

PREPARATION FOR DIAGNOSIS OF THE METABOLIC SYNDROME AND DISEASES INCLUDING THE SYNDROME

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BACKGROUND

The metabolic syndrome is characterized by an increased amount of adipose tissue inside the abdominal cavity (popularly called belly fatness), insulin resistance with increased risk of developing senile diabetes, i.e. diabetes type II (=NIDDM, non-insulin dependent diabetes mellitus), high levels of blood fats and high blood pressure. Parallel to this is an increased risk of coronary, apoplexy, sudden death and other arteriosclerotic conditions.

A hypothetical explanation to the metabolic syndrome could be an overproduction of cortisol, a stress hormone which causes an accumulation of fat inside the abdominal cavity, and insulin resistance. Theoretically this could, through secondary metabolic effects, explain the other disorders related to the metabolic syndrome.

In *Metabolism*, vol. 41, No 8, 1992, pages 882–886, it is shown that belly fat women have higher secretion of cortisol than “evenly fat” women. The same work describes the effects of acute mental stress on the production of cortisol. It was shown that belly fat women, at a given stress signal, produced more cortisol than “evenly fat” women. This suggested, but did not prove, that there may be a relationship between stress and belly obesity. A dexamethasone inhibitor test was carried out with 1 mg dexamethasone and subsequent measurement of cortisol content in serum. No difference in inhibitory effect on the production of cortisol could be found between the groups of belly fat women and evenly fat women and standard values.

Cortisol analogues, e.g. dexamethasone, have for many years been used to track so called endogenous (often hereditary) depressions in humans. The mechanism behind the test is however so far unknown.

OBJECT OF THE INVENTION AND MOST IMPORTANT CHARACTERISTICS

The object of the present invention is to find a diagnostic test by which individuals, running the risk of being affected by one or more of the symptoms and/or conditions characteristic to the above described metabolic syndrome, can be identified at an early stage. In the present invention this is accomplished by a diagnostic system, which as an active substance has cortisol agonists of a dose in an interval in which a difference in the inhibitory effect of the autonomous cortisol production between individuals with the metabolic syndrome or one or more of the related risk/conditions and normal values are obtained. Preferably the cortisol agonist is a synthetic cortisol analogues with a glucocorticoidal and/or mineral corticoidal effect, e.g. dexamethasone. The invention also concerns a diagnostic system for the purpose of diagnosing the metabolic syndrome, comprising a cortisol agonist of a dosage described above, and an agent for measuring the content of cortisol in saliva or serum.

DESCRIPTION OF DRAWINGS

FIG. 1 shows the hormone signal axis along the cerebrum-hypothalamus-hypophysis-adrenal.

FIG. 2 shows serum cortisol readings after different doses of dexamethasone given to two groups of individuals, divided according to their body fat distribution.

DESCRIPTION OF THE INVENTION

The purpose of the invention is the novel medical use of cortisol agonists, which here refers to all synthetic cortisol agonists with glucocorticoidal and/or mineral corticoidal effects. The novel medical usage is as a diagnostic preparation for diagnosing the metabolic syndrome and related conditions such as belly fatness, insulin resistance, high blood fat and high blood pressure.

The invention emanates from the hypothesis that during chronic negative stress the hormone signal axis along cerebrum-hypothalamus-hypophysis-adrenal is strengthened, which secondarily likely leads to a down regulation of the GR (glucocorticoidal)—and/or MR (mineral corticoidal)—receptors (cf. Figure). This in turn could lead to a vicious circle where the inhibitory effect of GR and/or MR on CRF (cartocotropin releasing factor, a signal substance from hypothalamus stimulating the ACTH release from hypophysis)—secretion would attenuate. As a result of this the cortisol inhibition via the GR- and/or MR receptors would be weakened and thus, every given stress situation would lead to higher cortisol secretion (cf. Figure).

In an attempt to test the above hypothesis we have in a scientific study measured the basal concentration of cortisol and then given dexamethasone, a synthetic cortisol analogue, that is a synthetic hormone substance with the effect of cortisol, at varying dosage. The idea was that patients having the GR and/or MR receptors down regulated should have their cortisol production less inhibited when using dexamethasone (an example of a synthetic cortisol analogue) at low doses, particularly when compared to the initial value, which often may be somewhat higher in healthy persons. The inferior inhibitory effect is thus related to the uninhibited cortisol production. When tested on persons having normal weight, general overweight and on belly fat persons, we found that the hypothesis agrees with reality. Belly fatness is fatness inside the abdominal cavity in contrast to general fatness. Those belly fat individuals had also significantly lower basal cortisol values at 8.00 o'clock when comparing serum cortisol with the control. Values over or equal to 400 nmol/l were here considered normal values.

The trial group was 22 men between 40 and 60 years. Eight of them were not fat according to the BMI (body mass index) definition $<25 \text{ kg/m}^2$ and 14 were fat with a BMI >25 . 12 men had a WHR (waist hip ratio) <1.0 and 10 had a WHR >1.0 .

Dexamethasone was administered in doses of 0.05, 0.125, 0.25 and 0.5 in an arbitrary order with 1 week intervals.

Dexamethasone was taken at 22.00 o'clock and the cortisol content was measured at 8.00 o'clock on the following morning. To establish the inhibitory effect at least 3 hours and at most 24 hours should pass between the intake of the cortisol agonist and measurement of the cortisol content.

FIG. 2 shows differences (delta values) between measured cortisol content and basal values (not inhibited) after different doses of dexamethasone. A comparison has been made between men with WHR <1.0 (open squares) and men with WHR >1.0 (filled squares).

Belly fat individuals were thus shown to have significantly inferior inhibition by dexamethasone (a synthetic cortisol analogue) at low doses. The effect was found at doses between 0.05 and 0.5 mg. This should be compared to the above-mentioned test in which no effect could be established at a dose of 1 mg dexamethasone. Thus it has now surprisingly been shown that with low doses of dexamethasone a significantly inferior inhibition of the autoproduction of cortisol by belly fat individuals is obtained.