Assessment of the awareness and management of cardiovascular complications of acromegaly in Italy. The COM.E.T.A. (COMorbidities Evaluation and Treatment in Acromegaly) Study

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ABSTRACT. ***Background:*** **During the course of acromegaly, cardiovascular, respiratory, and metabolic co-morbidities contribute to enhanced mortality. In 2002, the Pituitary Society and the European Neuroendocrine Association sponsored a Consensus Workshop in Versailles during which guidelines for diagnosis and treatment of co-morbidities in acromegaly were defined. However, as for other guidelines previously issued in the field, no data are available on their clinical application.** ***Aim:*** **The aim of this work coordinated by the Italian Study group on co-morbidities evaluation and treatment in acromegaly (COM.E.T.A.) was to assess, on a national basis, the application in the clinical practice of the Versailles criteria for diagnosis and treatment of cardiovascular co-morbities in acromegaly.** ***Materials and methods:*** **In January 2007 an *ad hoc* designed questionnaire was sent by mail to 130 endocrine Centers in Italy.** ***Results:*** **The guidelines have been generally well perceived and translated in clinical practice. Specifically: 1) echocardiography is considered the mainstay for the diagnosis and follow-up; 2) ambulatory blood pressure monitoring and blood lipid assessment are performed in most hypertensive patients; 3) most endocrinologists directly manage hypertension and are aware of the uncertainty of the effect of the control of the disease on blood pressure levels; 4) ACE inhibitors and angiotensin receptors blockers are first-choice anti-hypertensive treatment; 5) approximately half of the centers consider somatostatin analogues of paramount relevance for biochemical control of disease; 6) awareness that left ventricular hypertrophy and heart failure are the most relevant cardiovascular complications is high although the impact of ischemic, arrhythmic, and valvular complications on prognosis is less well perceived.** ***Conclusion:*** **The results of the present survey suggest that previuosly issued guidelines are generally carefully followed in the clinical practice. On the other side, a certain lack of awareness of emerging aspects of the cardiovascular co-morbities of acromegaly confirms the necessity of periodically updating the guidelines based on the availability of new clinical information.**

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INTRODUCTION

During the natural course of acromegaly, cardiovascular, respiratory, and metabolic co-morbidities contribute to significantly enhanced mortality (1-4). Even if a definitive link between myocardial dysfunction and increased mortality has not been established yet, some studies (5, 6) support the conclusion that optimal biochemical control of acromegaly is associated with decreased cardiovascular mortality. Several studies emphasized the role of GH and IGF-I excess in the occurrence of a specific acromegalic cardiomyopathy which is characterized by ventricular concentric hypertrophy, hyperkinetic syndrome, and blunted cardiac response to exercise in terms of ejection fraction (7). Ventricular hypertrophy is independent of changes in blood pressure or preload and is also observed in young patients suggesting a primary pathogenetic role of GH/IGF-I excess (7). At an early stage, increased cardiac contractility with high cardiac output and lowered peripheral vascular resistance is observed ("hyperkinetic syndrome"). Subsequently, when interstitial fibrosis develops, decreased diastolic filling wave is observed with a decrease in the early to late mitral and tricuspidal velocity rate accompanied by an increase in isovolumetric relaxation time. Finally, ventricular dilatation and impairment of systolic and diastolic function, along with mitral and aortic disease, may lead to cardiac failure. Patient's age and disease duration seem to be the main determinants in the development of acromegalic cardiomyopathy (7).

Controlling GH hypersecretion (8) can reverse some features of acromegalic cardiomyopathy such as myocardial hypetrophy and diastolic dysfunction, particularly in patients younger than 45 yr, those with short history of GH hypersecretion, and those in whom GH hypersecretion is controlled for more than 5 yr (7, 9-17). However, the treatment of acromegaly fails to improve the long-term prognosis when congestive heart failure, chronic dilated cardiomyopathy, and left ventricular systolic dysfunction are already present (10, 17). This may be particularly true in case of resistance to treatment (18).

In April 2002, the Pituitary Society and the European Neuroendocrine Association sponsored a Consensus Work-

*See the appendix for the COM.E.T.A. Study Group members.

Key-words: Acromegaly, awareness, cardiomyopathy, echocardiography, hypertension, questionnaire.

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shop in Versailles, during which criteria and guidelines for diagnosis and treatment of co-morbidities in acromegalic patients were defined. According to these guidelines, at the time of diagnosis, cardiac hypertrophy should be excluded by echocardiography (4). Follow-up depends on individual cardiovascular risk (considering the initial findings) and the biochemical control of the disease (4). Pre-operative treatment with somatostatin analogs for 3 months has been recommended until surgery is considered safe because it may improve cardiovascular function (7).

Hypertension is the most frequent cardiovascular abnormality in acromegaly with a prevalence ranging from 18 to 60% (19). More precise assessments such as ambulatory blood pressure monitoring (ABPM) and evaluation of the hypertension-associated atherosclerosis and coronary artery disease have been proposed by some authors (4). Twenty-four-h electrocardiogram (ECG) recording may be required to exclude arrhythmias (4). Effective acromegaly control (8) often does not lead to regression of hypertension, and it may be necessary the use of anti-hypertensive drugs considering also the presence of concomitant conditions like diabetes (4).

Finally, according to the above-mentioned guidelines the assessment of the metabolic associated risk factors (diabetes and hyperlipidemia) may be evaluated at diagnosis and during long-term follow-up (4).

So far, no data have been reported subsequently on the application of these guidelines in the clinical setting. The aim of the Italian Study group on co-morbidities evaluation and treatment in acromegaly (COM.E.T.A.) was to assess, *via* a national survey, the awareness and the compliance to the Versailles criteria for diagnosis and treatment of cardiovascular co-morbidities in acromegaly.

MATERIALS AND METHODS

As previously reported for other endocrine diseases for the diagnosis and management of which clinical guidelines have been issued (20, 21), an *ad hoc* questionnaire developed to assess their translation in the clinical practice has been shown to be a very useful investigational tool. Therefore, in early January 2007 a questionnaire focusing on cardiovascular co-morbidities was prepared and sent by mail to 130 endocrine Centers in Italy selected on the basis of the presence of an active pituitary unit/expert.

The questionnaire was structured with 2 first introductive questions aimed to ascertain whether acromegaly was considered disease of primary relevance by the interviewed endocrinologists both for diagnosis and treatment and 2 following different sections, the first one consisting of 11 questions focusing on prevalence, diagnosis, treatment, and monitoring of hypertension in acromegalic patients as observed and handled at each single site (Table 1A) and the second one made of 13 questions

Table 1A - *COM.E.T.A. Questionnaire - Section I: hypertension.*

Question no.	
1	Which percentage of acromegalic patients referring to your Center is affected by hypertension?
2	Which percentage of acromegalic patients present severe hypertension?
3	Which instrumental evaluations are used in your Center to make the diagnosis of hypertension?
4	Which assessments are commonly requested in your Center for the acromegalic patient affected by hypertension?
5	Who is going to prescribe the antihypertensive treatment to acromegalic patients in your Center?
6	Are other co-morbidities going to influence the anti-hypertensive treatment in the acromegalic patient?
7	Which percentage of acromegalic patients appear to have hypertension controlled just by somatostatin analogues treatment?
8	Which relevance has the control of blood pressure in the acromegalic patient?
9	Which anti-hypertensive is considered the first choice drug for the acromegalic patient?
10	Which follow-up is usually planned for the acromegalic patient affected by hypertension?
11	Which instrumental or laboratory assessment is of primary relevance during the follow-up of the acromegalic patient affected by hypertension?

Table 1B - *COM.E.T.A. Questionnaire - Section II: cardiac complications.*

Question no.	
1	Which instrumental evaluations are most commonly requested in your Center for acromegalic patients?
2	Which complication is more commonly observed in acromegalic patients affected by cardiomiophathy?
3	Which condition is more commonly associated to the development of cardiomiopathy in acromegalic patients?
4	Which condition is mainly influencing the prognosis in acromegalic patients affected by cardiomiopathy?
5	Which percentage of acromegalic patients in your Center present left ventricular hypertrophy?
6	Which percentage of acromegalic patients in your Center present and is treated for cardiac rhythm disturbances?
7	Which percentage of acromegalic patients in your Center present clinically relevant alterations of cardiac valves?
8	Which percentage of acromegalic patients referring to your Center is affected by clinically relevant cardiac ischemia?
9	Which cardiovascular co-morbidities in your Center are directly handled by the endocrinologist?
10	Does control of GH/IGF-I axis improve left ventricular hypertrophy?
11	Which treatment mostly influence the cardiomiopathy in acromegalic patients?
12	During the cardiologic follow-up of acromegalic patients which conditions are mostly influencing the choice and the timing of assessments?
13	Which cardiological follow-up assessments are foreseen in your Center for the acromegalic patient?

focusing on diagnosis and handling of cardiac co-morbidities of the disease (Table 1B).

RESULTS

General features

One hundred and twenty-seven questionnaires were returned to the COM.E.T.A. coordinating Center by the end of February 2007. Only one questionnaire in which 24 answers were not duly completed was not included in the analysed data.

Participation in the study exceeded 96% of the contacted Centers, and results of this investigation as per the answers received are reported here below.

Acromegaly was considered a disease of primary relevance for 99 (78.6%) of the interviewed endocrinologists and 86.5% of acromegalic patients resulted to be directly followed in the Center in which the diagnosis of acromegaly was made. The majority of the endocrinologists reported to follow directly hypertension (82%) but not left ventricular hypertrophy (32%), congestive heart failure (19%), and arrhythmias (8%).

Specific findings

Hypertension

Hypertension could be detected in 36-50% of the acromegalic patients according to 50 (40%) of the interviewed endocrinologists, however 30 (23.8%) of them attributed to this comorbidity a greater prevalence (>50% of acromegalic patients). Diagnosis was reported to be performed by random BP assessment or ABPM according to 68 (54%) of the answers received. In 39 cases (31%) the diagnosis of hypertension may be made considering the presence of anti-hypertensive treatment and in 23 cases (18%) by cardiologic consultation.

Most frequently used instrumental and laboratory assessments have been indicated echocardiography and doppler ultrasound of carotid arteries respectively by 121 (96%) and 80 (63.5%) of the interviewed specialists. Plasma lipid profile and catecholamines were reported to be also frequently evaluated in hypertensive patients by 105 (83.3%) and 41 (32.54%) of the specialists, respectively. Only 2 (1.59%) of interviewed endocrinologists did not prescribe any of these examinations while some of them (33, 26%) suggested other instrumental and laboratory assessments (Fig. 1).

Anti-hypertensive treatment was reported to be directly prescribed by endocrinologists in 90 (71.43%) of the Centers while therapy was prescribed by a cardiologist in 48 (38.1%) Centers or by an Internist or a General Practitioner in 15 (12%) and 10 (8%) of the cases, respectively. Diabetes, cardiac hypertrophy, and arrhythmias were the co-morbidities which most influence antihypertensive therapy prescription according to 100 (79.4%), 79 (62.7%), and 67 (53.2%) of the interviewed endocrinologists, respectively; while only in 8 cases (6.3%) no one co-morbid conditions seemed to influence the anti-hypertensive therapy prescription. Only 1 (0.79%) interviewed endocrinologist included lipid profile among the relevant co-morbid conditions.

One hundred and five of the interviewees (83.3%) stated that blood pressure control was very important in the management of the acromegalic patient and, according to 48 (38.1%) of the answers, control can be reached successfully by normalisation of GH and IGF-I hypersecretion with somatostatin analogs in 20 to 60% of the acromegalic patients. ACE inhibitors and angiotensin receptors blockers (ARB) were reported to be the most widely used drugs to treat hypertension being prescribed by 77 (61%) as first choice anti-hypertensive while β-blockers or calcium antagonists or other orally effective anti-hypertensive agents were currently used in less than 5.0% of the cases. Interestingly, about one third (31%) of the interviewees declined to select the first choice anti-hypertensive treatment (Fig. 2).

Random BP assessment every 3 months was reported to be used in 77 (61%) Centres for the follow-up of patients although a yearly or biannual ABPM was reported in 29 (23.0%) and 15 (12%) Centers, respectively. Less frequently (13, 10%) biannual random BP assessment was used. About 15% (18) of the interviewees used other strategies for the follow-up of hypertension in acromegalic patients (Fig. 3).

In the follow-up of hypertension echocardiographic examination every 12 months was deemed mandatory by 103 (81.7%) of the specialists. More than 20% of the interviewees considered mandatory a yearly ABPM or a yearly evaluation of lipid profile. By 16% of the endocrinologists, doppler ultrasound of carotid arteries was considered the most important examination in the follow up of these patients. In 14 cases (11%) other examinations (especially *fundus oculi*) were mentioned.

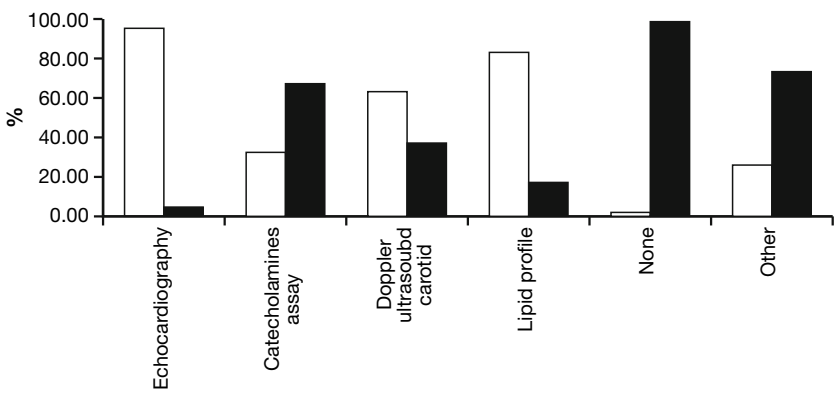

Fig. 1 - *Instrumental and laboratory assessments in hypertensive patients with acromegaly at diagnosis. White bars represent positive responses, and black bars represent negative responses.*

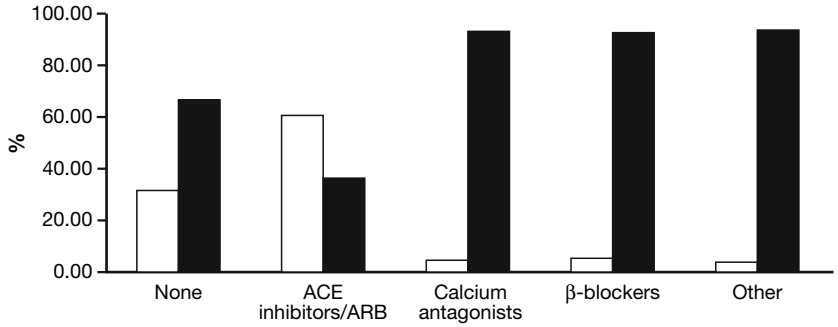

Fig. 2 - *First choice anti-hypertensive treatment in acromegalic patients. White bars represent positive responses, and black bars represent negative responses. ARB: angiotensin receptors blockers.*

Cardiomyopathy

As far as clinical aspects of acromegalic cardiomyopathy were concerned, left ventricular hypertrophy was the condition reported by 104 (82.5%) of the interviewed endocrinologists as the most relevant aspect observed in acromegalic patients, followed by diastolic dysfunction, congestive heart failure and systolic dysfunction, which were considered the most relevant complications by 37 (30%), 15 (12%), and 3 (2.3%) of the endocrinologists, respectively.

Left ventricular hypertrophy could be detected in 20-60% of the acromegalic patients according to 87 (69%) of the interviewed endocrinologists; however, for 20 of them (16%) this percentage exceeded 60% of patients.

The control of GH and IGF-I axis improves left ventricular hypertrophy in 20-60% of patients according to 80 (63%) endocrinologists and for 14 (11 %) this percentage may exceed 60%. More than half of the interviewees reported that arrhythmias, valvular alterations, and cardiac ischemia could be detected in less than 20% of the patients.

Congestive heart failure, even if considered less frequent, was thought to have the greatest influence on prognosis of patients as reported by 94 (74.6%) of the endocrinologists, other conditions influencing prognosis being considered cardiac ischemia by 26 (20.63%), arrhythmias by 19 (15.8%), and valvular alterations by 11 (8.73%) (Fig. 4).

Disease duration and unsatisfactory control of GH and IGF-I hypersecretion were reported as the major risk factors correlated to the development of the acromegalic cardiomyopathy by 93 (73%) and 67 (53%) of the endocrinologists, respectively. Fourty-four (35%) specialists considered hypertension the factor more correlated to cardiomyopathy. Finally, 22 of the interviewees (18%) mentioned age as the most important risk factor for cardiomyopathy development and only one specialist mentioned diabetes as other risk factor.

For 83 endocrinologists (65.7%), in the management of the acromegalic cardiomyopathy is not important the therapeutic tool employed but the achievement of the biochemical control of the disease; while 17 (13%) and 32 (25%) of them reported that, neurosurgery and somatostatin analog, respectively, represented the best option.

Considering the evaluation of acromegalic cardiomyopathy, at diagnosis, independently of the presence of hypertension, echocardiography was still the examination most frequently prescribed (114, 90%) together with a standard 12-lead ECG and 24-h ECG prescribed by 88 (70%) and 19 (15%) of the specialists, respectively (Fig. 5A). During the follow-up, yearly echocardiography (88%) and yearly 12-lead ECG (65%) remained the most frequently prescribed examinations (Fig. 5B).

Finally 86 (68.2%) of the specialists deemed as extremely important biochemical control of acromegaly to plan visit schedules and instrumental or laboratory assessments for the cardiovascular follow-up of acromegalic patients and considered less important the basal cardiopathy (54%), the concomitant presence of diabetes (40%) and age (24%).

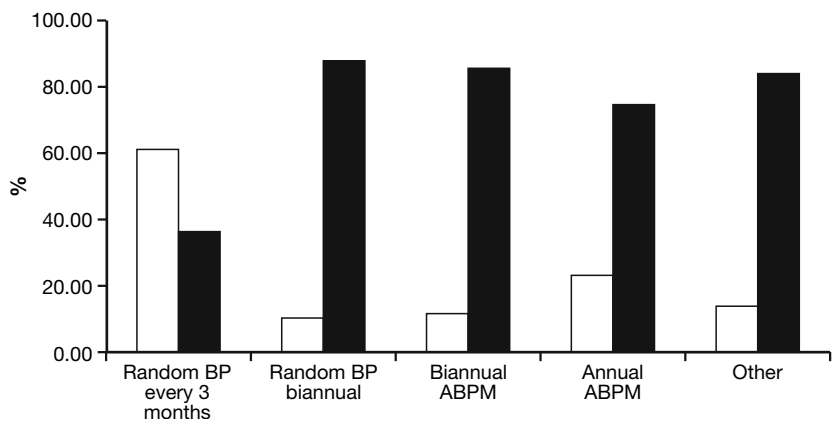

Fig. 3 - *Instrumental assessments for the follow up of hypertension in acromegalic patients. White bars represent positive responses, and black bars represent negative responses. BP: blood pressure; ABPM: ambulatory blood pressure monitoring.*

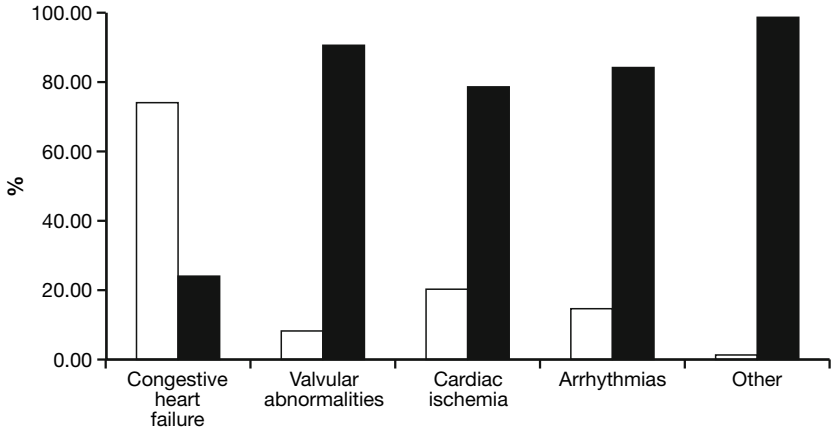

Fig. 4 - *Cardiovascular diseases conditioning prognosis in acromegalic patients. White bars represent positive responses, and black bars represent negative responses.*

DISCUSSION

From the analysis of the answers received to this ad hoc questionnaire, several interesting points of discussion arise since most of the interviewed endocrinologists reported to follow directly acromegalic patients from diagnosis to therapy and during the whole follow up. The large majority of them are aware of the clinical relevance of hypertension and cardiomyopathy in the management of acromegalic patients and they directly deal with the diagnosis of these complications. Concerning treatment, they directly manage hypertension and, even only in some cases, left ventricular hypertrophy, but they generally send the patient to the specialist for the treatment of congestive heart failure and arrhythmias.

The prevalence of hypertension is perceived to be slightly higher than that reported in the literature (7); in fact, a quarter of the endocrinologists interviewed reported in their series a prevalence higher than 50%.

More than the half of the endocrinologists have reported the necessity to use, in the diagnosis and in some case also for the follow up of hypertension, ABPM, for a more precise assessment of blood pressure, as suggested by Versailles guidelines (4) and this is particularly interesting if we consider that very few studies (22-25) have so far used ABPM in the evaluation of hypertensive acromegalic patients.

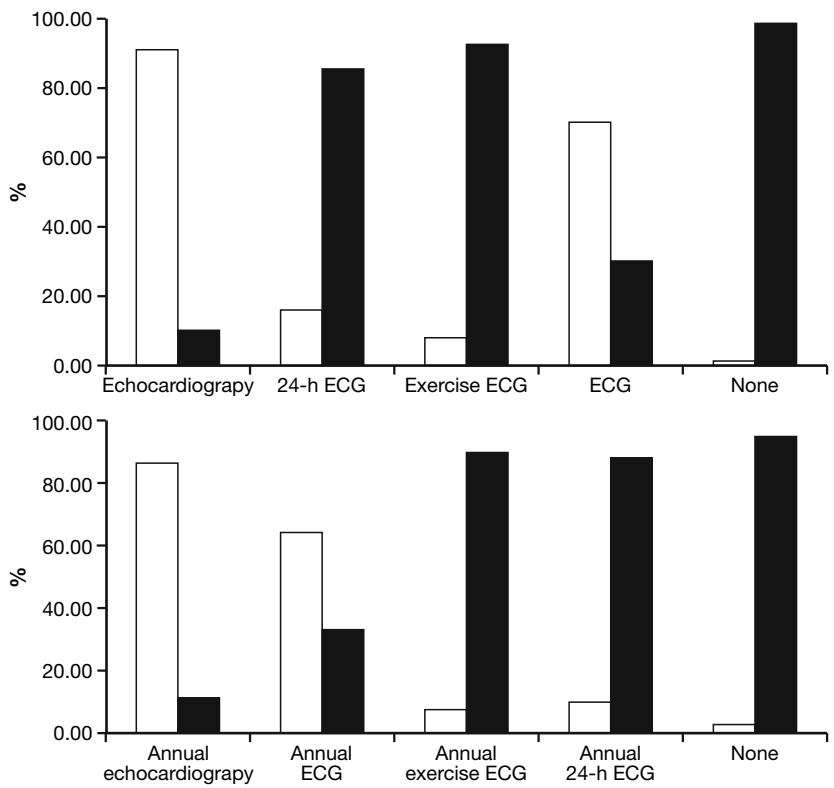

Fig. 5 - *A) Evaluation of acromegalic cardiomyopathy at diagnosis. White bars represent positive responses, and black bars represent negative responses. B) Evaluation of acromegalic cardiomyopathy during follow up. White bars represent positive responses, and black bars represent negative responses. ECG: electrocardiogram.*

Consistently with literature data (7), and with the consensus statement on acromegalic complications (4), yearly echocardiography is considered the mainstay for the diagnosis and follow-up of cardiovascular complications of acromegaly. Finally, more than the half of the interviewees, use doppler ultrasound of carotid arteries in hypertensive acromegalic patients at diagnosis but rarely during follow-up.

Concerning the metabolic profile, blood lipid assessment is performed in most hypertensive acromegalic patients. Interestingly, even if glucose profile was not included in the proposed list of the examinations to be prescribed in hypertensive acromegalic patients, it was often added in the group of "others". This observation and the fact that most of the endocrinologists include diabetes between the co-morbidities which most influence anti-hypertensive therapy, suggest that they consider clinically relevant the association hypertension-diabetes, as suggested by several studies (23, 26-28) and underlined also in Versailles guidelines (4). Probably in line with this observation, ACE-inhibitors and ARB, frequently used in diabetic patients, were the most widely used drugs to treat hypertension in acromegaly and prescribed by 61% of the endocrinologists as first choice anti-hypertensive treatment. The choice of these drugs could have a pathophysiologic basis considering that an activation of the renin-angiotensin-aldosterone (RAA) system is described in acromegaly (29) and some interviewees reported useful to evaluate the RAA system as additional examination to catecholamines. Moreover ACE-inhibitors, are used to limit cardiac remodeling and they are proven to be effective in reducing mortality and morbidity in patients with heart failure (29). Anti-hypertensive treatments are largely used because, as also reported in the consensus statement on acromegalic complications (4), most endocrinologists are aware of the uncertainty of the effect of the control of the GH/IGF-I axis on blood pressure levels.

On the other hand, endocrinologists seem to be aware of the importance of effective acromegaly control (8) for the management of cardiomyopathy. In fact, disease duration and unsatisfactory control of GH and IGF-I axis are reported as the major risk factors correlated with the development of the acromegalic cardiomyopathy respectively by 73% and 53% of the endocrinologists. Approximately, half of the centers considered somatostatin analogs of paramount relevance for biochemical control of disease and of its cardiovascular co-morbidities such as hypertension and left ventricular hypertrophy. Finally, 68% of the specialists deemed as extremely important the biochemical control of acromegaly to plan visit schedules and instrumental or laboratory assessments for the cardiovascular follow-up of acromegalic patients. The endocrinologists interviewed seemed also to be aware that, as indicated in the consensus statement on acromegalic complications (4), elderly patients with acromegaly should be followed indefinitely for management of cardiovascular disease.

The awareness that left ventricular hypertrophy and heart failure are the most relevant cardiovascular complications in acromegalic patients was high among interviewed endocrinologists, but the relevance of other cardiac complications (ischemic, arrhythmic, and valvular) to prognosis was less well perceived. In fact, while the endocrinologists demonstrated to be aware that the global prognosis of acromegalic patients with chronic congestive heart failure was poor (8), they did not consider that the poor prognosis may depend on the fact that, at an advanced stage of cardiomyopathy, fibrosis, arrhythmias, and valvular abnormalities may be irreversible. Because congestive heart failure seems to be rare, several cardiac deaths would appear to be due to arrhythmias and for this reason 24-h ECG recording was recommended in the consensus statement on acromegalic complications (4). From the questionnaire emerged that only 15% and 10% of the endocrinologists prescribe 24-h ECG recording at diagnosis and during the follow up, respectively. More than half of the interviewees reported that arrhythmias, valvular alterations and cardiac ischemia could be detected in less than 20% of the patients. Even if to date no prospective data are available to infer the prognostic value of these cardiac complications in acromegalic patients, their prevalence seems to be underestimated in the questionnaire. In fact, up to 40% of acromegalic patients can suffer from conduction disorders, and it is questioned whether recovery from acromegaly improves this rate (7, 30, 31). The overall prevalence of mitral and aortic abnormalities is high both in patients with active (86%) and controlled (73%) disease (7). Finally there are no definitive epidemiological data on the prevalence of coronary artery, peripheral, and cerebro-vascular disease in acromegaly but *post-mortem* and cardiac catheterization studies described a predominant involvement of small coronary arteries and thickening of intramural coronary arteries. For these reasons and considering the numerous cardiovascular risk factors of acromegalic patients, exercise ECG should be done if angina is present, and the medical treatment of coronary artery disease should be administered as indicated clinically in addition to treating acromegaly, as suggested in Versailles guidelines (4).

A limitation of this study, as for all similar surveys (20, 21), is that we cannot be certain that responses to the questionnaire reflected real clinical practice. In fact, answers may be biased by own perception being not corroborated by objective data. Moreover, we do not know whether answers may be representative of views of other specialists such as neurosurgeons or cardiologists. However, since the interviewed endocrinologists were largely pituitary experts and they follow directly acromegalic patients from diagnosis to therapy and during the whole follow up, they not only seem to be the specialists more suitable to respond to such a questionnaire but also more likely to give answers closer to clinical reality. Furthermore, the accuracy of the selection of involved centers was confirmed by the very high percentage of endocrinologists reporting acromegaly of primary relevance for their clinical work and directly following the patient with acromegaly. Interestingly, this may mean that despite the relatively low figures of incidence of new cases of acromegaly diagnosed in each center [from 1 to 4-6 acromegalic patients, on average, as it can be confirmed by data of a recent multicenter national interventional trial on *de novo* patients (32)] the chronic and disabilitating nature of acromegaly has prompted many Endocrine centers to create a Pituitary unit dedicated to the follow-up of these patients.

In conclusion, the results of this national survey among Italian endocrinologists concerning the awareness and the management of cardiovascular complications in acromegaly suggest that available international guidelines have been generally well perceived and apparently translated into clinical practice.
Specifically:

1. echocardiography is considered the mainstay for the diagnosis and follow-up of cardiovascular complications of acromegaly;
2. ABPM and blood lipid assessment are performed in most hypertensive acromegalic patients;
3. most endocrinologists directly manage hypertension in acromegaly and are aware of the uncertainty of the effect of the control of the GH/IGF-I axis on blood pressure levels;
4. ACE inhibitors and ARB are first choice anti-hypertensive treatment;
5. approximately half of the centers consider somatostatin analogs of paramount relevance for biochemical control of disease and of its cardiovascular co-morbidities such as hypertension and left ventricular hypertrophy;
6. awareness that left ventricular hypertrophy and heart failure are the most relevant cardiovascular complications in acromegalic patients is high although the prognostic relevance of other cardiac complications (ischemic, arrhythmic, and valvular) is less well perceived.

This last apparent lack of awareness of emerging cardiovascular complications of acromegaly is probably due to the quite marginal role to them attributed at the time of the Consensus guidelines (2003). In our view this aspect confirms a dual validity of the survey: in fact, it allows the understanding on one side of the application of the guidelines in the clinical practice, and on the other side the necessity of updating guidelines which is obviously periodically mandatory depending on the availability of new clinical information.

APPENDIX

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