DESCRIPTION OF RESEARCH PROPOSAL

PROPOSED TITLE OF DOCTORAL THESIS:

Resistin and its role in vivo and in vitro in cardiological, diabetic, obese patients as well as in individuals with metabolic syndrome risk factors. Relationship to other inflammatory factors, adipose tissue hormones, and insulin resistance. Study of oxidative stress parameters. Effect of other physiological and pharmaceutical factors.

Reference to the study literature on resistin

- **Adipose tissue**

Adipose tissue is a specific type of connective tissue in which adipocytes predominate. The main roles of adipose tissue are energy storage, "insulation" to avoid heat loss through the skin and the creation of protective layers around specific organs.[3,4] At the same time, however, adipocytes are capable of regulating functions such as reproduction, immune response, blood pressure control, coagulation, fibrinolysis and angiogenesis. [5,6] Adipose tissue is therefore considered an endocrine gland working in close cooperation with the central nervous system through expression of receptors for both pituitary hormones and hypothalamic releasing agents [6,7,8]

In adipocytes are produced and secreted a variety of proteins called cytokines or adipokines with remarkable structural and functional heterogeneity. Some of them are TNF-a, IL-6, MCP-1, proteins involved in hemostasis (PAI-1, TF), blood pressure regulation (angiotensinogen), glucose homeostasis (adiponectin), regulation of food intake (leptin), angiogenesis (VEGF), but also many other substances (such as resistin, visfatin, apelin). [12,13,14]

But in the state of obesity the balance of production of these substances is disturbed. In obesity, adipose tissue becomes dysfunctional, resulting in the overproduction of pro-inflammatory lipokines and lower production of anti-inflammatory lipokines. glucose and type 2 diabetes, dyslipidaemia, hypertension and early heart disease [15,16,17]

- **RESISTIN**

One of the main substances secreted by adipose tissue and macrophages in humans is resistin. There are three physiological roles suggested for resistin:

1. participation in the regulation of metabolism in general and in particular of glucose and the development of insulin resistance
2. the mechanism of lipogenesis and
3. involvement in inflammatory processes. [20.21]

The term resistine was originally suggested for its role in insulin resistance while its serum concentration ranges from 7-22 ng / ml. Resistin belongs to a family of cysteine-rich proteins called RELMs (resistin-like molecules). Human resistin consists of 108 amino acids, with a molecular weight of 12.5 kDa. [27, 28, 29]

Resistin expression is increased in response to growth hormone, hyperglycaemia, dexamethasone, endothelin-1, PPARα, male sex hormones, neuropeptide Y and aging, while decreasing in response to insulin, thyroid hormones, thiazolidinedione, epinephrine, isoproterenol and PPARγ.[38.43] Higher concentrations of resistin have been observed in women according to studies in healthy volunteers. [38.39,44]

Resistin is likely to be involved in food intake awareness, as resistin mRNA levels are decreased during fasting and increased after eating, following both glucose and insulin concentrations. [46,47] It has been reported that resistin is also expressed in the hypothalamus and is capable of activating hypothalamic neurons. According to that resistin is a potential contributor to hypothalamic eating disorders (anorexia), similar to leptin and insulin. [48,49,50]

Some studies have linked insulin resistance and diabetes to resistin levels, but others have found no association. There are currently many questions and few answers regarding the role of resistin in metabolism. In addition, the importance of resistin in plasma and its association with other biological parameters remains unclear at present. [45,61,62]

Plasma resistin concentration is also found to be elevated in patients with heart failure, with levels of resistin to be directly related to the severity of heart failure, suggesting a correlation between them. [24,25,26]

Recent studies show that there is a correlation between levels of resistin and heart disease [47,48,49.63] For example, women with coronary heart disease have high levels of resistin. What is the role of resistin in the development of the disease remains unknown, although in patients with atherothrombotic stroke and high resistin levels are associated with increased mortality risk within 5 years. [50,51,64] Also increased levels of resistin in patients with heart failure is correlated with the severity of their heart failure. [72,75,76] Although these studies show no cause-and-effect relationship, elevated plasma resistin levels appear to be an indicator of poor prognosis in patients with cardiovascular disease [52,63,64,65].

Resistin expression is stimulated by TNF-a and IL-6, both of which are elevated in obesity, which provides an explanation for the elevated levels of resistin in obesity. Resistin increases endothelin-1 release, which causes endothelial dysfunction. Resistin also increases the expression of VCAM-1 and MCP-1, both of which are involved in premature atheromatosis. It has also been shown that high plasma resistin levels are associated with an increased risk of hypertension in non-diabetic women [69,70,72]

The therapeutic potential of lipokines in the treatment of insulin resistance, endothelial dysfunction, obesity, eating disorders, the development of atheromatosis as well as in the treatment of type 1 and type 2 diabetes are still under investigation. But it is a promising field of action.

The purpose of our study is to evaluate the levels of resistin in patients with cardiovascular disease, diabetics, obese and metabolic syndrome patients, to determine if there is any association with diagnosis, prognosis, progression or treatment. of their disease. Look for possible links to other physiological or pharmaceutical factors in the above diseases. Note whether other factors in vitro and in vivo may affect resistin levels or disease progression.

Research project methodology

1. **Selection of patients**

- Selection of patients with heart failure (n = 30) without obesity or metabolic syndrome and without diabetes
- Selection of patients with type II diabetes without heart disease and obesity (n = 30).
- Selection of patients with obesity without diabetes or heart disease (n = 30)
- Selection of people with metabolic syndrome without a diagnosis of heart disease, diabetes, and overweight (n = 30)
- Selection of patients with eating disorders (bulimia, anorexia nervosa)
- Selection of healthy individuals in the age range corresponding to the patient group (n = 30)

2. **Blood tests**

   General haematological (general blood, CRP), general biochemical control (electrolytes, fasting sugar, glycosylated hemoglobin, urea, creatinine, transaminases, alkaline phosphatase). Estimation of lipid profile. Hemostatic control assessment. Also measuring Resistin levels (Elisa).

3. **3. Oxidative stress measurement (serinth device) ***

   Oxidative stress is associated with uncontrolled oxidation of biomolecules by exogenous sources (UV, ozone or environmental contamination) as well as endogenous factors (ROS - Reactive Oxygen Species). The measurements will be made using the Serinth device in the physiology laboratory at the University of Western Attica.

4. **Testing for haemostasis and insulin resistance**

   Measurement of basic parameters of hemostasis (screening test) and measurement of insulin resistance

5. **Monitoring the effect of medication**

   It will be observed if any medication has an effect on resistin levels and which in relation to individuals in the same group who do not receive appropriate treatment as well as to individuals in the healthy population.

6. **Correlations between clinical and laboratory indicators.**

7. **Specific association of resistin, inflammatory and hemostatic parameters.**

   Level correlations will be made to the patient groups as far as possible before and after each treatment.

8. **Statistical processing.**

   Statistical processing of the results will take into account demographics such as the age and sex of each individual in order to determine the effect of these parameters.

9. **Time structure of the research project**

   Patient groups are initially separated and evaluated.

   Subsequently, measurements are made per group initially and if possible after the outcome of each treatment process. The first two years will serve to collect blood samples correctly. Then all samples will be counted for the above parameters to be statistically evaluated as groups and as a whole.

10. **Expected results**

    We expect that there will be statistical differences in some groups in relation to healthy individuals and between them, to clarify a clear relationship between resistin and certain pathologies and its biological role.

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