without allowing any premedication during the two periods of attack and remission. There was a control group containing 45 healthy volunteers. Serum total IgE and histamine levels were measured by enzyme-linked immunosorbent assay and fluorimetric methods, respectively. Mean and standard errors of serum histamine (ng/ml) and total IgE (IU/ml) levels were found in the control group to be 48.16 +/- 2.70 and 38.31 +/- 3.20, in the migraine with allergy group 159.11 +/- 4.60 and 303.30 +/- 42.50 and in the migraine without allergy group 105.01 +/- 8.50 and 79.07 +/- 2.70, respectively. Total IgE levels in migraine with allergy group were found to be significantly ($P < 0.0001$) above that in the control and another group, suggesting an influence of an IgE-mediated mechanism on migraine. Although the plasma histamine levels, which were significantly elevated ($P < 0.0001$) in patients with migraine, both during headache and symptom-free periods, when compared with the control group, indicate that there is an increased susceptibility to histamine in allergic conditions, this molecule has also an unrelated role in migraine. The relationship between allergy and migraine can be based, in part, on an IgE-mediated mechanism, and histamine release plays an important role. Thus, the avoidance of allergic conditions in migraine patients may be a simple, helpful way for prophylaxis or their treatment.

Scand J Immunol . 2003 Mar;57(3):286-90

One-year prevalence of migraine in Austria : a nation-wide survey.

This study presents the first nation-wide survey of migraine in Austria . A sample of 997 Austrian > or = 15 years old were interviewed personally (face-to-face) in a random sample in the whole country. Diagnosis of migraine was based on the International Headache Society (IHS) classification. Of the Austrian adult population 10.2% were identified to suffer from IHS migraine, 5.6% from migraine without aura, 2.3% from migraine with aura and 2.3% from borderline migraine. Another 8.5% have possible migraine. Other primary headaches were reported in 30.7%. Sex, age, working status and region were found to be the main demographic influencing factors. Further influences were stress, spinal column problems or weather changes. The most used acute medications were over-the-counter drugs, doctor attendance rate was very low. Working people with migraine dropped out of work 14 days per year, which adds up to 6.8 million working days per year. This remains a substantial economic factor. The findings indicate that migraine sufferers in Austria need to be more informed about their illness and what to do against it, especially encouraging doctor visits.

Cephalalgia . 2003 May;23(4):280-6

Pathophysiology, epidemiology, and impact of migraine.

Despite a decade of progress, migraine headache remains prevalent, disabling, underdiagnosed, and undertreated in the United States . Migraine affects approximately 12% of the population, and the economic burden in terms of annual cost of labor lost to migraine disability is between \$5.6 and \$17.2 billion. The threshold for migraine may be genetically determined, although recent genetic and neurophysiologic studies point to migraine as possibly a channelopathy. Cerebral cortical and brain stem changes occur in migraine. Head pain and associated symptoms of migraine can be explained by activation of the trigeminal vascular system. Evidence has also been accumulated that suggests the release of nitric oxide is an important trigger mechanism. Introduction of the triptans has dramatically advanced acute migraine pharmacotherapy, and preventive therapy has greatly improved; however, public health initiatives may be needed to further advance diagnosis and treatment of this common and disabling disorder.

Clin Cornerstone. 2001;4(3):1-17

The early use of ergotamine in migraine. Edward Woakes' report of 1868, its theoretical and practical background and its international reception.

Although ergot had been used in obstetrics for several centuries, it was proposed for the treatment of migraine only in the 19th century. The British ENT-surgeon Edward Woakes (1837-1912) recommended ergot as a vasoconstricting agent for migraine and other neurogenic conditions associated with vasodilatation in 1868. He subscribed to the theory of vasodilatation by sympathetic deficit, presented in the early 1850s by Brown-Sequard and Claude Bernard. Du Bois-Reymond proposed vasoconstriction by sympathetic overactivity as the cause of migraine in 1860; Brown-Sequard opposed this in favour of vasodilatation. Vasodilatation due to sympathetic deficit in migraine was again supported by Mollendorf, with clinical evidence, in 1867. Woakes' paper of 1868

introduced ergot as a vasoconstrictor for the same condition. Reception abroad was prompt. A German version appeared in 1869, and Eulenburg cited Woakes in his textbook of 1871. Eulenburg presented the use of ergot for migraine as a routine measure in the second edition of his textbook in 1878, and in a paper published in 1883. The method was internationally accepted, but it became really popular only after the isolation of pure ergotamine in 1918, resulting in the first reliable compounds with stable properties and predictable effects. Contrary to Woakes' theory, in the early 20th century ergot was used for migraine because of its well-documented adrenolytic properties, as migraine was by then again believed to be a sympathotonic and vasospastic condition.

Cephalalgia . 2002 Oct;22(8):686-91

Central 5-HT receptor hypersensitivity in migraine without aura.

Serotonin has long been implicated as a key neurotransmitter in migraine. There is a dearth of research specifically examining 5-HT_{1A} receptor sensitivity in migraine despite the importance of this receptor in regulating central serotonergic tone. In this study we examined the hypothesis that migraine without aura is associated with hypersensitivity of central 5-HT_{1A} receptors, using a 5-HT_{1A} neuroendocrine challenge drug and comparing serum prolactin responses between a test group with migraine and a matched group of healthy controls. Twelve female subjects fulfilling International Headache Society (IHS) criteria for migraine without aura were evaluated. Following an overnight fast, subjects presented for testing at 9am . An intravenous canula was inserted and serum prolactin was assessed at baseline and every 30 min for 3 h following a single dose of 30 mg oral buspirone, a 5-HT_{1A}-receptor agonist. Subjects were assessed during the first 5 days of the menstrual cycle. No subjects were taking psychotropic medication or migraine prophylactic treatment. Patients with current or previous psychiatric disorder, daily headache or analgesic overuse were excluded. 16 healthy female volunteers matched for age and menstrual status were also evaluated and served as controls. There was no difference in baseline prolactin between groups. There was a significant rise in prolactin following buspirone in both groups. Subjects with migraine had a significantly increased prolactin response to buspirone (delta max) compared to controls ($P < 0.001$). This study supports the hypothesis that migraine without aura is associated with a relative hypersensitivity of central 5-HT_{1A} receptors. This is of relevance given the role of the 5-HT_{1A} receptor in controlling raphe 5-HT tone and in the possible association between migraine and anxiety and depression.

Cephalalgia. 2003 Feb;23(1):29-34

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