METABOLIC SYNDROME MAY BE IMPROVED FOLLOWING A LONG-TIME ADMINISTRATION OF A NUTRITIVE SUPPLEMENT CONTAINING EMBRYONARY PEPTIDES

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Metabolic Syndrome (MS) is a polymorph disease with a high frequency especially in older age. Any randomized study with nonhospitalized subjects might include those bearing MS, that greatly influenced the final results. Eighty subjects aged 50-75 years (38 men and 42 women) had consumed daily 4 caps of purified Embryonary Peptides (EP) for 60 days. The samples of blood from each subject were obtained before and after administration. Therefore, each subject was his own control. In all subjects, after administration, regardless of the MS presence, total cholesterol and LDL-cholesterol had decreased approximately 30 % as compared with the initial values. Significant decreases of insulin and cortisol were also observed, but associated with modifications of PSA, CEA and IGF-I. The magnitude of these changes was lower in subjects with MS. The long-lasting modifications induced by EP seem to have an adaptive-regulatory character, affecting the lipid metabolism (already modified in MS), as well as some pathways from steroid biosynthesis. Thus, EP might act similarly to some stimulatory factors, such as IGF-1, in a reversible stage of MS.

Key words: metabolic syndrome, embryonary peptides.

INTRODUCTION

Metabolic Syndrome (MS) was introduced by Reaven in 1988 (1) and soon was internationally accepted as one of the greatest problems for public health, being a major source of cardiovascular diseases and type 2 diabetes. The criteria to define MS include a group of severe anomalies such as abdominal obesity, insulin resistance, hyperinsulinemia, hypertension, hyperglycemia and dyslipidemia (2-4). Actually, to diagnose MS, it is not so easy, as several studies emphasized the multifaceted aspects of this condition (5). Even the presence of three criteria (according to ATP III recommendations) does not provide an accurate diagnosis, as each of the accepted parameters has a frequency between 30-20 % (5). Therefore, NCEP ATP III

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and WHO recommendations require the presence of clinical couples and afterwards of clinical triad. According to other views, such criteria are too narrow and define the acute cases, mostly obese in irreversible condition (6).

In previous papers (7, 8), we noticed significant decreases of the oxidative stress and the blood levels of some lipid components, such as total cholesterol (TC), LDL-cholesterol, triglycerides (TG). It should be mentioned that the drugs which decrease the blood TC, of statins type (Simvastatin), also decrease the oxidative stress (9), already present in MS (10) but so does the administration of embryonary peptides (EP) (8). Therefore, a possible effect of EP on the condition of MS is the motivation of the present study.

Even associated with a hypocaloric diet, the utilisation of statins to decrease blood cholesterol provides modest results, not long-lasting and with unpleasant effects. By using hypocholesterolemic drugs, the blood level of trigycerides, apolipoproteins and insulin is not affected. In such way the administration of a standardized nutritive supplement containing EP is devoid of toxic and side effects. In a previous randomized study on subjects between 50-75 years (8), we observed great individual variations after the administration of EP, which might be explained by the presence of a chronic condition of MS among the subjects.

MATERIALS AND METHODS

From a higher group of nonhospitalized subjects, 80 volunteers participated in this trial, as recommended by their general practitioner. The group consisted of 38 men and 42 women, between 50-75 years. Most subjects were in good health condition, but a few had clinical problems, in chronic evolution under medical control. During whole study, the subjects remained at home and no diet restriction was required. These subjects did not interrupt their specific medication. The patients gave their informed consent and the local ethic committee approved the study. During all trial, no side effects were reported.

Humanofort is the Trade Mark of the nutritive supplement based on a purified extract from embryonated chicken eggs according to an original procedure under license: OSIM patent 112, 102, 1997. After all toxicological, pharmacological, bacteriological tests were fulfilled, Humanofort received the approval of the Ministry of Health Nr. 5675 from 11.11.2002, as nutritive supplement. The final product, Humanofort contains as active compounds two oligopeptides with 5,000 and 10,000 Daltons accepted as Embryonary Peptides (EP). Each cap of Humanofort contained 500 mg purified extract (EP).

Before treatment, all subjects were investigated by their general practitioner and samples of blood and urine were obtained. All the biochemical results included the initial values and were compared with those obtained after the end of the trial. Therefore, each subject was his own control. After the first collection of blood samples, each subject used 4 caps of Humanofort per day (two in the morning and two

in the evening) for 60 days. After this period, samples of blood and urine were obtained for each subject. Both initial and final blood samples were analyzed by the same laboratory (Synevo Medicover). All the biochemical, hematological and hormonal analyses were performed according to the methods recommended by EU. For quantitative variables, the results were expressed as the arithmetic mean ± standard deviation.

RESULTS

As observed at the end of this study, the biochemical effects obtained after the administration of EP greatly depend on the initial values of the lipid components, as well as on the personal characteristics of the subjects. Therefore, we present in Table 1 the baseline characteristics of all the subjects participating in this study, regardless of the possible presence of MS. Eventually, the initial aim of this study was to test the decreasing effect of EP on lipid components.

Table 1. Baseline characteristics of the subjects participating in the study

Variables	Men	Women
Count	38	42
Age (years)	66 ± 7	67 ± 9
BMI (kg/m^2)	27.5 ± 4.7	30.6 ± 5.8
Obese (%)	13	23.8
Cardiovascular history (%)	31.5	42.8
Diabetes (%)	26.3	14.3
Liver and biliary disorders (%)	21	33.3

BMI = Body mass index calculated as weight divided by squared height (meters).

The clinical characteristics of the subjects showed a normal distribution of the disorders in chronic state for their age. Gender differences are obvious, especially overweight, as women had more cardiovascular affections, where a lipid overburden is an aethiological source. In agreement, BMI values exceed the physiological limit of 25 kg/m^2, especially in women.

Surprisingly, type 2 diabetes was more frequent in men. But, as mentioned before, generally, this group of subjects were in relatively satisfactory health for their age and their clinical problems were in chronic state, under medical control.

After the administration of EP, according to the methodology presented above, significant variations of the biochemical parameters were obtained. We investigated a wide range of biochemical parameters, including those frequently modified in old persons, such as glucose, urea, uric acid, creatinine, which were at superior limits of physiological range according to their age. Similar results were obtained for hematological parameters. Great individual modifications were present, sometimes in opposite directions.

As these high individual variations appeared only for lipid components, a possible presence of MS was suggested. The possible presence of MS should greatly influence both the initial values of parameters and the effects of EP. To select among all subjects those with MS was not so easy, as according to previous reports (2-4, 7), the frequency of three recommended criteria is approximately 30 % and with high individual variations.

Basic characteristics and % frequency of the parameters which define the presence of the Metabolic Syndrome (MS) in the selected subjects.

The results presented in Table 2 emphasized the difficulties, already mentioned (2-4, 7) regarding the frequency of the symptoms which define the presence of MS. In both groups (men and women) we did not find any case of hyperinsulinism, if we report to the normal, wide limits. The frequency of the biological changes (hypertension and type 2 diabetes) was also within accepted limits for this age. As we mentioned above, no diet restriction was required and the subjects did not use the hypocholesterolemic drugs.

Our results emphasized the almost total presence of anomalies of lipid components, especially of total cholesterol (TC), LDL and triglycerides (TG). The HDL cholesterol was within physiological limits, both in men and women. This observation was contrary to the previous reports (2-4, 7). In this situation, the cardiac risk factors (recommended by AETHNA 2000 Program), respectively the TC/HDL ratio was approximately 4.5 corresponding to a moderate risk.

Table 2. Basic characteristics and % frequency of the parameters which define the presence of the Metabolic Syndrome (MS) in the selected subjects

Components	**Men**		**Women**		**Normal**
	Values	% MS	Values	% MS	Values
Count	18		20		
Age(years)	67±6		69±8		
BMI (kg/m^2)	29.4±5.3	85	30.5±6.2	95	27
Hypertension (%)		40		75	114/90
Type 2 Diabetes		55		30	
Total cholesterol mg/dl (TC)	244.8±12	100	276.5±13	100	200
HDL cholesterol mg/dl	38.4±10	66	55.8±9	74	40-50
LDL cholesterol mg/dl	160.7±14	90	200.7±16	95	150
Triglycerides mg/dl (TG)	278.6±12	80	269.5±18	80	160
Insulin (U/ml)	12.5±6	80	10.5±8	84	5-25
Cortisol basal (mmol/L)	546.8±27	75	512.7±24	80	65-530
CRP (mg/dl)	0.87±0.4	60	0.95±0.8	65	0.50
CEA (ng/ml)	3.42±1.7	50	3.82±l.7	50	4.6
IGF-l (ng/ml)	315.8±27	67	246.3±14	5	64±188

BMI = Body mass index; CRP = C reactive protein; CEA = Carcino Embryonic Antigen; IGF1 = Insulin-like Growth Factor; % MS = % frequency of modified values.

Our initial results for the group with MS did not show increased values of transaminases (under 8 %), as it was reported in cases of severe obesity (9), suggesting a liver failure. But our results, also showed for subjects with MS the presence of significant modifications of Protein C Reactive (CRP) and IGF-I. These observations suggest other possible affections, such as inflammations and a stress condition (high cortisol). All these observations suggest the right selection of subjects with MS, in an incipient, possible reversible step of evolution.

Next, we studied the effects of EP administration on all subjects, both in the absence and presence of MS (Table 3).

According to the results presented in Table 3, the administration of EP to all

Table 3. The effects of EP administration on some biochemical parameters of the entire lot of subjects

A. MEN

	With Metabolic Syndrome			**Without Metabolic Syndrome**		
Paramet.	Initial	After	Diff.(P)	Initial	After	Diff.(P)
Count	18			20		
T.Chol	244.8±12	219.6±+9	<0.05	238.5±+7	204.6±8	<0.01
HDL	38.4±10	47.3±7	<0.05	45.8±5	58.2±5	<0.05
LDL	160.7±14	131.4±5	<0.01	147.3±8	125.4±7	<0.01
TG	278.6±12	246.8±8	<0.05	257.4±6	174.5±8	<0.01
Insulin	12.5±5	6.5±2	<0.05	8.4±2	5.5±1.8	<0.05
Cortisol	546.8±17	470.3±15	<0.05	516.7±18	394.4±16	<0.01
CRP	0.87±0.4	0.92±0.7	NS	0.63±0.3	0.54±0.3	NS
CEA	3.2±l.6	2.9±1.3	NS	2.82±l.6	2.45±1.2	NS
IGF-1	315.8±27	228.7±15	<0.01	246.3±14	172.6±12	<0.01

B. WOMEN

	With Metabolic Syndrome			**Without Metabolic Syndrome**		
Param.	Initial	After	Diff.(P)	Initial	After	Diff.(P)
Count.	20			22		
T.Chol.	286.5±13	253.7±16	< 0.05	255.7±12	224.3±15	<0.01
HDL	55.8±9	63.2±6	NS	61.8±7	65.3±7	NS
LDL	201.8±16	176.4±13	<0.05	168.7±12	126.8±14	<0.01
TG	269.5±18	234.3±12	<0.05	251.8±13	215.8±10	<0.01
Insulin	12.5±6.1	7.2±2.6	NS	7.4±3.5	4.4±1.6	<0.05
Cortisol	512.7±24	443.5±18	<0.05	520.6±22	417.5±17	<0.01
CRP	0.95±0.8	0.73±0.6	NS	1.06±0.4	0.58±0.8	<0.05
CEA	3.82±1.3	3.10±0.6	NS	2.24±0.8	1.38±0.6	NS
IGF-1	246.27±27	195.4±18	<0.05	223.7±15	152.7±13	<0.01

All parameters were expressed in the same units as in Table 2.

subjects induced significant changes, dependent on several factors, among them sex, initial values and the presence of MS. All these factors, including the age, induced a great individual variety of results, which influenced the statistical interpretation.

In spite of these difficulties, as seen in Table 3, the administration of EP produced significant modifications, mostly of adaptive-regulatory type, such as the decrease of lipid components. The changes of insulin and cortisol as well as of IGF-1 towards physiological range should be also included. These modifications are more clear-cut in subjects without MS.

The administration of EP did not produce significant modifications of usual biochemical parameters, such as glucose, urea, uric acid, which were already within physiological range (under 8 % exceptions). At the end of this study, no unpleasant side effects were reported, but the pathological ailments-aging related remained in chronic condition. As the subjects kept a sedentary style of life, the BMI was not modified significantly.

DISCUSSION

Our results demonstrated the efficiency of EP in MS.The presence of MS was the main grouping criteria (Table 1). According to Table 2, half of the initial subjects were selected as having MS, probably in an incipient stage. Our criteria of selection were the presence of three conditions (2-4, 7): increased BMI and TG and the presence of cardiovascular disorder or type 2 diabetes. Anyway, total cholesterol was increased in all subjects, as a consequence of aging. In the same way, other modifications might be explained, such as increased LDL, TG, as well as some independent parameters, such as cortisol, CRP, IGF-1. Secondly, as we mentioned, in all subjects, the levels of HDL cholesterol and insulin were within the physiological range, possibly compensatory. In this way, the factors of cardiac risk (recommended by AETHNA 2000 Program), such as TC/HDL and Apolipoproteins B/A ratio remained to a moderate level (6). Based on these observations, the difference between the groups with MS *versus* those without MS was the presence of pathological conditions (hypertension and diabetes) in various degrees. The obesity was present in few cases, therefore the liver was not affected (9). Hyperinsulinaemia associated to MS, quoted by other studies (2-4), is probably present in young subjects.

The administration of EP decreases significantly especially lipid components in all subjects. A significant greater effect observed in subjects without MS is a proof for the existence of metabolic pathways, which are certainly affected in severe evolution of MS. In our subjects with incipient MS, these pathways were still reversible, as being modified by the administration of EP. Therefore, the effects induced by EP should have a clinical interpretation.

EP may act on lipid components by complex mechanisms, not yet identified. A first way might be the oxidative stress, present significantly in both aging (10) and MS (7), as statins exert a similar effect (8). As triglycerides are decreased in the blood (unsaturated fatty acids are components), the target for free radicals action should be restrained (11) and oxidative stress will decrease (5).

EP from the nutritive supplement might act similarly to some growth factors, such as IGF (1 and 2) or EGF, FGF, NGF possessing also a peptide structure. As the administration of EP modifies both insulin and IGF-I regulation (Table 3), regardless of MS presence, an interaction would be suggested. It is known that insulin modifies regulatorily the level of triglycerides in the blood and tissues (12, 13), thus, this hormone might be involved by acting directly on lipases or through the penetration of TG into cells (13, 14).

The last mechanism, which might be involved in order to explain EP action, might be the interaction with neurohormonal axis hypothalamic-pituitary-gonads/adrenal gland. Indeed, the administration of EP also produced modifications of cortisol and of some steroid hormones (DHEA and testosterone), as well as of some antigens (CEA and PSA) not yet presented. This last hypothesis is further under research.

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