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Cardiovascular Risk Factors in
Acromegaly

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Cardiovascular Risk in Acromegaly

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ABSTRACT

OBJECTIVE: Cardiovascular disease is one of the most important causes of death in acromegalic patients. The aim of this study is to compare the presence of cardiovascular risk factors between acromegalic patients and a control population and evaluate the impact of disease control in these factors.

DESIGN: 11 acromegalic patients with active disease and 12 controlled were evaluated for blood pressure, body mass index, fasting glucose, coagulation status and lipidic profile. A group of 11 subjects with non-functioning pituitary adenoma was used as control population.

RESULTS: Significant differences were found in lipidic profile, glucose and coagulation status in both active and controlled patients. Higher levels of fasting glucose and fibrinogen were present in both acromegalic groups. Active patients had higher levels of antithrombin III and controlled ones higher levels of high density lipoprotein cholesterol, compared with controls. Differences between active and controlled acromegalic patients consist in reduction of total cholesterol, low density lipoprotein cholesterol and antithrombin III in the last.

CONCLUSIONS: There is some reduction in cardiovascular risk factors with control of the disease, but possibly without return to basal levels.

Introduction

Acromegaly is a disease resulting of Growth Hormone (GH) excess production. It is a rare disorder, with an estimated annual incidence of 3 to 4 cases per million inhabitants per year and a prevalence of 40 to 70 cases per million.¹ In Portugal, acromegaly's prevalence and incidence are, respectively, 56.5 cases per million inhabitants and 2.9 cases per million inhabitants per year.² The mean age at diagnosis is 44 years, after mean symptom duration of 8 years. It seems to affect men and women equally.¹

In more than 90% of cases, acromegaly is caused by a monoclonal benign pituitary tumor³ (adenoma – figure 1). GH overproduction will be responsible for the stimulation of hepatic production of insulin-like growth factor 1 (IGF-1) and, elevated levels of both hormones will cause a number of systemic manifestations. Patients usually present with frontal bossing, enlarged nose and lips, prognathism, increased interdental space, oily skin, deep voice and acral enlargement.³ Increased sweating, joint manifestations, carpal tunnel syndrome, visual changes, headache, colon polyps, sleep apnea and reproductive, metabolic and cardiovascular disorders can also be present.⁴

Diagnosis is based on clinical presentation and levels of fasting or random GH and IGF-1. It is excluded when random GH level is lower than 0.4 µg/L and IGF-1 level is within the age and sex adjusted normal range. If one of these values is altered, an oral 75 g glucose load (OGTT – Oral Glucose Tolerance Test) is taken. To rule out acromegaly, the GH level should fall to 1 µg/L or less.⁵

The primary treatment of acromegaly is pituitary surgery. Medical therapy can be used after unsuccessful surgery, when the tumor is nonresectable or there are important comorbidities, and while awaiting the effectiveness of radiation therapy. Radiotherapy is left as a last resort, when the tumor continues to grow and is not responsive to medical treatment or when the patient has an aggressive tumor with invasion of local structures.⁴ Cure is achieved when IGF-1 levels are in the age and sex adjusted normal range and GH level after OGTT is lower than 1 µg/L.⁵

Acromegaly is associated with increased mortality when compared with age-matched control population. Cardiovascular, cerebral, cancerous and respiratory disorders are considered to be the main causes of death in acromegaly, being cardiovascular disease the most important one (around 40%).^{1, 6} High levels of GH/IGF-1 are associated with increased cardiac mass and diastolic dysfunction, which is followed by systolic dysfunction in long course disease.^{7, 8} There is also an increase of cardiovascular risk factors in acromegaly. In different studies, the prevalence of hypertension ranges from 18 to 60%.^{6, 9-12} It is related and involved in worsening of acromegalic cardiomyopathy¹³ and an independent mortality predictor in acromegaly.¹⁴

The prevalence of impaired glucose tolerance in patients with acromegaly is estimated to be between 16 and 46%.¹⁵ Diabetes Mellitus is present in 19 to 56% of acromegalic patients, a higher prevalence than among general population.^{15, 16} Abnormalities of glucose metabolism are also significantly correlated with increase in blood pressure in this disease.¹⁷

Although there is evidence of an abnormal lipid profile in active acromegalic patients, there is some controversy when trying to determine which values are changed. Total cholesterol (TC) appears unchanged compared with normal population¹⁸⁻²⁰ whereas triglyceride (TG) levels appear higher^{18, 21} or unchanged.¹⁹ Low^{21, 22} or unchanged^{19, 20} levels of high-density lipoprotein cholesterol (HDL-C) were also found, as well as the presence of small and/or dense low-density lipoprotein cholesterol (LDL-C).^{19, 22}

Acromegalic patients have lower visceral and subcutaneous fat mass and increased intermuscular fat mass, which may be related with insulin resistance in this disease. It is also associated with increased lean body mass.^{23, 24}

Some studies reveal disruption of coagulation and fibrinolytic system. Fibrinogen levels seem to be consistently higher,²⁵⁻²⁹ whereas plasminogen activator inhibitor-1 (PAI-1) is either elevated²⁷ or unchanged^{28, 29} in acromegalic patients. There is some evidence of the presence of higher levels of antithrombin III (ATIII), lower levels of protein S and unchanged levels of protein C and coagulation factor VIII.^{26, 27} C-reactive protein, an acute phase reactant, is shown to be lower^{25, 28, 30} or unchanged²⁶ in acromegaly.

Studies report amelioration of cardiac function and some cardiac risk factors with complete or partial biochemical control of acromegaly.^{28, 31-34} There seems to be a decrease in blood pressure (BP) with control of the disease.^{11, 28, 31, 33, 34} However, changes in metabolic parameters are not well established. Some studies show increase in insulin sensitivity and better glucose regulation,^{28, 32, 34} while others show no modification in majority of patients.^{30, 35} As to lipidic profile, some studies can't find any difference between active and controlled patients,³⁰ while others report increase in HDL-C and decrease in TC, LDL-C and TG.^{22, 28} Levels of fibrinogen were found to be either similar^{25, 26} or reduced^{28, 29} and levels of CRP were found to be either similar²⁶ or increased²⁸ after control of acromegaly. There is some evidence of decrease in PAI-1²⁸ and maintenance of Factor VIII levels.²⁶

As discussed above, there are no certainties about the changes in cardiovascular risk factors with control of acromegaly. Also, there are few studies approaching some risk factors, specially coagulation status. The aim of this study is to compare the presence of cardiovascular risk factors between acromegalic patients and a control population (non-functioning pituitary adenomas) and to evaluate the changes in these factors with control of the disease. Body mass index (BMI), blood glucose, BP, TC, HDL-C, LDL-C and TG will be compared among each group. Protein S, Protein C, Antithrombin III, Factor VIII, Fibrinogen and genetics of PAI-1 will also be evaluated and compared.

Subjects and Methods

This study was approved by the Ethical Committee for Health of Hospital de São João (HSJ). It was a case-control study, performed in patients selected from the Endocrinology department of HSJ database. All patients included signed an informed consent form.

Subjects

Subjects were selected from Endocrinology department database. Patients who had died, whose follow up was lost or had the last surgery more than 10 years ago, were excluded. Patients without data available on computer

internal network and without laboratory analysis made in the previous year were also excluded. Selected subjects were summoned by telephone call and those who refused, couldn't come to the hospital or didn't answer were also excluded from the study.

This study included 23 acromegalic patients (table 1), 11 (5 men/6 women) with active disease and 12 (4 men/8 women) with controlled disease. Mean age was 50.64 ± 12.63 in active group and 54.00 ± 12.57 in controlled disease group. In both groups, most patients had macroadenomas at diagnosis. In active disease group, there were 3 newly diagnosed patients, who didn't make any kind of treatment to the date of study. All other patients in this group underwent previous surgery and had necessity of medical therapy after that. Among controlled patients, only one was treated with radiotherapy and medical treatment. All other patients had previous surgery, 6 of them not having the need for medical therapy.

Eleven controls (6 men/ 5 women) with non-functioning pituitary adenomas were evaluated. They were diagnosed with non-functioning adenoma, which has no hormonal hypersecretion. Elevated urinary free cortisol or cortisol after suppression test with dexamethasone, hyperprolactinemia, elevated thyroxine with high levels of thyroid-stimulating hormone or hypersecretion of GH were not proven. Diagnosis was confirmed with histological analysis after surgical resection. Mean age in this group was 51.36 ± 13.76 .

Study Protocol

Disease status was evaluated by IGF-1 levels and GH suppression after OGTT, when appropriate. Active disease was defined as IGF-1 levels over sex and age adjusted normal range or GH after OGTT over $1 \mu\text{g/L}$. IGF-1 is expressed as percentage of upper limit of normal range (ULN).

Anthropometric characteristics (height and body mass) were obtained from the last consultation register and body mass index (BMI) was calculated ($\text{body mass}/\text{height}^2$). Blood pressure was also obtained from the same consultation and was measured by blood pressure monitor.

Last available laboratory analysis of each patient were consulted and blood levels of glucose, total cholesterol (TC), low-density lipoprotein cholesterol

(LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) were collected.

To evaluate coagulation status of included patients, blood samples were taken and levels of fibrinogen, protein S, protein C, AT III and coagulation factor VIII were measured. An evaluation of plasminogen activator inhibitor 1 (PAI-1) genetic polymorphisms was also made.

For statistical purposes, besides levels measured alone, patients were also categorized as having or not hypertension, hyperglycemia and hyperlipidemia. Hypertension was defined as SBP $\geq$ 140 and/or DBP $\geq$ 90, or being medicated for hypertension. Hyperglycemia was defined as having fasting glucose over 110 mg/dL or being medicated for diabetes mellitus. Hyperlipidemia was defined as having hypercholesterolemia and/or hypertriglyceridemia (TC $>$ 200; LDL-C $>$ 130; HDL-C $<$ 60; TG $>$ 150).

Laboratory Analysis

Blood samples from acromegalic patients and controls were taken by venopunctures. Fibrinogen was measured by Clauss Method and AT-III, Protein C and Protein S were measured by functional methods, using reagents obtained from Diagnostica Stago (Asnieres-sur-Seine, France). Factor VIII levels were measured by coagulometric methods (Siemens Healthcare Diagnostics, Newark, Germany).

For 4G/5G PAI-1 gene polymorphisms, DNA was extracted using QIAamp (Hilden, Germany) and real-time polymerase chain reaction (PCR) using LightCycler (Roche Molecular Biochemicals, Mannheim, Germany) was performed. A hybridization probes technique (sequence-specific fluorescent detection with oligonucleotide hybridization probes that are coupled to suitable fluorophores) was applied. A mix with 2 μ l genomic DNA (100 ng), 10.8 μ l H₂O, 1.6 μ l MgCl₂ (3 mM), 1 μ l of each primer (10 μ mol), 0.8 μ l of each probe (5 μ mol) and 2 μ l DNA-Master hybridization probes was used. Oligonucleotide primers and probes were synthesized by TIB MOLBIOL (Berlin, Germany) and cycling conditions involved initial denaturation (95 $^{\circ}$ C for 600 s), followed by 45 cycles with denaturation at 95 $^{\circ}$ C for 0 s, hybridization at 59 $^{\circ}$ C for 5 s and extension at 72 $^{\circ}$ C for 2s. Melting curves were obtained by slowly heating the sample to 75 $^{\circ}$ C. Melting points of the two alleles were at 59 $^{\circ}$ C

and 658°C. For better differentiation of heterozygotes, amplified products were run on agarose gel.³⁶

Serum glucose, TC, LDL-C, HLD-C and TG were measured by conventional methods with an Olympus AU5400® automated clinical chemistry analyzer. (Beckman-Coulter®, Izasa, Porto, Portugal). IGF-1 was measured by solid phase, enzyme labelled chemiluminescent immunometric assay and GH by solid phase, two-site chemiluminescent immunometric assay (Immulite 2000®).

Statistics

Statistical analysis was made in Statistical Package for Social Sciences (SPSS). Values were tested for normality distribution by Kolmogorov-Smirnov and Shapiro-Wilk tests and log-transformed to achieve normal distribution when necessary. Parametric unpaired t-test was used to compare the groups. Spearman Rank Order Correlation coefficient was used to look for association between levels of IGF-1 or GH and variables in study. Pearson's correlation was used to search association among the variables studied. In order to find if there was association between being in a group and having hypertension, hyperglycemia or hyperlipidemia, Chi-square test was used. P values under 0.05 were considered significant.

Results

Table 2 summarizes comparison (GH, IGF-1 levels, %ULN, BMI, BP, lipidic profile and glucose status) among the three evaluated groups. Patients with active disease, as expected, had significantly higher levels of GH and IGF-1 than controlled ones.

BMI and levels of SBP and DBP were not significantly different among the three groups, although they were slightly higher in acromegalic patients. Active group had the highest mean blood pressures, and controlled group the highest levels of BMI. However, DBP was lowest in controlled acromegaly group.

TC was slightly higher in active patients than controls, but the result was not statistically significant. When compared with controlled patients, the

difference was significant, with the active group having higher levels. HDL-C was higher in acromegalic patients, being significantly different between controlled patients and controls. In what concerns LDL-C, it was significantly lower in controlled patients when compared with active acromegalic ones. Levels were slightly higher in active patients than controls. Triglycerides were not significantly different among the three groups, being slightly higher in control group.

Blood glucose was significantly higher in controlled acromegaly group and higher with borderline significance in active acromegaly group, when compared separately with control group. No difference was found between active and controlled acromegaly groups (although somewhat higher in active group).

When categorizing patients as having hyperglycemia, hypertension and hyperlipidemia (table 3), higher percentages of all three variables were found in acromegalic patients when compared with controls. Hypertension prevalence was higher in controlled acromegalic group. Hyperglycemia and hyperlipidemia had the higher percentages in active disease group. However, significant correlation between those categories and the three studied groups was found only in hyperglycemia ($p=0.002$).

Coagulation status of the three evaluated groups is summarized on table 4. Levels of protein C and S were similar among the groups. As to fibrinogen levels, these were significantly higher in acromegalic groups when compared with control group. There were no significant differences in these values between active and controlled patients (controlled patients having slightly higher levels). ATIII was significantly higher in active acromegaly when compared with control group and when compared with controlled acromegaly. There was no difference between control and controlled acromegaly groups. Although levels of coagulation factor VIII were slightly higher in controls than controlled acromegalic patients and in controlled acromegalic than active acromegalic patients, these values were not significantly different.

When considering all acromegalic patients, significant positive correlation was found between ATIII and IGF-1 levels ($r=0.654$; $P=0.001$) and ATIII and GH levels ($r=0.498$; $P=0.013$). Dividing acromegalic patients in active and controlled groups, negative correlation was found between TC and GH in the

active group ($r=-0.675$, $P=0.032$) and positive correlation was found between LDL-C and IGF-1 levels in controlled disease group ($r=0.630$, $P=0.038$). Within the active acromegaly group, a negative correlation was found between GH and fibrinogen levels ($r=-0.610$; $P=0.046$).

A positive, significant correlation was found between glucose levels and BMI ($r=0.478$; $P=0.005$) and glucose and SBP ($r=0.428$; $P=0.013$). There was also found positive significant correlation between TC and LDL-C, TC and DBP, HDL-C and TG, LDL-C and DBP, SBP and DBP, BMI and SBP, protein C and DBP, protein C and HDL-C, coagulation factor VIII and fibrinogen.

No correlation was found between hypopituitarism and the variables studied.

Genetic polymorphisms of PAI-1 were evaluated. In control group, 54.5% were heterozygotes, 27.3% homozygotes by deletion and 18.2% homozygotes by insertion. Within active acromegaly group, 36.4% were heterozygotes, 18.2% homozygotes by deletion and 36.4% homozygotes by insertion (genetic polymorphism was not available for one patient). In controlled acromegaly group, 58.3% were heterozygotes, 25.0% homozygotes by deletion and 16.7% homozygotes by insertion. No differences among the groups were found.

Discussion

Since patients with non-functioning pituitary adenoma have no hormones production, these were used as control subjects.

In this study, prevalence of hypertension in both acromegalic groups was within the range found in other studies (18 to 60%).^{6, 9-12} Although not significant, BP levels and prevalence of hypertension were slightly higher in acromegalic groups than in control group, results previously found in other studies.¹⁰ When comparing active and controlled acromegalic patients, BP levels seem to be slightly lower in controlled group, but hypertension prevails over active group. This happens probably because a higher percentage of patients in controlled group were taking anti-hypertensive medication. The tendency to slightly lower levels of BP in controlled acromegalic patients is in concordance with other studies, that show higher levels in active disease than

in controlled disease.^{28, 31, 33, 34} One study shows lower frequency of hypertension in active than in controlled acromegalic patients.¹¹ As in other studies, no correlation was found between IGF-1 and GH levels and BP.^{10, 17, 33} Fedrizzi et al. found no correlation among these values when including all acromegalic patients (active and controlled), but found correlation between SBP and IGF-1 levels in active acromegalic patients.¹¹

BMI was reported as being higher in acromegalic patients than controls in several studies.^{25, 37, 38} In the present study, no significant difference was found in BMI, with a slight tendency for controlled patients to have higher values, results that are in agreement with other studies.^{32, 39} However, there is evidence that acromegalic patients have different body composition: lower visceral and subcutaneous fat mass and increased intermuscular fat mass, with an increase in lean body mass and body water.^{23, 24} These changes probably make BMI less indicated when trying to deduce body composition or obesity presence in these patients, suggesting other measurements should be used.

Prevalence of Diabetes Mellitus has been reported as being higher among acromegalic patients than in general population.^{15, 16} Higher insulin resistance and higher glucose and insulin levels in acromegalic patients compared with healthy subjects were also reported.^{26, 38} Findings in this study show significantly higher levels of fasting glucose and prevalence of hyperglycemia in all acromegalic patients when compared with control subjects. Although there seems to be a tendency for controlled acromegalic patients to have lower levels of fasting glucose, this difference is not statistically significant. Studies show different results after treatment of acromegaly: some report increase in insulin sensitivity and amelioration of glucose regulation,^{28, 32, 34} others show no modification in glucose, insulin and insulin resistance.^{30, 35} The results here reported suggest that there is an improvement in fasting glucose in controlled patients, but with glucose status remaining worse than in control subjects, which should be taken in account when evaluating acromegalic patients, even when having disease control. A significant correlation between fasting glucose levels and SBP was found, an association also previously established.^{15, 17}

Comparing lipidic values between control and active acromegaly groups, there appears to be higher TC and LDL-C, similar HDL-C and lower TG levels and higher hyperlipidemia prevalence. Yet, these values are not statistically significant. Other authors have found TC levels to be similar, HDL-C lower or unchanged and TG higher or unchanged when compared with a control population¹⁸⁻²². Results regarding LDL-C appear to report either similar or higher levels in acromegalic patients;^{19, 20, 22} in these studies, higher levels of small and/or dense LDL-C were consistently reported.^{19, 22} Controlled acromegalic patients appear to have a better lipidic profile with significant lower levels of TC and LDL-C than active patients. When compared with control population, there seems to be a better lipidic profile with significant higher levels of HDL-C. However, there is a higher percentage of hyperlipidemic controlled patients, because more of them were under anti-dyslipidemic medication. This suggests close attention and control of dyslipidemia in acromegalic controlled patients is effective and probably additive to control of the disease. Studies reported increase in HDL-C and decrease in TC, LDL-C and TG with control of the disease, supporting the present findings.^{22, 28}

Within active acromegaly group, there seems to be a significant negative correlation between GH and TC levels. When considering controlled acromegaly group there is a positive association between IGF-1 and LDL-C levels. Maison et al. suggest different effects of GH and IGF-1 on lipidic profile.⁴⁰ One study reports that administration of GH antagonist in acromegaly increase TC⁴¹ and another that GH is responsible for lowering LDL-C by accelerating its elimination rate.⁴² Szkodziński et al, report that administration of statins and low fat diet in hypercholesterolemic patients reduce IGF-1, TC and LDL-C.⁴³

Different studies find elevated levels of fibrinogen in acromegalic patients, with decrease of those levels after treatment.²⁵⁻²⁹ Residual risk with higher levels in treated patients than controls was found in some studies.^{25, 28, 29} In the present study, higher levels of fibrinogen were also found in both active and controlled acromegaly groups when compared with control group. No differences were found between active and controlled group. Few studies evaluate the role of protein C, protein S and ATIII in acromegaly. Erem et al

showed higher levels of ATIII, lower levels of protein S and no difference in protein C levels between acromegalic patients and a control population²⁷. In this study, higher levels of ATIII were found in active acromegalic patients when compared with both control population and controlled patients, with no differences found between control and controlled acromegaly groups. Similar levels of proteins C and S were found among the three groups. Levels of coagulation factor VIII were similar in evaluated groups, as in other studies that found no significant difference in factor VIII levels between acromegalic patients and control subjects or between remission and active disease.^{26, 27} High fibrinogen levels in acromegalic patients suggest the existence of a pro-coagulation status in acromegaly, with residual risk in controlled disease. However, ATIII levels may be elevated in response to high fibrinogen, counterbalancing its effect. Coagulation status in acromegalic patients should be further studied.

PAI-1 polymorphisms were no different among the three groups, which suggest no genetic predisposition for this factor is present in acromegalic patients.

In conclusion, patients with active acromegaly have subtle changes in BP, and relevant changes in lipidic profile, glucose and coagulation status. With control of the disease, there is amelioration of these parameters, but probably with a residual risk superior to control subjects. Although trying to deduce cardiovascular risk, this study is not able to access morbidity and mortality risk in acromegalic patients.

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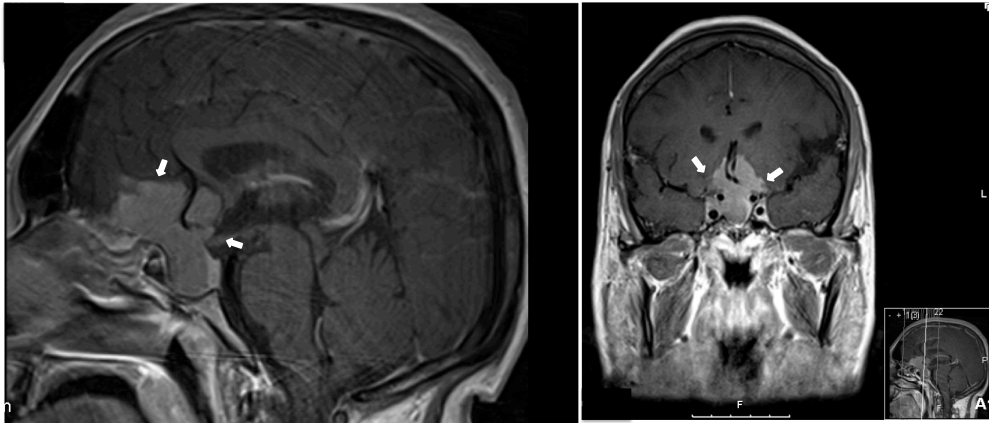


Figure 1. Magnetic Resonance of a pituitary macroadenoma with suprasellar extension and mass effect over several cerebral structures.

Table 1. Clinical Characteristics of control subjects, patients with active acromegaly and controlled acromegaly.

Parameter	Controls	Active Acromegaly	Controlled Acromegaly
Number of patients	11	11	12
Sex (male/female)	6/5	5/6	4/8
Age*	51.36 ± 13.76	50.64±12.63	54.00±12.57
Disease duration	_____	3.91±3.05	7.42±8.16
Macro/Microadenoma	11/0	9/2	11/1
Previous surgery (yes/no)	11/0	8/3	11/1
Previous radiotherapy (yes/no)	0/12	0/11	1/11
Medical treatment (SMS analogs/GHR antagonists/No)	_____	6/2/3	6/0/6
Hypopituitarism (yes/no)	4/7	1/10	0/12

Values are expressed as means ± Std. Deviation

SMS analogs: somatostatin analogs; GHR antagonists: Growth Hormone Receptor antagonists

* No statistically significant differences in age among groups

Table 2. GH and IGF-1 levels and %ULN in patients with acromegaly. BMI, BP, lipidic profile and glucose status in control, active acromegaly and controlled acromegaly groups.

Parameter	Controls	Active Acromegaly	Controlled Acromegaly	P-value		
				(a)	(b)	(c)
GH (µg/L)	_____	11.57±10.80	1.25±1.34	_____	_____	0.01
IGF-1 (µg/L)	_____	612.00±373.22	230.33±70.17	_____	_____	0.007
%ULN	_____	250.42±134.61	95.75±14.88	_____	_____	0.003
BMI (Kg/m ²)	28.91±4.76	29.06±5.72	31.53±5.93	ns	ns	ns
SBP (mmHg)	126.55±23.31	133.45±19.59	129.25±15.98	ns	ns	ns
DBP (mmHg)	74.55±16.12	76.27±11.29	72.67±8.74	ns	ns	ns
TC (mg/dL)	188.55±41.25	201.73±34.57	170.42±31.67	ns	ns	<0.05
HDL-C (mg/dL)	47.36±6.48	46.55±11.46	56.08±12.51	ns	<0.05	ns
LDL-C (mg/dL)	111.09±31.40	130.82±31.48	96,82±25,23 ^a	ns	ns	0.01
TG (mg/dL)	135.09±49.12	121.91±32.94	105.82±40.87 ^a	ns	ns	ns
Blood glucose (mg/dL)	87.91±13.19	151.2±102.5	108.33±23.43	0.05	<0.05	ns

Values are expressed as means ± Std. Deviation; ^a No data available for 1 subject

GH – Growth Hormone; IGF-1 - Insulin-like Growth Factor 1; %ULN - percentage of Upper Limit of Normal Range; BMI – Body Mass Index; SBP – Systolic Blood Pressure; DBP – Diastolic Blood Pressure; TC – Total Cholesterol; HDL-C – High Density Lipoprotein Cholesterol; LDL-C – Low Density Lipoprotein Cholesterol; TG – Triglycerides.

(a) Controls vs Active Acromegaly; (b) Controls vs Controlled Acromegaly; (c) Active Acromegaly vs Controlled Acromegaly; ns: non significant.

Table 3. Hypertension, hyperglycemia and hyperlipidemia in studied groups.

Category	Control	Active Acromegaly	Controlled Acromegaly
Hypertension	27.3%	36.4%	50%
Hyperglycemia*	0%	72.7%	58.3%
Hyperlipidemia	54.5%	81.8%	66.7%

*P=0.001

Table 4. Coagulation status in control, active acromegaly and controlled acromegaly groups.

Parameter	Controls	Active Acromegaly	Controlled Acromegaly	P-value		
				(a)	(b)	(c)
Fibrinogen (mg/dL)	356±86	427±62	437±107	<0.05	<0.05	ns
Protein C (U/mL)	1.17±0.21	1.17±0.20	1.20±0.26	ns	ns	ns
Protein S (U/mL)	0.97±0.19	1.07±0.22 ^a	1.02±0.16	ns	ns	ns
Antithrombin III (U/mL)	0.95±0.16	1.13±0.09	1.02±0.16	<0.05	ns	0.05
Factor VIII (%d.N.)	134.90±33.45	120.08±32.61	129.32±45.42	ns	ns	ns

(a) Controls vs Active Acromegaly; (b) Controls vs Controlled Acromegaly; (c) Active Acromegaly vs Controlled Acromegaly; ns: non significant.

^a No data available for 1 subject

Anexos

Anexo I

Parecer da Comissão de Ética para a Saúde do Hospital de São João

Exma. Sra.
Ana Sofia Amado
Rua Jaime Moniz, 26
3810-123 Aveiro

13.JAN.12 090934

Sua referência

Sua comunicação de

Nossa referência

Data N.º

ASSUNTO

Submissão de pedido para a realização de Projecto de Investigação

Projecto de Investigação – “Alteração dos fatores de risco cardiovascular em doentes com Acromegalia”

Junto envio em anexo cópia do parecer da Comissão de Ética para a Saúde.

Com os melhores cumprimentos.

Porto, 13 de Janeiro de 2012

O Secretário da Comissão de Ética para a Saúde


Dr. Pedro Brito

Na resposta indicar a «Nossa referência» - Em cada ofício tratar só de um assunto.

Comissão de Ética para a Saúde do HSJ
Parecer

Projecto de investigação: "Alterações dos factores de risco cardiovascular em doentes com acromegalia".

Promotor:

- Não aplicável.

Concepção e pertinência do estudo

- Trata-se de um estudo a realizar no âmbito de uma tese de mestrado integrado na Faculdade de Medicina do Porto, que tem como objectivo principal verificar a existência da redução de factores de risco cardiovascular, nomeadamente hipertensão arterial, dislipidemia, factores de coagulação e diabetes, em função do tipo de tratamento aplicado (grupo tratado e grupo control).
- Serão seleccionados doentes acromegálicos seguidos na consulta de Endocrinologia do Hospital de S. João EPE, que serão divididos por 3 grupos de estudo: a) 30 doentes com doença activa; b) 30 doentes tratados cirurgicamente; c) 30 doentes tratados com fármacos do tipo dos análogos da somatostatina.
- Serão recolhidos dados antropométricos, dados sobre composição corporal obtida por BIA, pressão arterial, glicemia e vários outros parâmetros analíticos que poderão estar relacionados com o risco cardiovascular.
- No entanto, alguns dos parâmetros analíticos a avaliar não farão parte dos procedimentos habituais a efectuar nos doentes acromegálicos (exemplos: activador tecidual do plasminogénio; proteínas C e S e anti-trombina III). Se assim for, esta avaliação tem custos adicionais, pelo que deve ser referenciado qual o tipo de financiamento e por que entidade será feito o financiamento dos respectivos custos.
- O estudo terminará em Abril de 2012.
- O estudo é importante, pertinente e está bem fundamentado.
- Os critérios de inclusão e exclusão estão suficientemente detalhados.
- No protocolo do estudo submetido à CES, não está explicitado se a informação constante na folha de obtenção de consentimento/informação ao participante, "a realização de um exame físico com recolha de parâmetros vitais", será efectuado pelo elo de ligação, Professor Davide Carvalho ou pela Investigadora Principal, a aluna do 6º ano do mestrado integrado de Medicina, Ana Sofia Amado. Depreende-se que tais procedimentos serão efectuados pelo Médico/elo de ligação.
- A Investigadora Principal, a aluna do 6º ano do mestrado integrado de Medicina, Ana Sofia Amado, tendo como elo de ligação aos doentes do hospital, o Médico Endocrinologista Professor Davide Carvalho, Director do Serviço de Endocrinologia do Hospital de S. João EPE, dispõe das competências técnicas e científicas para a realização do estudo.
- O estudo será realizado no Serviço de Endocrinologia do Hospital S. João EPE que dispõem das condições necessárias para a realização do estudo. O estudo está autorizado pelo Director de Serviço Professor Davide Carvalho.

- Benefício/Risco

- Dada a natureza e características do estudo não haverá benefícios, riscos ou incómodos para os participantes no estudo.

– **Respeito pela liberdade e autonomia do sujeito do ensaio**

- A folha de informação submetida à CES contém toda a informação relevante relacionada com o tipo de estudo proposto.
- A gratuidade do sujeito do ensaio em participar no estudo é igualmente garantida.
- Estão consignados os direitos e referenciadas as (não) consequências para o sujeito do estudo em não participar e, uma vez dado o seu consentimento, ter a possibilidade de exercer o direito de não continuar no estudo sem que daí resulte qualquer modificação dos cuidados médicos a prestar.

– **Confidencialidade dos dados**

No protocolo submetido à CES é referido que “serão usadas 2 fichas uma em que se colocará a identificação do doente e um número...”. Assim, a confidencialidade dos dados pode não estar garantida, pelo que, deverá haver apenas uma ficha para colheita de dados onde figure um número de código.

– **Indemnização por danos**

Não aplicável.

– **Continuação do tratamento**

Não aplicável.

– **Propriedade dos dados**

Não aplicável.

Conclusão

Em face da análise do protocolo do estudo “Alterações dos factores de risco cardiovascular em doentes com acromegalia”, proponho a sua aprovação pela CES do HSI, depois de obtidas as respostas às questões formuladas em itálico e em sublinhado.

Porto, 28 de Julho de 2011

O Relator

Prof. Manuel Vaz Silva

As questões foram respondidas adequadamente.

17/10/2011

Manuel Vaz Silva

CES

COMISSÃO DE ÉTICA PARA A SAÚDE

8. TERMO DE RESPONSABILIDADE

Eu, abaixo-assinado, Ana Sofia Duarte Amado,
na qualidade de Investigador Principal, declaro por minha honra que as informações prestadas neste questionário são verdadeiras. Mais declaro que, durante o estudo, serão respeitadas as recomendações constantes da Declaração de Helsínquia (com as emendas de Tóquio 1975, Veneza 1983, Hong-Kong 1989, Somerset West 1996 e Edimburgo 2000) e da Organização Mundial da Saúde, no que se refere à experimentação que envolve seres humanos.

Porto, 18 / julho / 2011

28/07/2011

Ana Amado

O Investigador Principal

A Comissão de Ética para a Saúde tendo aprovado o parecer do Relator, aguarda que o Investigador/Promotor esclareça as questões nele enunciadas para que possa emitir parecer definitivo.

[Assinatura]
Prof. Doutor Filipe Almeida
Presidente da Comissão de Ética

PARECER DA COMISSÃO DE ÉTICA PARA A SAÚDE DO HOSPITAL DE S. JOÃO

emitido na reunião plenária da CES

de

*Em reunião me foram
cebam e esclarecimentos
prestados pelo investigador*

A Comissão de Ética para a Saúde APROVA por unanimidade o parecer do Relator, pelo que nada tem a opor à realização deste projecto de investigação.

2011/10/14

[Assinatura]
Prof. Doutor Filipe Almeida
Presidente da Comissão de Ética

Anexo II

Normas de Publicação na revista Hormones

INSTRUCTIONS FOR PREPARATION OF MANUSCRIPT

HORMONES publishes articles related to:

- Original research findings on humans or experimental animals
- Complete reviews of the Literature
- Case reports
- Puzzling cases: Undiagnosed cases or cases in which the final diagnosis was unexpected
- Editorial Comments
- News and Views
- Book Reviews
- Letters to the Editor
- Short notes on etymology of medical terms
- History of Endocrinology

PREPARATION OF MANUSCRIPT

- Must be written in English
- Use wide margins
- Number all pages
- Use separate pages for title page, references, footnotes, tables, legends

The title page should include

- Full title
- Abbreviated title of not more than 40 characters
- Authors' names and institution affiliations
- Corresponding author's address, telephone number, fax and e-mail
- Key words up to 8
- Grants or fellowship supports

ABSTRACT

For research papers the abstracts must be structured: OBJECTIVE, DESIGN, RESULTS, CONCLUSIONS. Not exceeding 200 words (not necessary for review articles)

Abstract is not necessary for review articles. Describe briefly the background, the aim of the study or the hypothesis tested, the methods used, the results and the conclusions.

MAIN TEXT

Follow the usual architectural model, namely: introduction, subjects or

experimental animals and methodology, results, discussion Laboratory values should be stated in both the international system (SI units) and in metric units in parenthesis. The abstract should be stated only in SI units. Temperatures should be written in degrees Celsius

FOOTNOTES

The text should be numbered consecutively at the foot of each page using a line for separation from the text

FIGURES

For electronic submission use a separate file for each figure in one of the three acceptable formats TIF, EPS, JPG (at least 300dpi). For mail submission send 3 sets of figures for the reviewers and 2 original sets for press requirements. Mark with a soft pencil only on the back the number of the figure, the name of the first author and the presentation (top) with an arrow. Number in Arabic numerals. TABLES should be presented on separate plain pages as printed text. Tables require a concise heading.

REFERENCES References should be cited consecutively in numerical order in the text (as superscript outside the punctuation) and the same numerical order must be followed on a separate sheet at the end of the manuscript. The title of the Journals used follow the abbreviated style used in the index medicus. The author is responsible for the accuracy of references.

Examples of References

- *Papers published in Journals:*

Mahagan T, Lightman SL, 2000 A simple test for growth hormone deficiency in adults. J Clin Endocrinol Metab 85: 1473-1476

When the number of authors exceeds six, the designation et al must be used after the third author

- *Books*

Mazzaferri EL 1993 Thyroid carcinoma. Papillary and follicular. In: Mazzaferri EL, Samaan N (eds) Endocrine tumors, Blackwell Scientific Publications Inc, Cambridge; pp, 278-333

SUBMISSION PROCEDURES

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- Mail Submission of an original and four copies, typewritten on one side, double spaced on standard paper. Manuscript accompanied by a disk with the text in electronic form. Please label the outside of the diskette with the first author's name and the word processing program and version (e.g., Word-Perfect 5.0).
Provision of a statement signed by all authors that the manuscript has not been published or submitted elsewhere.
Personal communications should not be included in the references. They may be cited in the text in parentheses. Papers in press may be mentioned in the references given the Journal.
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Manuscripts will become the permanent property of HORMONES and should not be published elsewhere without written permission from the authors and Journal.

Manuscripts are submitted to HORMONES with the understanding that they have not been simultaneously submitted to other journals

ETHICAL CONSIDERATION

Authors should state these, when applicable. The relevant statement should also be accompanied by a notation of approval by the institutional committee on human research, whenever applicable