Accepted Preprint first posted on 17 May 2012 as Manuscript EJE-12-0084

Predictors of morbidity and mortality in acromegaly, an Italian survey

M. Arosio[1], G. Reimondo[2], E. Malchiodi[3], P. Berchialla[4], A. Borraccino[4], L. De Marinis[5], R. Pivonello[6], S. Grottoli[7], M. Losa[8], S. Cannavò[9], F. Minuto[10], M. Montini[11], M. Bondanelli[12], E. De Menis[13], C. Martini[14], G. Angeletti[15], A. Velardo[16], A. Peri[17], M. Faustini-Fustini[18], P. Tita[19], F. Pigliaru[20], G. Borretta[21], C. Scaroni[22], N. Bazzoni[23], A. Bianchi[5], M. Appetecchia[24], F. Cavagnini[25], G. Lombardi[6], E. Ghigo[7], P. Beck-Peccoz[3], A. Colao[6] and M. Terzolo[2] for the Italian Study Group of Acromegaly*

[1]Unit of Endocrine Diseases and Diabetology, "S. Giuseppe" Hospital, Multimedica Group, Department of Medical Sciences, University of Milan (MA); [2]Unit of Internal Medicine, "S. Luigi Gonzaga" Hospital, Department of Clinical and Biological Sciences, University of Turin (GR, MT); [3]Unit of Endocrinology and Diabetes, "Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico", Department of Medical Sciences, University of Milan, (EM, PBP); [4]Department of Public Health and Microbiology, University of Turin (PB, AB); [5]Division of Endocrinology and Internal Medicine, Catholic University School of Medicine, Rome (LDM, AB); [6]Department of Molecular and Clinical Endocrinology and Oncology, "Federico II" University of Naples (RP, GL, AC); [7]Division of Endocrinology, Diabetology and Metabolism, Department of Internal Medicine, University of Turin (SG, EG); [8]Pituitary Unit, Department of Neurosurgery, San Raffaele Scientific Institute, University "Vita-Salute", Milan (ML); [9]Department of Medicine and Pharmacology, University of Messina (SC); [10]Department of Endocrine and Medical Sciences, University of Genoa (FM); [11]Division of Endocrinology, Joined Hospitals of Bergamo (MM); [12]Section of Endocrinology, Department of Biomedical Sciences and Advanced Therapies, University of Ferrara (MB); [13]Department of Internal Medicine, General Hospital, Treviso (EDM); [14]3rd Internal Medicine, Department of Medical and Surgical Sciences, University of Padua (CM); [15]Department of Internal Medicine and Endocrine Sciences, University of Perugia (GA); [16]Department of Internal Medicine, Section

of Endocrinology and Metabolism, University of Modena (AV); [17]Endocrine Unit, Department of Clinical Physiopathology, University of Florence (AP); [18]Department of Internal Medicine, Endocrine Unit, "Bellaria" Hospital, Bologna (MFF); [19]Division of Endocrinology, "Garibaldi" Hospital, Catania (PT); [20]Endocrinology and Diabetes Unit, "Azienda Ospedaliero-Universitaria", Department of Medical Sciences, University of Cagliari (FP); [21]Division of Endocrinology and Metabolism, Department of Internal Medicine, "S. Croce" and "Carle" Hospital, Cuneo (GB); [22]Endocrinology, Department of Medical and Surgical Sciences, University of Padua (CS); [23]Endocrinology Unit, "S. Antonio Abate" Hospital, Gallarate, Milan (NB); [24]Endocrinology Unit, "Regina Elena", National Cancer Institute, Rome (MA); [25]Division of Endocrinology and Metabolic Diseases, "San Luca" Hospital, "Istituto Auxologico Italiano IRCCS", University of Milan (FC), Italy.

Short title: Epidemiology of acromegaly in Italy

Key words: acromegaly, epidemiology, GH, IGF-I, remission, diabetes mellitus, hypertension

Counts of words: abstract 226, text 4369

Correspondence to:

Prof Maura Arosio

Unit of Endocrine Diseases and Diabetology

Ospedale S. Giuseppe

Via S Vittore, 12

20123 Milan, Italy

Phone +39 02 85994288

Fax +39 02 50320605

E-mail maura.arosio@unimi.it

Disclosure Summary: The authors have nothing to disclose

*** Italian Study Group on Acromegaly**

Participating centres:

1. Department of Medical Sciences, University of Milan, Unit of Endocrine Diseases and Diabetology, "S. Giuseppe" Hospital, Multimedica Group, Arosio M, Montefusco L.
2. Department of Clinical and Biological Sciences, University of Turin, Unit of Internal Medicine, S. Luigi Gonzaga Hospital, Angeli A., Terzolo M., Reimondo G., Zaggia B.
3. Department of Medical Sciences, University of Milan, Unit of Endocrinology and Diabetes, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Beck-Peccoz P, Spada A, Ferrante E, Malchiodi E
4. Department of Molecular and Clinical Endocrinology and Oncology, University of Naples, Lombardi G., Colao A, Pivonello R.
5. Department of Medical and Surgical Sciences, University of Padua, Sicolo N., Martini C., Maffei P.
6. Department of Internal Medicine, Section of Endocrinology and Metabolism, University of Modena, Velardo A.
7. Department of Medicine and Pharmacology, University of Messina, Trimarchi F, Cannavò S.
8. Department of Internal Medicine, General Hospital, Treviso, De Menis E.
9. Unit of Endocrine and Metabolism, Department of Internal Medicine and Medical Sciences, Policlinico Universitario A. Gemelli, Catholic University School of Rome, De Marinis L, Bianchi A., Cimino V.
10. Section of Endocrinology, Department of Biomedical Sciences and Advanced Therapies, University of Ferrara, Degli Uberti EC, Ambrosio MR, Bondanelli M.
11. Division of Endocrinology, Ospedali Riuniti di Bergamo, Pagani G., Montini M, Attanasio R.
12. Department of Internal Medicine, Endocrine Unit, Bellaria Hospital, Bologna, Faustini-Fustini M
13. Endocrine Unit, Department of Clinical Physiopathology, University of Florence, Mannelli

M., Peri A.

14. Division of Endocrinology, Department of Medical and Surgical Sciences, Hospital/University of Padua, Mantero F., Scaroni C.
15. Pituitary Unit, Department of Neurosurgery, San Raffaele Scientific Institute, Università Vita-Salute, Milan, Mortini P, Losa M.
16. Division of Endocrinology and Metabolism, S. Croce and Carle Hospital, Cuneo, Borretta G., Razzore P.
17. Department of Internal Medicine and Endocrine Sciences, University of Perugia, Angeletti G., Della Torre D.
18. Endocrinology and Diabetes, Department of Medical Sciences, University of Cagliari, Mariotti S., Pigliaru F.
19. Division of Endocrinology, Diabetology and Metabolism, Department of Internal Medicine, University of Turin, Ghigo E., Grottoli S.
20. Endocrinology Unit, S. Antonio Abate Hospital, Gallarate, Milan, Mainini AL, Bazzoni N
21. Endocrinology Unit, Regina Elena National Cancer Institute, Rome, Appetecchia M, Baldelli R
22. Endocrinology, Department of Internal and Specialistic Medicine, University of Catania, Garibaldi-Nesina Hospital, Catania, Vigneri R, Tita P
23. Department of Endocrine and Medical Sciences, University of Genoa, Minuto F, Giusti M, Ferone D.
24. Division of Endocrinology and Metabolic Diseases, IRCCS San Luca Hospital, Istituto Auxologico Italiano, University of Milan, Cavagnini F.

Abstract

Objective: To describe demographic and hormonal characteristics, co-morbidities (diabetes mellitus and hypertension), therapeutic procedures and their effectiveness, as well as predictors of morbidity and mortality in a nation-wide survey of Italian acromegalic patients.

Design: Retrospective multicentre epidemiological study endorsed by the Italian Society of Endocrinology and performed in 24 tertiary referral Italian centres . The mean follow-up time was 120 months.

Results: A total of 1512 patients, 41% M, mean age: 45±13 years, mean GH: 31±37 mcg/L, IGF-I: 744±318 ng/ml, were included. Diabetes mellitus was reported in 16% of cases, hypertension in 33%. Older age and higher IGF-I levels at diagnosis were significant predictors of diabetes and hypertension. At the last follow-up, 65% of patients had a controlled disease, of whom 55% were off medical therapy. Observed deaths were 61, with a standardized mortality ratio (SMR) of 1.13 (IC95%: 0.87-1.46). Mortality was significantly higher in the patients with persistently active disease (1.93; IC95%: 1.34-2.70). Main causes of death were vascular diseases and malignancies with similar prevalence. A multivariate analysis showed that older age, higher GH at last follow-up, higher IGF-I levels at diagnosis, malignancy and radiotherapy were independent predictors of mortality.

Conclusions. Pre-treatment IGF-I levels are important predictors of morbidity and mortality in acromegaly. The full hormonal control of the disease, nowadays reached in the majority of patients with modern management, reduces greatly the disease-related mortality.

Introduction

Acromegaly is a serious and disfiguring rare disease, resulting from chronic exposure to elevated GH and IGF-I concentrations, mostly due to a pituitary GH-secreting adenoma.

Almost all the epidemiological studies reported that acromegaly is associated with increased mortality with respect to the general population, mostly due to cardiovascular events and stroke (1-4). Some (1,5-7), but not all the surveys (8-11), also showed an increased mortality for respiratory complications, and even more controversial are the findings about increased mortality for cancer (4,12,13).

Studies published between 1970 and 1995 reported standardized mortality ratio (SMR) of 1.89-3.31, but more recent surveys showed SMR ranging from 1.16 to 2.14 (3,4). These data were interpreted to reflect an improvement of treatment modalities achieved over the years with the introduction of new drugs (2-4). Conventional external radiotherapy was found to decrease survival mostly in female patients according to some (7,9,11) but not all the studies (3,6,10).

All the surveys agree that post-treatment GH levels are the strongest outcome predictor, (1,3,6-11,13) but less agreement exists on the role of IGF-I concentrations either at diagnosis or after treatment (8-11,13,14). Since GH and IGF-I act on a wide range of biochemical pathways and modulate intermediate metabolism and cell growth, it is not surprising that acromegaly is a systemic disease, associated with a number of co-morbidities. Hypertension is reported to be present in 17% to 51% and diabetes mellitus in 9% to 23% of patients (15) contributing to increased mortality (5,12,13), whereas a better control of these associated conditions could increase survival (2).

Thus, an increased mortality in acromegaly depends on several factors, some of which changed over the years. Due to the low prevalence of acromegaly, of about 60 patients per million inhabitants (15), only nation-wide surveys may produce significant data on patient outcome and predictive factors. This study presents epidemiological data on a large population of Italian acromegalic patients followed-up for more than 10 years, and includes mostly patients treated after the introduction of somatostatin analogs (SSAs). The survey has the following aims: 1) to

describe the demographic, clinical and hormonal characteristic of this well-defined acromegalic population, 2) to evaluate the kind of therapies preferred by Italian endocrinologists and their effectiveness, and 3) to assess the long-term outcome of the disease and what factors were predictive of morbidity and mortality. At the best of our knowledge, this is the first large–scale epidemiological study on acromegaly in Italy.

Materials and methods

Study design

All the major endocrinological centres in Italy were invited to participate to the survey, that was endorsed by the Italian Society of Endocrinology. Twenty-four tertiary referral centers, most of which University Hospitals, accepted to participate to the study and collected clinical and biochemical data of all acromegalic patients who were proactively followed at the center. The number of patients from each centre ranged from 19 to 185 (Fig. 1).

Inclusion criteria were age at diagnosis >18 years, Italian residence and diagnosis of acromegaly made between 1 January 1980 and 31 December 2002 according to standard biochemical criteria at the time of enrollment, with at least 1-year follow-up after diagnosis. Patients with GH hypersecretion due to ectopic GHRH secretion and Multiple Endocrine Neoplasia type 1 were excluded. The mean follow-up time from diagnosis to the end of the study was 120 months (median 90 months; IQR: 42-170 months). Data were collected retrospectively by local investigators in a computerized database form developed using Access 2000 software (Microsoft Corporation 1999) and approved by all participants. Periodic meetings were organized in order to make the recording process as homogeneous as possible for all centres. All patients had given their informed consent to the collection of their data according to Ethic Committee indications of each centre. Patients' demographics, estimated date of appearance of typical clinical signs (i.e. change in shoes size, need to have rings enlarged and coarsening of facial features), pituitary imaging (tumor size and extension), hormonal data at baseline and during the follow-up period (serum GH levels; serum IGF-I levels; associated hyper-secretions, pituitary deficiencies) were collected for each patient. Diabetes mellitus and hypertension were investigated in order to study their impact

on mortality. Hypertension was diagnosed by the presence of systolic blood pressure ≥140 mm/Hg or diastolic blood pressure ≥90 mm/Hg or use of anti-hypertensive therapy. Diabetes mellitus was established on accepted international diagnostic criteria at the moment of diagnosis or use of specific drugs. In addition, the occurrence of cardio- and cerebro-vascular events and malignancies during follow-up were reported. After treatment, acromegalic disease was considered controlled when basal GH (mean of at least 3 samples) levels were below 2.5 mcg/L and/or nadir GH after an oral glucose load was less than 1 mcg/L and circulating IGF-I levels were normal according to an age adjusted normal range (16). The causes of death were obtained from death certificates or medical records. Data on mortality and sex- and age- adjusted distribution of diabetes and hypertension were then compared to those of the general Italian population using data reported by the Italian National Institute of Statistic (Health of All – Italia. Available at http://www.istat.it/sanita/Health), in year 2008 for mortality and 2005 for prevalence of co-morbidities.

Methods

GH and IGF-I assays have changed over the years and were different among the participant centres. The IGF-I values were compared with an appropriate age-adjusted range and expressed also as Standard Deviation Score (SDS) using the following formula: (IGF-I value - 50th percentile)/(97th percentile-3rd percentile) divided by the corresponding z-score. Data collected at the end of nineties by the University of Genoa (Prof M Minuto and A Barreca) from more than 4000 Italian normal subjects of different regions, from 0 to 100 years, and including a minimum of 50 subjects for every 5 years of age, served as reference range (17). In particular, for the purpose of the present study, the following normal ranges (3° - 97° centiles) were used : 18-20 years: 69-736 ng/ml; 21-25 years: 72-415 ng/ml; 26-30 years: 76-378 ng/ml; 31-35 years: 98-318 ng/ml; 36-40 years: 60-280 ng/ml; 41-45 years: 77-260 ng/ml; 46-50 years: 68-286 ng/ml; 51-55 years: 63-252 ng/ml; 55-60 years: 62-263 ng/ml; 61-65 years: 62-241 ng/ml; 66-70 years: 40-201 ng/ml; 71-75 years: 41-217 ng/ml; 76-80 years: 29-269 ng/ml; 81-85 years: 25-264 ng/ml.

The choice to use a large unique Italian normative database, although offering some advantages, has self-evident important limitations due to variability of IGF-I reference ranges in the many assays used in different centres over the years, and could constitute a bias.

Statistical analysis

Data were expressed as the mean ± SD and/or as the median and interquartile range (IQR 25-75%), as appropriate.

Prevalence of diabetes mellitus and hypertension in acromegalic patients was compared with data of the Italian population using direct standardization method and data reported by the Italian National Institute of Statistic in year 2005. Standardized rates along with 95% confidence interval, which was computed using the Armitage-Berry method, were reported.

Mortality for all causes was compared with the mortality of the Italian population by means of the standardized mortality ratio (SMR), which is the ratio of the observed number of deaths in the study sample to the number of deaths expected according to a set of reference mortality rates, adjusted for age, sex and calendar year. A SMR greater than 1 means a higher mortality than expected in the reference population. Finally, exact Poisson 95% confidence intervals were calculated.

The individual effect of demographic and clinical variables on the risk of developing diabetes mellitus, hypertension and mortality was evaluated by a logistic regression model. Univariate estimates of the Odds Ratios were presented along with their lower and upper 95% confidence intervals. Lastly, a multivariate model was built using backward selection including all variable found to be significant on univariate analysis. Interactions among variables were also checked. Model evaluation was carried out using a graphical examination of the residual diagnostics. Analyses were performed using R version 2.11.

Results

Population at baseline

A total of 1512 patients, 624 (41.2%) men and 888 (58.8%) women, were included into the study. The mean age at the time of diagnosis was 45 ± 13 years (median 46 years; IQR 36-54 years). Male patients were significantly younger than female patients (43 ± 13 *vs* 47 ± 13 years, P <0.001) (Fig. 2). Seventy percent of patients were diagnosed between 1990 and 2002.

Estimated duration of the disease prior to diagnosis was 74 months (median 60 months; IQR 36-96) without significant differences between the two genders.

Radiological imaging revealed a micro-adenoma in 30% and a macro-adenoma in 70% of available cases, respectively. The latter was intrasellar in 44% of cases. Tumor size and extension were missing in 7.6% of cases.

The mean GH concentration at diagnosis was 31.1 ± 37 mcg/L. The median GH was 20 mcg/L, IQR 10-36 mcg/L.

Nadir GH after glucose load was reported in 861 patients; in only 3 (0.3%) it was lower than 1 mcg/L. However, all these 3 patients showed typical clinical features, elevated IGF-I and a documented pituitary GH-secreting adenoma at surgery.

IGF-I serum levels were available at diagnosis in 1004 patients (66.4%). The mean value was 744 ± 318 ng/ml. The median IGF-I as age-specific Standard Deviation Score (SDS) was 8.53 (IQR 5.82-12.34); without differences between men and women being observed.

Hyperprolactinemia was reported in 250/1310 patients (19%). It was observed more frequently in women than in men (65.7% *vs* 34.3%, P <0.001) and in macro- than in micro-adenomas (80.5% *vs* 19.5%, P < 0.001). Nine patients had associated TSH hypersecretion and central hyperthyroidism.

At diagnosis, 392 (26%) patients had one or more pituitary deficiencies: 4.1% hypoadrenalism, 8.1% hypothyroidism, 16.4% hypogonadism and 0.6% diabetes insipidus. All were adequately treated. Pituitary deficiencies were equally distributed between the two genders except for hypogonadism that was more frequent in men (24.2% vs 10.9%, P< 0.0001). Smoking at the time of diagnosis was reported by 36% of patients, a share slightly greater than that reported for the general adult Italian population in the same years (about 30%) (18).

Co-morbidities: Diabetes Mellitus and Arterial Hypertension

Diabetes mellitus was reported in 16.2% of cases, 139 women and 106 men with an age standardized rate of 12.4% and 16.2% respectively (*P*= NS). Diabetes mellitus was diagnosed at an earlier age than in the general population (Fig. 3 A,B). A multivariate analysis considering age, gender, GH and IGF-I serum levels at diagnosis, and months of delay before diagnosis showed that older age, male gender and higher IGF-I but not GH levels at diagnosis were significant predictors of diabetes (Table 1).

Hypertension affected 33% of acromegalic patients and was equally distributed between women and men (age standardized rate: 33.7% *vs* 28.7%, respectively *P*= NS); however, it also appeared at younger age than in the normal population (Fig. 3 C,D). A multivariate model considering age, gender, GH and IGF-I serum levels at diagnosis, and months of delay before diagnosis showed that older age and higher IGF-I levels at diagnosis were significant predictors of hypertension (Table 1).

Treatment

Several treatments are used to achieve cure in acromegaly, alone or in combination (Table 2). Eigthy percent of patients underwent surgical procedures. Pharmacotherapies were used in 75% of patients. The kind of medical therapy was reported in 720 cases: 74.6% (537/720) had been treated with short or long acting somatostatin analogs (SSA), 10.3% (74/720) with the dopamine agonists (DA) bromocriptine or cabergoline, 2.9% (20/720) with GH receptor antagonist and 12.2% (88/720) with both DA and SSA either sequentially or in combination. Radiotherapy was used in 18% (269/1512) of patients, with 14% of them (39/269) who received two or more cycles. Radiosurgery, mainly Gamma Knife was used in 5.6% of the patients.

Only 34.4% of patients received only one kind of treatment, while 47.9% received two, 16.5% three and 1.2 % four. Patients who received only one type of treatment underwent surgery in 53% of cases, medical therapy in 46% and radiotherapy in 1%.

Treatment choice was not different in patients bearing micro *vs* macro-adenomas and intra- *vs* extrasellar adenomas.

166

167 *Disease-specific outcomes*

168 The mean GH levels at the last follow-up were 4.9 ± 15 mcg/L (median 2 mcg/L, IQR 1-3.8). In
169 detail, GH levels decreased <2.5 mcg/L in 60.8% (below 1 mcg/L in 21.6% of the entire cohort).
170 Among the 695 patients who underwent a glucose load after therapy, 54.4% of them showed a
171 nadir GH <1 mcg/L.
172 At the last follow-up, IGF-I serum levels were available in 1321 patients (87% of the overall
173 cohort). The mean value was 293 ± 207 ng/ml and 802 patients (60.7%) achieved IGF-I levels in
174 the normal range. The median IGF-I SDS was 1.34 (IQR 0.11-3.50); it was significantly higher in
175 men than in women (1.95, IQR 0.33-4.39 *vs* 1.11, IQR 0.04-2.80, respectively; *P< 0.05).*
176 Hyperprolactinemia persisted in 6.2% patients. At the last follow-up, patients who received
177 pituitary conventional radiotherapy were more frequently hypothyroidal, hypoadrenal and
178 hypogonadal than patients who did not (62% vs 11%, 45% vs 10%, 57% vs 12%, *P*<0.001). At the
179 last follow-up. 932/1427 patients (65%) were reported with controlled disease by the attending
180 endocrinologist; among these, 55% (36% of the entire cohort) were off medical therapy. A
181 recurrence after an initial remission was reported in 23 patients (2.4%).
182 Patients who achieved disease control had undergone surgery in 86% of cases vs 69% of patients
183 with active disease.
184 An univariate model considering age, gender, GH and IGF-I (expressed either as SDS or absolute
185 value) at diagnosis, extension and size of the adenoma, delay of diagnosis, diabetes, hypertension
186 and hyperprolactinemia showed that male gender, extrasellar extension of the adenoma, highest
187 GH levels at diagnosis and diabetes were significant independent predictors of disease activity.

188

189 *Mortality*

190 By the end of 2002, 61 patients had died: 4.1% of men and 3.9% of women. The average age was
191 64 ± 12 years (median 66.5 years; IQR 53.5-70.7 years) without differences between genders.
192 Older age, higher GH at the last follow-up, higher IGF-I levels at diagnosis, malignancy and

conventional radiotherapy were independent predictors of mortality (Table 3). Of note that superimposable results were obtained by expressing IGF-I as absolute values or as SDS.

Conventional external radiotherapy was also significantly associated to an increased morbility for ischemic vascular diseases (35% in patients receiving radiotherapy *vs* 17% in the remainders, P<0.005), In our series, the prevalence of hypoadrenalism or hypogonadism was similar between deceased and alive patients.

Main causes of death were vascular diseases and malignancies with similar prevalence. Twenty-three patients died from vascular diseases, 27.9% from cardiovascular and 9.8% from cerebrovascular events. Women died more from stroke (20% vs 4%, P < 0.001) while men from heart diseases (41% vs 28%, P= NS). The prevalence of death from malignancies was 36% (22/61) with no differences between genders. The cause of death was unknown for 12 patients.

The expected deaths were 53, that gives a SMR for the total cohort not significantly higher than the general Italian population (1.13; 95% CI, 0.86-1.46). SMR was 1.93 (95% CI, 1.34-2.70) in the subgroup of patients with persistently active disease as compared with 0.59 (95% CI, 0.37-0.90) in the patients with controlled disease.

Discussion

In the present epidemiological study, the first so far in Italy and one the largest ever published, we have reported data on 1512 patients, representative of the acromegalic population in Italy. We assume to have included nearly the 45% of all the Italian acromegalica cases of that period, considering an Italian population of 57.000.000 inhabitants in 2002 and an estimated prevalence of acromegaly of 60 per million (15). Like other retrospective studies involving a long period of time, our survey presents some difficulties in the comparison of data collected across different centres. However, this is an inevitable trade-off to have the statistical power needed to answer important epidemiological issues.

The median age at diagnosis was 46 years, very similar to previous reports (11,15,19-22). In our

220 cohort, there was a prevalence of the female gender (59%) in agreement with most (9,21,22) even
221 if not all cohorts (Table 4) (13,20,23,24).
222 A higher prevalence of women was also described in one of the first epidemiological studies,
223 published by Davidoff in 1926 (25). Both a diagnostic bias due to the greater awareness of women
224 for their features or a real increased prevalence are possible explanations. However, it is of
225 interest that men are more often diagnosed before the age of 45 years and women later on, as
226 shown in Fig. 2, and in agreement with other series (21). Thus, a protective role of estrogen,
227 delaying clinical presentation of acromegaly during the reproductive period could be
228 hypothesized, since it is well known that estrogen reduces IGF-I concentrations in both normal
229 and acromegalic women (26-29).
230 The mean delay in diagnosis was 6 years similar to that reported in most recent series
231 (13,21,22,30). The delay in diagnosis was 10-20 years in the sixties (31), 9 years in the eighties
232 (23), and 6 years in the nineties, but in the last 20 years it does not seem to be shortened further
233 (21); thus, acromegaly remains an underestimated disease (30-33).
234 It is well known that the prevalence of diabetes mellitus and hypertension are higher in
235 acromegalic patients than in the general population. In our cohort, diabetes mellitus was reported
236 in 16% of cases, with respect to 4.5% of the Italian population. However, we cannot exclude to
237 have underestimated the real prevalence of the condition due to the retrospective nature of
238 our study and since an oral glucose load was missing in a number of patients. As in the
239 general population, the prevalence of diabetes increased with age, but starting at a younger age. In
240 literature, the prevalence of diabetes mellitus varies across a wide range, from 9% to 40% (Table
241 4) (8,15,19,22). Besides differences due to genetic background, nutritional habits, age, BMI and
242 referral pattern, it has to be considered that diagnostic criteria have been revised in the nineties
243 making comparisons even more difficult. We confirmed that older age is an independent predictor
244 of diabetes (22,23), while higher GH levels and delay of diagnosis were not, at variance with some
245 previous observations (23). In addition, male gender appeared to be at greater risk of developing
246 diabetes mellitus whereas no gender-related difference is evident in the general Italian population.

It is remarkable that only IGF-I levels at diagnosis, and not GH, predicted the presence of diabetes. This is intriguing, considering both old studies in which IGF-I levels often reflected elevated fasting blood glucose in acromegaly (34) and very recent epidemiological studies showing that in the general population subjects with IGF-I levels in the upper normal range are at increasing risk of developing diabetes mellitus (35).

Also the prevalence of hypertension varied remarkably across previous studies, from 18% to 60% (Table 4) with a mean prevalence of about 34% in a review collecting more than 2500 cases (36). Differences in diagnostic criteria and in techniques of blood pressure recording may explain most of the variability. In our series hypertension was found in 33% of patients, in comparison to 13.6% of the background population matched for gender and age. As in the general population, no gender difference was observed and the prevalence increased with age, so that nearby 50% of the acromegalic patients older than 55 years were hypertensive (Fig. 3 C,D), both findings being consistent with previous observations (37). We also confirmed that hypertension, like diabetes, in the acromegalic population occurs not only more frequently, but also earlier than in the general population. While higher GH levels at baseline were not an independent predictor of hypertension, IGF-I levels were, in keeping with a previous study (38). It is noteworthy that IGF-I has been implicated in the pathogenesis of essential hypertension (37,39), even if the mechanisms involved are still not clarified (37). To further underline the importance of IGF-I in the development of co-morbidities in acromegaly, as suggested by the pioneering work of Clemmons (34), a recent paper showed that IGF-I normalization by pegvisomant resulted in a significant improvement of either hypertension or diabetes mellitus (40).

Treatment approach obviously changed during the long study period. In particular, medical therapies and radiosurgery became more frequent starting to mid-nineties while conventional radiotherapy became progressively less used (11,20). Most of our patients (80%) underwent surgery at some time, a figure similar to several studies (11,13,19,21,24).

Pharmacotherapy was used in about three-quarters of our patients while radiotherapy and radiosurgery in 23% of cases, similarly to other series (20-21,24). Surprisingly, in our population

there were no differences in the choice of first line treatment on the basis of tumor size and extension; indeed, first-line treatment was surgical in 53.3% and medical in 45.9% of cases. To have a comparison with recent surveys, in the Belgian registry (20) primary medical therapy was used in 23% and in the German registry in 34% (21).

In our series, 65% of patients were considered in remission at the last follow-up. This figure reflects the results of years in which GH-antagonist was not yet available, but somatostatin analogs had already entered clinical practice, and is comparable or even higher than other databases. The global cure or control rate reported in the Belgian (20) and in the West Midlands (9) databases were 49% and 46%, respectively. In Spanish register, cure was reported in 31% (19) and in the Finnish database, either GH<2.5 mcg/L or normal IGF-I was achieved by 55% of patients (11) (Table 4). As expected, however, these figures are lower than those reported by single centres of excellence (10). We observed that male patients with extrasellar adenoma, higher GH levels at diagnosis and diabetes had the lowest probability of achieving control of their disease, all these factors being independent predictors.

It is well known that untreated acromegaly is associated with a decreased life expectancy (4). In our series, 61 patients (4%) died during 10 year follow-up, compared with 53 expected, without differences between genders, at variance with other groups of patients with pituitary diseases. For example among patients with hypopituitarism the mortality is greater in women (4). The median age of death of our series (66 year) is similar to what reported by other European studies (9,11,20). In the total cohort the mortality for all causes was not significantly higher than in the general Italian population, while in the subgroup of patients who did not achieve full hormonal control it was increased by about 2-fold. These findings are in agreement with most (4,8,10,19), even if not all (7, 13) recent series (Table 4). They confirm that the excess mortality associated with acromegaly can be greatly reduced by the modern management of the disease, that is able to successfully control hormonal hypersecretion in the majority of the patients. However, it has to be considered that an analysis of mortality in these cohorts, including ours, is complex due to the low number of deaths by epidemiological standards (4) and the presence of other

confounding factors such as the year of publication and differences among the populations of reference. In addition, due to the fact that only tertiary referral centres participated to the survey, mortality and morbidity rate were probably underestimated compared to the general Italian acromegalica population.

As in the general population, the main causes of death were found to be vascular diseases and malignancies. The reported prevalence of cerebrovascular death in acromegalic patients ranged from 12% to 21% in the different series (7,9,19,20), while in our population it occurred only in 9.8% of cases, mostly in female. The lower figure may be due to a limited use of conventional radiotherapy with respect to the oldest series. Cardiovascular death rate (27.8%) is comparable to data reported in Spanish (19) and Belgian registers (20), but is lower than in other European studies (1,7,9), and this likely reflects the lower cardiovascular mortality of the respective general populations (41). Conversely, death from malignancies(36%) was more frequent than that reported by other European surveys (7,19,20), and deserves further investigation.

Besides age at diagnosis and development of malignancy during follow-up, conventional radiotherapy (not including radiosurgery) and the last known GH value at follow-up were independent predictors of mortality, in keeping with other series (4,9,11). It may be expected that the new conformational techniques of radiotherapy could be less dangerous; however, the number of patients who underwent radiosurgery was too small to provide useful information about the possible link between this kind of therapy and survival. Hypertension and diabetes mellitus were significant predictors of mortality only in univariate but not in multivariate analysis, in keeping with the original study by Bates (6). This may be due to their tight correlation with age and IGF-I level at diagnosis. Interestingly, high IGF-I level at diagnosis was an independent predictor of mortality, whereas both basal GH concentrations and the last IGF-I concentrations were not. In this context, it is worth recalling that in the eighties IGF-I levels were considered by many experts the best marker of severity of the acromegalic disease (34). A strength of our study is the large number of acromegalic patients in whom IGF-I levels were available at diagnosis and this may explain why previous studies including a limited data set were not able to demonstrate a predictive

328 role for IGF-I (1,3,6-10,13). The limitation that IGF-I levels have been measured by different
329 assays was circumvented by comparing them with those of the largest Italian database, the one of
330 the University of Genoa, thus allowing to express IGF-I also as SDS in the statistical analysis.
331 Since we have obtained superimposable results with rough values or SDS, we think that our
332 conclusions are not significantly affected by this limitation.
333 In conclusion, we have confirmed that diabetes mellitus and hypertension are more frequent and
334 peak much earlier in acromegaly than in the background population. We have shown that male
335 patients with extrasellar adenomas, high GH levels at diagnosis and diabetes mellitus have the
336 lowest probability of achieving control of their disease. We have confirmed the deleterious effects
337 of conventional radiotherapy and the lack of a complete control of GH hypersecretion, but also
338 shown that modern management of the disease is associated with an almost normal life span.
339 However, we have not been able to confirm that the last known IGF-I level is an independent
340 predictor of mortality, while we have shown for the first time the importance of IGF-I levels at
341 diagnosis in causing morbidity and long-term mortality.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This work was supported by the Italian Society of Endocrinology.

Acknowledgments

We are very grateful to Dr E. Ferrante for his help in preparing the database, Dr B. Zaggia and Dr L. Montefusco for their help in managing the database and to Prof F. Faggiano for his help in designing the study. We thank the Italian Society of Endocrinology for technical and financial support and encouraging.

References

1.Orme SM, McNally RJQ, Cartwright RA & Belchetz PE. Mortality and cancer incidence in acromegaly: a retrospective cohort study. *Journal of Clinical Endocrinology & Metabolism* 1998 **83** 2730–2734

2.Holdaway IM. Excess mortality in acromegaly. *Hormone Research* 2007 **68** Suppl 5 166-172

3.Dekkers OM, Biermasz NR, Pereira AM, Romijn JA & Vandenbroucke JP. Mortality in acromegaly: a metaanalysis. *Journal of Clinical Endocrinology & Metabolism* **2008** 93 61–67

4.Sherlock M, Ayuk J, Tomlinson JW, Toogood AA, Aragon-Alonso A, Sheppard MC, Bates AS & Stewart PM. Mortality in Patients with Pituitary Disease. *Endocrine Reviews* 2010 **31** 301–342

5.Wright AD, Hill DM, Lowy C & Fraser TR. Mortality in acromegaly. *QJM: An International Journal of Medicine* 1970 **39** 1–16

6.Bates AS, Van't Hoff W, Jones JM & Clayton RN. An audit of outcome of treatment in acromegaly. *QJM: An International Journal of Medicine* 1993 **86** 293–299

7. Sherlock M, Reulen RC, Alonso AA, Ayuk J, Clayton RN, Sheppard MC, Hawkins MM, Bates AS & Stewart PM. ACTH deficiency, higher doses of hydrocortisone replacement and radiotherapy are

independent predictors of mortality in patients with acromegaly. *Journal of Clinical Endocrinology & Metabolism* 2009 **94** 4216–4223

8.Beauregard C, Truong U, Hardy J & Serri O. Long-term outcome and mortality after transsphenoidal adenomectomy for acromegaly. *Clinical Endocrinology (Oxf)* 2003 **58** 86–91

9.Ayuk J, Clayton RN, Holder G, Sheppard MC, Stewart PM & Bates AS. Growth hormone and pituitary radiotherapy, but not serum insulin-like growth factor-1 concentrations, predict excess mortality in patients with acromegaly. *Journal of Clinical Endocrinology & Metabolism* 2004 **89** 1613–1617

10.Biermasz NR, Dekker FW, Pereira AM, van Thiel SW, Schutte PJ, van Dulken H, Romijn JA & Roelfsema F . Determinants of survival in treated acromegaly in a single center: predictive value of serial insulin-like growth factor I measurements. *Journal of Clinical Endocrinology & Metabolism* 2004 **89** 2789–2796

11.Kauppinen-Mäkelin R, Sane T, Reunanen A, Välimäki MJ, Niskanen L, Markkanen H, Löyttyniemi E, Ebeling T, Jaatinen P, Laine H, Nuutila P, Salmela P, Salmi J, Stenman UH, Viikari J & Voutilainen E. A nationwide survey of mortality in acromegaly. *Journal of Clinical Endocrinology & Metabolism* 2005 **90** 4081–4086

12. Melmed S. Acromegaly and cancer: not a problem? *Journal of Clinical Endocrinology & Metabolism* 2001 **86** 2929–2934

13.Holdaway IM, Rajasoorya RC & Gamble GD. Factors influencing mortality in acromegaly. *Journal of Clinical Endocrinology & Metabolism* 2004 **89** 667–674

14.Swearingen B, Barker 2nd FG, Katznelson L, Biller BM, Grinspoon S, Klibanski A, Moayeri N,

Black PM & Zervas NT. Long-term mortality after transsphenoidal surgery and adjunctive therapy for acromegaly. *Journal of Clinical Endocrinology & Metabolism* 1998 **83** 3419–3426

15.Holdaway IM & Rajasoorya C. Epidemiology of acromegaly. *Pituitary* 1999 **2** 29–41

16.Giustina A, Barkan A, Casanueva FF, Cavagnini F, Frohman L, Ho K, Veldhuis J, Wass J, Von Werder K & Melmed S. Criteria for cure of acromegaly: a consensus statement. *Journal of Clinical Endocrinology & Metabolism* 2000 **85** 526–529

17. Aimaretti G, Boschetti M, Corneli G, Gasco V, Valle D, Borsotti M, Rossi A, Barreca A, Fazzuoli L, Ferone D, Ghigo E & Minuto M. Normal age-dependent values of serum insulin growth factor-I: results from a healthy italian population. *Journal of Endocrinological Investigation* 2008 **31** 445-449

18. Colombo P, Scarpino V, Zuccaro P, Apolone G, Gallus S & La Vecchia C. Smoking in Italian women and men, 2001. *Tumori* 2002 **88** 10-12

19. Mestron A, Webb SM, Astorga R, Benito P, Catala M, Gaztambide S, Gomez JM, Halperın I, Lucas-Morante T, Moreno B, Obiols G, de Pablos P, Paramo C, Pico A, Torres E, Varela C, Vazquez JA, Zamora J, Albareda M & Gilabert M. Epidemiology, clinical characteristics, outcome, morbidity and mortality in acromegaly based on the Spanish Acromegaly Registry. *European Journal of Endocrinology* 2004 **151** 439–446

20. Bex M, Abs R, T'Sjoen G, Mockel J, Velkeniers B, Muermans K & Maiter D. AcroBel – the Belgian registry on acromegaly: a survey of the 'real-life' outcome in 418 acromegalic subjects. *European Journal of Endocrinology* 2007 **157** 399–409

21. Petersenn S, Buchfelder M, Gerbert B, Franz H, Quabbe HJ, Schulte HM, Grussendorf M & Reincke M. Age and sex as predictors of biochemical activity in acromegaly: analysis of 1485

patients from the German Acromegaly Register. *Clinical Endocrinology (Oxf)* 2009 **71** 400–405

22. Fieffe S, Morange I, Petrossians P, Chanson P, Rohmer V, Cortet C, Borson-Chazot F, Brue T & Delemer B. Diabetes in acromegaly, prevalence, risk factors and evolution; data from the French acromegaly registry. *European Journal of Endocrinology* 2011 **164** 877-884

23. Nabarro JD. Acromegaly. *Clinical Endocrinology (Oxf)* 1987 **26** 481–512

24. Drange MS, Fram NR, Herman-Bonert V & Melmed S. Pituitary Tumor Registry: A Novel Clinical Resource. *Journal of Clinical Endocrinology & Metabolism* 2000 **85** 168–174

25. Davidoff LM. Studies in acromegaly III. The anamnesis and symptomatology in one hundred cases. *Endocrinology* 1926 **10** 461–483

26. Mccullagh EP, Beck JC & Schaffenburg CA. Control of diabetes and other features of acromegaly following treatment with estrogens. *Diabetes* 1955 **4** 13–23

27. Cozzi R, Barausse M, Lodrini S, Lasio G & Attanasio R. Estroprogestinic pill normalizes IGF-I levels in acromegalic women. *Journal of Endocrinological Investigation* 2003 **26** 347-352

28. Vallette S & Serri O. Oral estroprogestin: an alternative low cost therapy for women with postoperative persistent acromegaly? Pituitary 2010 **13** 311–314

29. Roemmler J, Bidlingmaier M & Schopohl J. Endogenous estradiol may influence IGF-I levels in acromegalic women treated with pegvisomant. *Pituitary* 2010 **13** 89-93

30. Reid T.J, Post KD, Bruce JN, Nabi Kanibir M, Reyes-Vidal CM & Freda PU. Features at diagnosis of 324 patients with acromegaly did not change from 1981 to 2006: acromegaly remains under-

recognized and under-diagnosed. *Clinical Endocrinology (Oxf)* 2010 **72** 203–208

31. Gordon DA, Hill FM & Ezrin C. Acromegaly: a review of 100 cases. *Canadian Medical Association Journal* 1962 **87** 1106–1109

32. Beckers A. Higher prevalence of clinically relevant pituitary adenomas confirmed. *Clinical Endocrinology (Oxf)* 2010 **72** 290-291

33. Cannavò S, Ferrau F, Ragonese M, Curtò L, Torre ML, Magistri M, Marchese A, Alibrandi A & Trimarchi F. Increased prevelence of acromegaly in a highly polluted area. *European Journal of Endocrinology* 2010 **163** 509-513

34. Clemmons DR, Van Wyk JJ, Ridgway EC, Kliman B, Kjellberg RN & Underwood LE. Evaluation of Acromegaly by Radioimmunoassay of Somatomedin-C. New England Journal of Medicine 1979 **301** 1138-1142

35. Schneider HJ, Friedrich N, Klotsche J, Schipf S, Nauck M, Völzke H, Sievers C, Pieper L, März W, Wittchen H, Stalla GK & Wallaschofski H. Prediction of incident 1 diabetes mellitus by baseline insulin like growth factor-I levels. *European Journal of Endocrinology* 2011 **164** 223-229

36. Bondanelli M, Ambrosio MR & degli Uberti EC. Pathogenesis and prevalence of hypertension in acromegaly. *Pituitary* 2001 **4** 239-49

37. Vitale G, Pivonello R, Auriemma R, Guerra E, Milone F, Savastano S, Lombardi G & Colao A. Hypertension in acromegaly and in the normal population: prevalence and determinants. *Clinical Endocrinology (Oxf)* 2005 **63** 470-476

38. Ohtsuka H, Komiya I, Aizawa T & Yamada T. Hypertension in acromegaly: hereditary hypertensive factor produces hypertension by enhancing IGF-I production. *Endocrine Journal* 1995

42 781-787

39. Diez J**.** Insulin-like growth factor I in essential hypertension. *Kidney International* 1999 **55** 744–759

40. Berg C, Petersenn S, Lahner H, Herrmann BL, Buchfelder M, Droste M, Stalla GK, Strasburger CJ, Roggenbuck U, Lehmann N, Moebus S, Jöckel KH, Möhlenkamp S, Erbel R, Saller B & Mann K. Cardiovascular Risk Factors in Patients with Uncontrolled and Long-Term Acromegaly: Comparison with Matched Data from the General Population and the Effect of Disease Control. *Journal of Clinical Endocrinology & Metabolism* 2010 **95** 3648-56

41. Muller-Nordhorn J, Binting S, Roll S & Willich S. An update on regional variation in cardiovascular mortality within Europe. *European Heart Journal* 2008 **29** 1316- 26

Figure legends:

Figure 1: Percentage distribution of patients throughout Italy

Figure 2: Distribution of acromegalic patients according to gender (males: closed bars, females: open bars) and age group at diagnosis

Figure 3: Percentage prevalence of diabetes mellitus (A) and hypertension (C) in the acromegalic population in respect to the Italian general population (B,D) according to age groups and gender (males: closed bars, females: open bars)

Table 1 Predictors of diabetes mellitus and hypertension (multivariate analysis)

	Diabetes Mellitus			Hypertension		
Variables	**OR**	**95% CI**	**P value**	**OR**	**95% CI**	**P value**
Age	2.26	1.68-3.05	0.001	2.84	2.32-3.48	0.001
Male sex	1.64	1.08-2.52	0.02	0.85	0.65-1.11	NS
GH at diagnosis	0.99	0.95-1.03	NS	0.97	0.91-1.03	NS
IGF-I at diagnosis (SDS)	1.11	1.00-1.24	0.05	1.50	1.12-2.01	0.02
Delay of diagnosis	1.14	0.92-1.41	NS	0.86	0.74-1.01	0.05

Table 2 Distribution of treatments modalities

Therapies	Patients n (%)
Surgery	**1222 (80)**
Surgery alone	262 (21.5)
In combination with pharmacotherapy	651 (53.3)
In combination with radiotherapy or radiosurgery	38 (3) / 10 (0.8)
In combination with two or more therapies	261 (21.4)
Pharmacotherapy	**1147 (75)**
Pharmacotherapy alone	203 (17.7)
In combination with radiotherapy or radiosurgery	23 (2) / 2 (0.2)
In combination with two or more therapies	919 (80.1)
Radiotherapy	**269 (18)**
Radiotherapy alone	4 (1.5)
Radiotherapy in combination	265 (98.5)
Radiosurgery	**85 (5.6)**
Radiosurgery alone	0 (0)
Radiosurgery in combination	85 (100)

Table 3 Predictors of mortality

Variables	OR	95% CI	P value
Univariate model			
Age	3.55	2.42-5.21	<0.001
Male sex	1.06	0.63-1.78	NS
Macroadenoma	0.85	0.47-1.54	NS
Delay of diagnosis	1.29	0.98-1.69	NS
GH at diagnosis	1.02	1.00-1.04	NS
IGF-I at diagnosis (SDS)	1.12	1.00-1.25	0.05
GH at FU	1.03	1.00-1.06	0.05
IGF-I at FU (SDS)	0.99	0.82-1.21	NS
Malignancy	11.98	6.95-20.64	<0.001
Diabetes	1.09	1.02-3.51	0.04
Hypertension	2.29	1.37-3.83	0.002
Radiotherapy	2.35	1.36-4.09	0.002
Hypoadrenalism	0.51	0.07-3.79	NS
Hypogonadism	1.15	0.55-2.41	NS
N° of therapies	0.51	0.27-0.99	NS
Smoking	1.44	0.72-2.85	NS
Multivariate model			
Age	4.58	2.62-7.99	<0.001
IGF-I at diagnosis (SDS)	1.14	1.01-0.25	0.04
GH at FU	1.06	1.03-1.10	<0.001
Malignancy	7.26	3.54-14.86	<0.001
Diabetes	0.87	0.37-2.06	NS
Hypertension	0.81	0.40-1.65	NS
Radiotherapy	4.32	1.97-9.45	<0.001

Table 4. European Registers

	Patients n°(M/F)	Age at diagnosis mean (M/F)	Macro-adenomas (%)	Diabetes Mellitus (%)	Hypertension (%)	Disease control (%)	SMR (IC 95%)
Ayuk et al, 2004 (9)	419 (178/241)	47	-	-	-	46	1.26 (1.03-1.54)
Mestron et al, 2004 (19)	1219 (478/741)	45	73	37.6	39.1	31	-
Holdaway et al, 2004 (13)	208 (125/83)	42	84	53	60	-	2.70 (2.10-3.50)
Kauppinen-Makelin et al, 2005 (11)	334 (161/173)	47.5 (45/49)	67	-	-	55	1.16 (0.85-1.54)
Bex et al, 2007 (20)	418 (213/205)	44 (42/46)	79	25.3	39.4	49	1.39 (0.96-2.03)
Petersenn et al, 2009 (21)	1485 (677/808)	44 (41/47)	79	-	-	-	-
Present Study	1512 (624/888)	45 (43/47)	70	16	33	65	1.13 (0.87-1.46)

Figure 1.

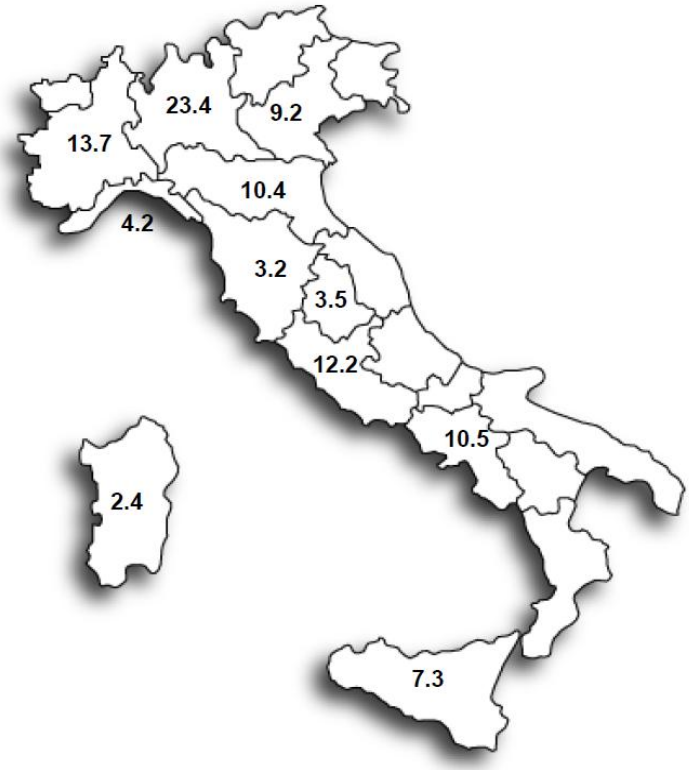


Figure 2.

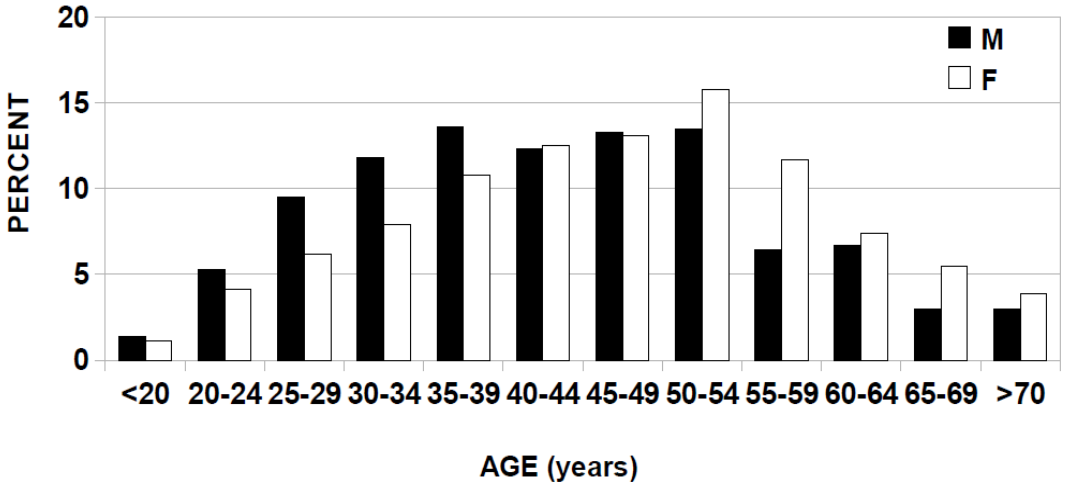
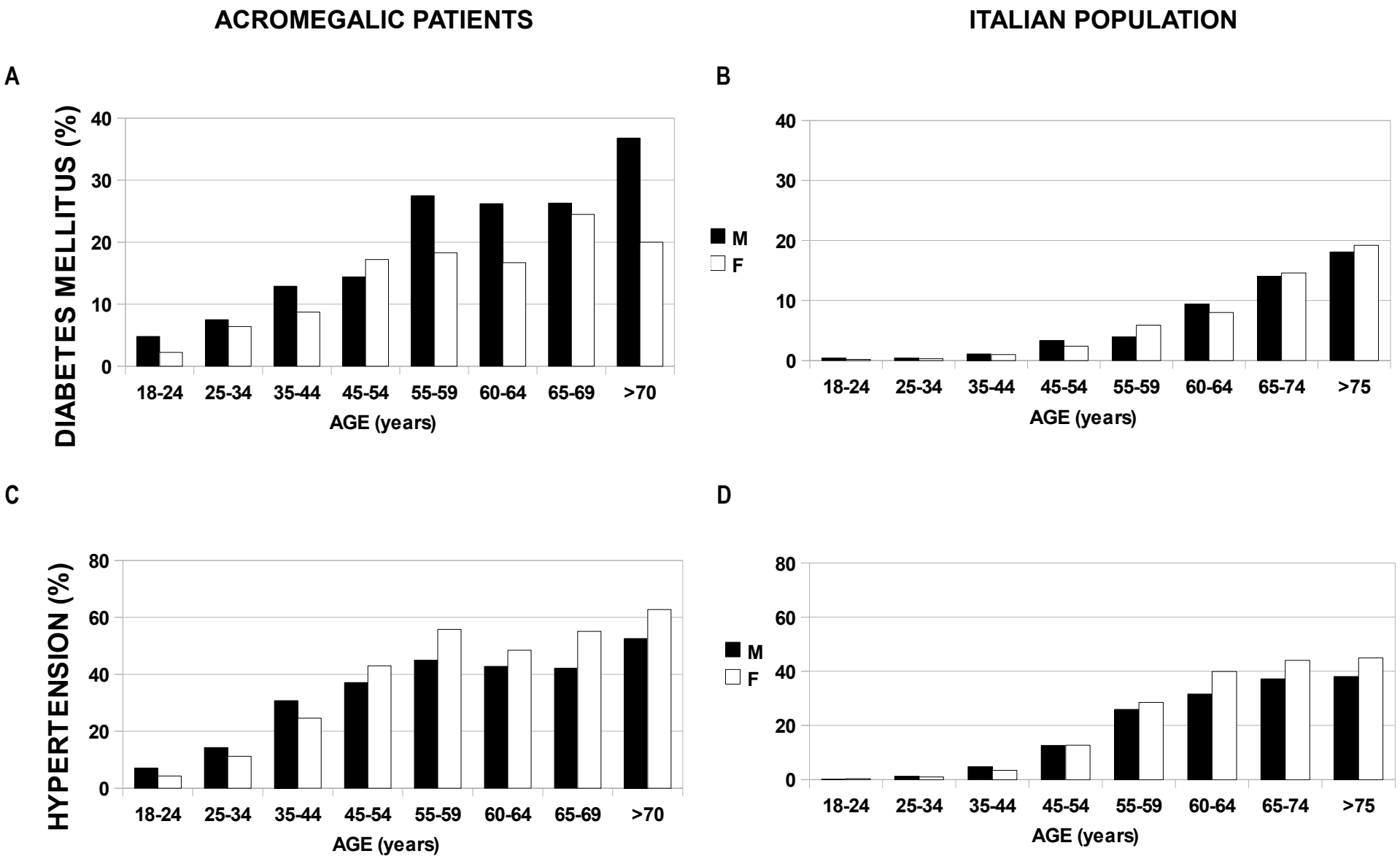

20
15
10
5
0
PERCENT
M
F
<20
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
>70
AGE (years)

Figure 3.


ACROMEGALIC PATIENTS
ITALIAN POPULATION
A
B
C
D
DIABETES MELLITUS (%)
HYPERTENSION (%)
0
10
20
30
40
60
80
M
F
18-24
25-34
35-44
45-54
55-59
60-64
65-69
65-74
>70
>75
AGE (years)