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Reduce cardiovascular risk through close follow up of the metabolic syndrome during menopause in women: a possible goal

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Summary

Women in menopausal syndrome (MS) have a major risk of CV events than fertile women. Menopausal syndrome and metabolic syndrome are often associated, having a common pathogenetic factor as hyperinsulinemia. The present study was aimed to evaluate the reduction of CV risk factors of the metabolic syndrome in women in MS and diabetes trough a composite therapeutic approach based on lifestyle changes and multiple medication (anorectic drugs, insulin sensitizers, statins, fibrates, anti-hypertensives). Results show that after treatment period a significant reduction of BMI, HDL-cholesterol, triglycerides, diastolic blood pressure and fasting blood glucose, as well as a significant reduction of score of relative cardiovascular risk.

Riassunto

Le donne in menopausa hanno un rischio di eventi cardiovascolari significativamente superiore a quello di donne in età fertile. Spesso menopausa e sindrome metabolica sono associate, incrementando così il rischio di eventi CV. Scopo di questo studio è stato quello di verificare l'efficacia di un trattamento combinato sia sullo stile di vita che farmacologico (anoressanti, insulino-sensibilizzanti, statine, fibrati, antipertensivi) in una coorte di donne diabetiche in menopausa e con sindrome metabolica. I risultati indicano una significativa efficacia del trattamento su BMI, HDL-colesterolo, trigliceridi, pressione sistolica e diastolica, glicemia a digiuno, realizzando una significativa riduzione del punteggio di rischio CV.

Introduction and scientific background

Already data from the Framingham Heart Study, started in 1947, show that European women in menopausal age have a coronary risk four times higher than fertile women, and the risk is greater as is the premature menopause. The same coronary artery disease, that in men takes at least 30 years to set in, develops in women in a period of 10-15 years. For this reason we can say that in post-menopausal an increasing percentage of the relative risk for ischemic heart disease is much greater than other typical climacteric disorders.

The path through which the menopausal hypoestrogenism can produce this "accelerated disease" in women, is the same through which the insulin resistance(namely a reduced response from the biological tissue to insulin) acts to generate the changes that are part of the so-called metabolic syndrome.

Further confirmation of the physiological interaction of these two conditions, is provided by the epidemiological importance of the Third National Health and Nutrition Examination Survey (NHANES). Estimating the prevalence of metabolic syndrome according to NCEP criteria, it showed that the age-specific proportion of that condition is increasing rapidly, resulting in excess of 30% in 50 years old persons and above 40% after 60 years old. Therefore, if we consider that the severity of this syndrome is related to an extent directly proportional to the risk of cardiovascular events, it is more than mere speculation's sake to deepen the relationship between the pathophysiological menopause and the natural history of

the metabolic syndrome.

The term metabolic syndrome, though recent (defined in 1998 by the WHO) is very effective in defining the set of clinical and / or laboratory changes that have as common denominator the insulin resistance. In order to give the metabolic syndrome a "global" importance, well illustrated by these epidemiological data, a decisive role has the adoption, in recent years, of the National Cholesterol Education Program diagnostic criteria (NCEP, ATP III, 2001), whose value was to have made it possible to identify subjects at risk, basing on the detection of simple and routine parameters. Indeed the success of such a clinic "formula" consists in its ability to translate into a genuine instrument of global prediction, accessible to any doctor beyond unnecessary specialist compartmentalisations.

From a strictly physiopathological view, insulin resistance is the real fulcrum around which the just defined metabolic disorders develop. In fact insulin resistance is able to promote the accumulation in the viscera of adipose depots poorly sensitive to insulin that, for such reason, are subjected to a specific lipolytic action that leads to an increase in free fatty acids (NEFA) in the portal circulation and liver: NEFA are here to serve as the substrate for the production of abnormal glucose and triglycerides and are able to interfere negatively on the hepatic clearance of insulin. These premises confirm the clinical-laboratory phenotype outlined above: abdominal obesity, the dyslipidemia characterized by high levels of triglycerides, low levels of HDL cholesterol and high levels of small and dense LDL, are the first corollary derived from insulin resistance.

Over time, insulin resistance and consequent hyperinsulinism in the kidneys act also by promoting distal sodium retention and, through the resulting Volem expansion, can ultimately have an adverse impact on the blood pressure. This abnormality may persist despite a successful pharmacological treatment of hypertension, and the relationship between hypertension and hyperinsulemia can be observed both in obese individuals and in non-obese ones.

Finally, continuing in tracing the natural history of the metabolic syndrome, when the mechanism of pancreatic compensation to insulin resistance - namely the increased production of insulin - is inadequate, the liver increases glucose production (with consequent increase in fasting blood glucose) due to a reduced use of glucose by the peripheral tissues(that leads to a post-prandial hyperglycemia): the glucose metabolism goes towards progressive changes that lead the subject from a reduced tolerance to carbohydrates to a manifest diabetes. It is not clear yet in the scientific literature, not even in the most recent one, how much the increased risk is associated with aging, and how much is instead hormone-dependent.

Given that the risk is itself linearly related to advanced age, genetic inheritance components, and the habit of cigarette smoking (now increasingly widespread than before among women),it is certainly necessary, according to several physiological changes that menopause is able to orchestrate, to establish as precisely as possible a risk profile for this particular era of women's lives.

Aim of the study

The goal of our study was to assess the impact of an early integrated therapeutic approach to improve the parameters of the metabolic syndrome in menopause.

Women reach the Menopause Center of our Policlinic mainly driven by the need to solve the so called "immediate" or at most "medium-term" problems of menopause. The most frequent diagnosis of admission for day-hospital in our division are "Menstrual irregularities", "genito-urinary dystrophy and atrophy" and "menopausal syndrome". Careful anamnesis, physical examination and some blood tests can also bring to light significant systemic changes, that although may appear in the least concern for the patient, they rather deserve, in consideration of what has been previously said, some specific attention.

Materials and methods

Among the patients that came to the Menopause Center of our Policlinic to undergo a gynecological control (driven by the need to resolve the gynecological disorders typical of the climacteric), we selected 45 women in pre-climacteric age (mean age 51.5 years). It seemed useful, however, to integrate the ATPIII parameters with some WHO diagnostic details, so finally we evaluated:

1. VISCERAL OBESITY/FAT (WHR,or Waist, or BMI)
2. BLOOD TRIGLYCERIDES >150mg/dL
3. TOTAL CHOLESTEROLAEMIA >220mg/dL or HDL <50mg/dL
4. BLOOD PRESSURE >130/180mmHg
5. IFG(impaired fasting glycaemia)or IGT(impaired tolerance to carbohydrates) or diabetes mellitus

Table 1.

	Time 0 (±DS)	After 6 months (±DS)	Average Difference	Confidence Interval 95%	p value (paired t- test)
Body Mass Index(Kg/mq)	33.2 (±4.59)	31.5(±4.4)	-1.68	-2.1 to -1.2	<0.0001
Cholesterol HDL (mg/dL)	44.4 (±12.4)	53.7 (±12.9)	9.31	6.1 to 12.5	<0.0001
Triglycerides (mg/dL)	196 (±61.5)	136.3 (±43.7)	-59.7	-73 to -46.4	<0.0001
Humeral systolic pressure(mmHg)	142.3 (±12.4)	125.1 (±10.6)	-17.22	-20.4 to -14	<0.0001
Humeral Dyastolic Pressure (mmHg)	87.6 (±9.1)	77.2 (±5.6)	-10.3	-13 to -7.7	<0.0001
Fasting blood glucose (mg/dL)	149.1 (±69.3)	115.9 (±31.1)	-33.2	-48.1 to -18.4	<0.0001

These women were then treated with diet, lifestyle changes and appropriate medications (anorectic drugs, insulin sensitizers, statins, fibrates, antihypertensives).The anthropometric and laboratory parameters considered were then reassessed after six months of treatment. Data were analyzed using the *paired t-test* for paired data and the comparison showed statistically significant improvements for all variables considered.

Results

Our data show that a timely and accurate approach to the metabolic syndrome in menopausal women, based on changes in lifestyle (diet, exercise, abstaining from smoking) and on appropriate drug therapies, leads to a significant improvement of all parameters of the metabolic syndrome. (Table 1)

Conclusions

Far from representing just a speculation's sake, it is certainly necessary, therefore, to find a diagnostic-therapeutic approach for this particular area of a woman's life, that could establish a risk profile as precisely as possible.

For the adoption of such a composite treatment program, to have methodological bases that take into account the underlying pathophysiological network to the different signs and symptoms, by which the patient may express the syndrome, can be effective. Therefore gynecologists, diabetology-endocrinologists, nutritionists, psychologists should be ready for a stable partnership in the creation of dedicated facilities for outpatients in peri- and postmenopausal age. Thus women can be considered from all points of view (gynecological, endocrine-metabolic, psychological)and each jurisdiction, exceeded every sectoralisation can cooperate to achieve that goal that now appears as the true challenge of this millennium: reducing cardiovascular risk and improve the quality of life after sixty years old.

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