MANAGEMENT OF ENDOCRINE DISEASE

Does gender matter in the management of acromegaly?

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Abstract

Gonadal steroids modulate the effects of GH, with oestrogens attenuating and androgens augmenting GH action. Whether these divergent effects influence the clinical manifestation, management and prognosis of acromegaly have not been carefully reviewed. This review examines whether there is a gender difference in epidemiology, presentation, quality of life (QoL), morbidity, treatments and mortality of acromegaly. Acromegaly is more common in women who present at an older age with longer diagnostic delay. At presentation, women have a higher GH relative to IGF-1 level than men. QoL is more adversely affected in women both before and after treatment. Prevalence of hypertension and diabetes are greater in women than in men with acromegaly. Treatment outcomes with SSAs are comparable between sexes, but women may require a higher dose of pegvisomant for equivalent response. Mortality in untreated acromegaly is more profoundly affected in women; however, improved treatments in recent decades have resulted in normalisation of standard mortality ratios in both sexes. We conclude that gender does matter in the management of acromegaly, with women presenting later in life, with greater diagnostic delay, higher prevalence of comorbidities and experiencing worse QoL.

*European Journal of
Endocrinology*
(2020) **182**, R67–R82

Introduction

Gender is defined by the Oxford Dictionary as the state of being male or female as expressed by social or cultural distinctions and differences, rather than a biological one. There are numerous genetic, epigenetic, environmental, social and psychological factors underlying gender identity (1). Several diseases show gender dimorphism. Autoimmune diseases occur more frequently in women than in men, a phenomenon attributable to genetic and

the regulatory effects of oestrogens on the immune system (2). For pituitary disease, prolactinomas, which are the most common among functioning adenomas, occur more frequently in women than in men (3). There is strong experimental evidence for a pathogenic role of oestrogens in pituitary tumourigenesis, particularly for prolactinomas (4, 5, 6). However, the question as to whether acromegaly is influenced by gender is not known.

Invited Author's profile

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Early studies reported a mild preponderance of women among patients with acromegaly (7, 8). A recent large study observed that diagnosis is delayed and that IGF-I levels are lower at diagnosis in women with acromegaly (9). There are physiological interactions between gonadal steroids and the GH axis that could influence biochemistry and symptomatology associated with acromegaly between the sexes. The clinical picture of acromegaly arises from hypersecretion of GH, the effects of which are mediated directly or indirectly through IGF-I, causing soft tissue, musculoskeletal, cardiovascular and metabolic changes. The fluid-retaining and diabetogenic properties are direct effects of GH, while the growth promoting effects are IGF-I mediated (10). Gonadal steroids modulate the secretion and action of GH. Androgens enhance the action of GH on fluid retention and on protein anabolism (11). In contrast, estrogens exert an opposite effect by inhibiting the production of IGF-I from the liver (12). These divergent effects of androgens and oestrogens on GH action may influence the clinical picture of acromegaly in men and women.

Based on the considerations mentioned previously, this narrative review will examine whether there is a gender effect on acromegaly by critically examining the demography, biochemistry, natural history, symptomatology, morbidities, management, treatment outcomes and mortality of this disease. A literature search was conducted in Pubmed and Medline using the terms 'acromegaly' and 'gender'. Journal articles were individually reviewed for relevance, quality, size and exclusion of duplicate data.

Epidemiology

The epidemiology of acromegaly has been widely reported in large population studies, conducted in Europe, United Kingdom and Asia (Table 1). In 1980, Alexander *et al.* (8) reported on patients identified through treating clinicians, hospital records and death certificates. In a population of 3 100 000 (Newcastle, UK), 164 patients with acromegaly were identified, with 57% being female (8). This female predominance has been replicated in several (13, 14, 15, 16), but not all (17, 18, 19) studies. A summary of the gender distribution (Table 1) reveals that of an overall total of 5955 patients, 53.9% were female. Incidence data, where available, corroborates prevalence data, with higher female incidence in some (13, 16, 20) but not all studies (19). Burton *et al.* reported female incidence at 12 cases per million person-years and male incidence at ten cases per million person years (13). Gruppetta *et al.* reported standard incidence ratio of 0.31 per 100 000 per year, with 70.6% of cases being female (16). Park *et al.* reported a higher incidence in females than males (4.06 per million persons vs 3.09 per million persons) (20). Conversely, Tjornstrand *et al.* reported equivalent incidence between male and female subjects (19).

They were all large, population-based studies performed within the constraints of different national health care systems, data collection and reporting practices, limitations in accuracy of reporting/ registering patients. These factors are likely to account for some of the conflicting observations, wherein a few studies have

Table 1 Gender distribution and prevalence of acromegaly in population studies.

Year	Author	Country	Population	Data source	Female distribution			Prevalence (per 100 000)		
					Number	Females	%	Number	Males	Females
2016	Burton <i>et al.</i> (13)	USA	50 170 946	Insurance claims data	2241	1165	52	7.8	7.7	7.7
2013	Kwon <i>et al.</i> (14)	South Korea	48 456 369	Secondary and tertiary centres of South Korea	1350	743	55	2.8	1.3	1.5
2004	Mestron <i>et al.</i> (15)	Spain	NA	Nationwide database	1219	741	60.8	3.4	NA	NA
2007	Bex <i>et al.</i> (18)	Belgium, Luxembourg	10 850 000	Nationwide survey	418	205	49	4.1	NA	NA
2016	Dal <i>et al.</i> (33)	Denmark	5 534 738	Nationwide database	405	190	47	8.5	NA	NA
1980	Alexander <i>et al.</i> (8)	UK	3 100 000	Regional data	164	93	57	4	NA	NA
2014	Tjornstrand <i>et al.</i> (19)	Sweden	1 590 640	Nationwide registry	53	26	49	3.3	1.7	1.6
2015	Agustsson <i>et al.</i> (17)	Iceland	330 000	National Health Service	53	21	39.6	13.7	NA	NA
2013	Gruppetta <i>et al.</i> (16)	Malta	417 608	Central hospital registry	52	30	57.7	12.4	10.6	14.3
Total					5955	3215	53.9			

not observed a higher prevalence in women. Nevertheless, the collective data reveal evidence that acromegaly affects more women than men.

Age at diagnosis

Numerous population and registry studies have reported on age at diagnosis with acromegaly, results of which are summarised in Fig. 1 (9, 14, 16, 17, 18, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30). Of the 15 studies surveyed, ten reported that men were significantly younger than women at diagnosis, by a median of 4.5 years (total $n=10\,372$, range 1.8–6.6 years) (9, 14, 21, 22, 24, 25, 26, 27, 28, 30). Other studies demonstrated a trend towards younger diagnosis in men than women, without reaching statistical significance (total $n=1763$) (16, 17, 18, 23, 29). The difference in age at diagnosis is highly consistent between studies providing compelling evidence for a true gender dimorphism.

Diagnostic delay

The question as to whether a later age of diagnosis in women may be due to a delay in diagnosis has been investigated in a number of studies (Table 2). In the Liege Acromegaly Database ($n=3143$), Petrossians *et al.* (9) reported that female patients had a median delay to diagnosis of 2 years longer than their male counterparts. Additionally, female patients consulted a higher number of physicians before achieving diagnosis (9). Similarly, data from the Swedish National Patient registry ($n=135$) demonstrated that median time to diagnosis was 4.6 years earlier in men than in women (31).

Figure 1

Median age at diagnosis of acromegaly in males and females from 15 international studies.

In the only study to specifically evaluate gender discrepancy in diagnostic evaluation of acromegaly, Kreitschmann-Andermahr *et al.* ($n=165$) found that women waited 2.5 years longer than men for correct diagnosis and consulted more doctors (4.0 vs 2.7) (32). The authors proposed that early symptomatology of acromegaly may be erroneously attributed to menopausal symptoms. In contrast to the previously mentioned studies, a large German registry study ($n=1485$) reported 1 year longer time to diagnosis in men than in women (22). Dimorphism in clinical presentation has not otherwise been widely investigated in large population and registry studies (8, 13, 14, 15, 16, 17, 18, 19, 23, 24, 25, 26, 27, 28, 29, 30, 33). Evidence supports diagnostic delay in women with acromegaly compared with men.

Biochemistry at diagnosis

GH secretion and action are modulated by gonadal steroids (10). In normal subjects, testosterone enhances GH secretion (11, 34) and responsiveness (10, 35, 36, 37, 38, 39). By contrast, oestrogens attenuate GH action reducing IGF-1 production (10). These regulatory effects of sex steroids result in women having higher levels of GH than men but with similar levels of IGF-I (12, 40, 41).

In acromegaly, sex steroids affect GH-IGF-1 relationship in a similar way. In a study of 76 patients with acromegaly, Tanaka *et al.* (42) observed the mean IGF-I concentration and IGF-1/GH ratio to be significantly lower in women than in men despite both genders having similar mean GH concentrations. When stratified to age groups below and over 50 years, the gender difference in IGF-I was significant only among the younger patients. In a recent single-centre retrospective evaluation of 463 surgically treated acromegalic patients, Park *et al.* (26) reported similar gender dimorphism in biochemistry. The mean preoperative IGF-1 in women was 15% lower than in men, despite similar GH levels. This effect was present in the pre-menopausal but not in the post-menopausal age group. Parkinson *et al.* (43) reported on 60 patients with acromegaly with varying degree of control. A linear relationship between GH and IGF-1 was observed, with female patients having consistently lower levels of IGF-1 for a given GH concentration. Several epidemiological studies (total $n=1906$) have provided further evidence for gender dimorphism in biochemistry at diagnosis, reporting lower IGF-1 in women, despite similar GH levels between genders (14, 29, 33). In a large German Registry ($n=1485$), both GH and IGF-1 were observed to be lower in women compared with their male counterparts.

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Table 2 Delay in the diagnosis of acromegaly in males and females.

Year	Author	Country	n	Median time to diagnosis (years)		P-value
				Males	Females	
2017	Petrossians <i>et al.</i> (9)	Belgium, Bulgaria, France, Netherlands, Italy, Sweden, Czech Republic, Germany, Portugal, Spain	3173	8	10	0.015
2012	Arosio <i>et al.</i> (21)	Italy	1512	5	5	NS
2009	Petersenn <i>et al.</i> (22)	Germany	1485	6	5	<0.001
2016	Kreitschmann-Andermahr <i>et al.</i> (32)	Germany	165	1.6 [^]	4.1 [^]	0.001
2018	Granfeldt (31)	Sweden	135	1.8	6.4	0.018

[^]Mean.

In summary, there is strong evidence for a gender effect on the biochemistry of acromegaly, characterised by a lower IGF-I in women for equivalent GH status, likely explained by an attenuating effect of oestrogens on the action of GH.

Tumour size

Tumour size at presentation has important implications for treatment efficacy and outcomes, with larger, more invasive tumours associated with worse prognosis (18, 33). Several studies have found that women presented with significantly larger and more invasive tumours than men. Park *et al.* (26) observed that women had significantly larger tumours than men and a higher proportion of tumours with cavernous sinus invasion (29.2% vs 20.2%). Similarly, Colao *et al.* (29) reported significantly larger tumours in women than in men within the younger age group (age < 40 years). By contrast, in a large multicentre registry study, Petrossians *et al.* (9) observed that men had significantly larger tumours than women at diagnosis. In this study, tumour size was inversely proportional to age and larger tumours were not observed in patients older than 30 years. However, several studies have not found a significant difference in tumour size between genders (16, 17, 22, 24, 27, 33). A plausible explanation for gender dimorphism in tumour size is delay to diagnosis in women arising from oestrogen modulation of the GH/IGF-1 pathway (26). However, further studies are required to investigate the interaction between patient age, gender and tumour size in acromegaly.

Quality of Life (QoL)

Pituitary disease impairs quality of life, with a greater negative impact in female patients (44). The question as to whether this is the case for acromegaly has been

addressed in a number of studies, summarised in Table 3. Contributors to reduced QoL in acromegaly include physical, psychological, aesthetic, social, demographic and treatment factors (45). There are three longitudinal studies that have reported the impact of gender in QoL in active acromegaly. Webb *et al.* (46) evaluated 106 patients with acromegaly, of which 42 had active disease. Females had worse QoL scores on all aspects of assessment, particularly mental and physical scores. Similarly, Vandeva *et al.* (47) performed a cross-sectional longitudinal study of 212 patients with acromegaly over a 6-year period. Female gender was a negative predictor on all aspects of QoL scores, except for appearance. By contrast, in a longitudinal study of 41 patients who underwent successful surgery for acromegaly, Fujio *et al.* (48) reported no gender differences in QoL scores in active disease.

The previously mentioned longitudinal studies also evaluated QoL in disease remission and observed persistence of patterns following cure (46, 47, 48). Several other studies have investigated QoL in patients with acromegaly in remission. Psaras *et al.* (49) demonstrated that in men persistent joint complaints had the largest effect on QoL, whereas in women, persistence of hypertension posed a significant perceived threat to health. In a longitudinal study of patients with treated acromegaly, Van der Klauww *et al.* (50) observed that women had more impairment in role functioning due to emotional problems and perceived health over time. Biermasz *et al.* (51) evaluated QoL in 118 subjects with successfully treated acromegaly, observing no significant difference between genders.

There are several studies that have investigated QoL in mixed cohorts of patients at various stages of treatment. Anagnostis *et al.* performed a case control study of 40 patients, of which 62.5% were in remission, demonstrating that female gender was a negative predictor

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Table 3 Gender and Quality of Life assessments in acromegaly.

Year	Reference	Country	Study	n	Assessment tool	Disease activity	Gender effect
Longitudinal studies							
2006	Webb <i>et al.</i> (46)	Spain	Case-control, longitudinal	106	EuroQoL, AcroQoL*	Active disease	F > M
						Remission	F > M
2015	Vandeva <i>et al.</i> (47)	Bulgaria	Cohort, longitudinal	212	AcroQoL*	Active disease	F > M
						Remission	F > M
2017	Fujio <i>et al.</i> (48)	Japan	Cohort, longitudinal	41	SF-36	Active disease	Nil
						Remission	Nil
2008	Van der Klauww <i>et al.</i> (50)	The Netherlands	Cohort, longitudinal	82	HADS, NHP, AcroQoL*, MFI-20, SF-36	Remission	F > M
2019	Tseng <i>et al.</i> (56)	Taiwan	Cohort, longitudinal	272	AcroQoL*	Mixed	Nil
Cross-sectional and case-control studies							
2004	Biermasz <i>et al.</i> (51)	The Netherlands	Case-control	118	SF-36, MFI-20, NHP, AcroQoL*, HADS	Remission	Nil
2011	Psaras <i>et al.</i> (49)	Germany	Cohort	55	AcroQoL*, ACCQ*, SF-36	Remission	F > M
2005	Rowles <i>et al.</i> (54)	Spain	Cohort	80	AcroQoL*, EuroQoL, PGWB, SSS*	Mixed	Nil
2006	Kauppinen-Makelin <i>et al.</i> (27)	Finland	Cohort	231	15D	Mixed	Nil
2007	T'Sjoen <i>et al.</i> (53)	Belgium	Cohort	291	AcroQoL*	Mixed	F > M
2013	Kepicoglu <i>et al.</i> (55)	Turkey	Cohort	133	AcroQoL*	Mixed	Nil
2014	Anagnostis <i>et al.</i> (52)	Greece	Case-control	40	AcroQoL*, POMS	Mixed	F > M

*Disease specific assessment tool.

F > M, females affected more than male patients on QoL scores; Nil, no significant difference between genders in QoL scores.

of QoL scores, particularly in physical appearance, mood and relationship scores (52). In a Belgian nationwide cohort study with patients with varying levels of disease activity, male gender was associated with significantly worse QoL scores (53). Several other studies, reporting on patients at varying stages of disease activity, have observed no significant difference in QoL between genders (27, 54, 55, 56).

In summary, numerous studies examining QoL in acromegaly, heterogenous methods, assessment tools and patient cohorts have yielded mixed results, precluding clear conclusions. However, there is nonetheless some evidence that QoL appear to be poorer in females in acromegaly.

Morbidity

Cardiovascular risk

Cardiovascular risk is increased in patients with acromegaly, contributing to enhanced mortality (57, 58, 59). Hypertension and diabetes are among the best studied CV risk factors in acromegaly. When compared with the general population, prevalence of diabetes and hypertension are elevated in acromegalic patients (60) and

reduced after successful disease control or cure (59, 61). There is a clear gender dimorphism in cardiovascular disease in the general population, with a strong male predominance (62). There are limited data regarding gender distribution in cardiovascular risk in acromegaly, from studies in largely heterogenous patient groups, with controlled and uncontrolled disease.

Hypertension

In a retrospective, comparative study from Germany, 133 patients with acromegaly were compared with 665 matched controls from the general population (59). Patients with acromegaly had significantly higher prevalence of hypertension than their age and gender-matched controls. Women, but not men, had significantly higher Framingham Risk Scores than their matched controls. In a large Mexican registry study ($n=2057$), the prevalence of hypertension was significantly higher in women compared with men (32% vs 24%) (63). Another large registry from Italy ($n=1512$) reported a similar trend, (33.7 vs 28.7%), which did not reach statistical significance (21). By contrast, Gonzalez *et al.* reported that, although successful treatment reduced blood pressure, hypertension persisted in some patients without a gender difference (60). Overall, evidence from retrospective studies suggests a

higher prevalence of hypertension among women with acromegaly, which is opposite to that of the general population (64).

Diabetes

Type 2 diabetes is one of the most common comorbidities in acromegaly and is a major contributor to cardiovascular risk (65). Insulin resistance develops as a direct consequence of the action of GH. As GH levels are higher in women for comparable IGF-I status, it is conceivable that women may be at more risk of diabetes compared to men. Gender differences in diabetes in acromegaly are infrequently reported in epidemiological studies (Table 4). In a large Mexican multi-centre registry study of over 2000 patients, the prevalence of diabetes was nearly 50% higher in females (30.4 vs 21.6%) (63); however, mean GH levels were slightly higher in males. In a later outcome evaluation in 522 patients after various modes of treatment in this cohort, Gonzalez *et al.* (60) observed the prevalence of diabetes remained higher in women but did not comment on comparative GH concentrations. In a Danish population study of 405 patients, the prevalence of diabetes was higher in women (HR 6.2 vs 2) but higher GH concentrations were observed in men (33). A multicentre study of 649 patients from Canada observed no difference in the prevalence of diabetes between genders, but did not provide corresponding GH data (17). In a large Italian registry study of 1512 patients, the diabetes was associated with male gender and IGF-1, but not GH, on multivariate analysis (21). However, a detailed metabolic study of over 300 patients from one of the participating centres reported that women had higher fasting insulin levels, higher visceral adiposity levels, lower insulin sensitivity index, lower HDL cholesterol and a higher prevalence of metabolic syndrome (66). The prevalence of diabetes was more than two-fold higher in women (51 vs 19%) despite mean GH levels being higher in men (31 vs 26 ug/L). This study highlights the power of single centre studies employing a range of interrelated investigations to focus on specific measures of

interest not possible from heterogeneous large multicentre or registry studies. A recent nationwide population-based cohort study from Korea has reported a higher prevalence of diabetes in females (57 vs 51%) with acromegaly from insurance claims data (20). In summary, data from epidemiological and registry studies are conflicting, while evidence from a single-centre undertaking focussed metabolic investigations and from a nationwide claims database observed a higher female prevalence of diabetes. Further, careful studies are required to determine whether diabetes affects more females than males with acromegaly.

Sleep disordered breathing

Sleep disordered breathing (SDB) is common in patients with acromegaly (33). GH excess affects the structure and function of the respiratory apparatus, resulting in macroglossia, pharyngeal soft tissue hypertrophy and abnormalities of the pharynx lumen (67). The prevalence of obstructive sleep apnoea (OSA) in the general population is reported at 9–38% with a male predominance (13–33% vs 6–19%) (68). Wide variation in reported prevalence stems from significant methodological heterogeneity in OSA epidemiological studies. In patients with active acromegaly, prospective polysomnography studies report prevalence of OSA ranging from 44 to 87% (69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79). SDB diminishes QoL and increases morbidity and mortality (80). Gender dimorphism observed in the general population appears to be preserved in acromegaly, although data are sparse, from small heterogeneous studies (33, 70, 72, 75, 81, 82). In summary, studies on gender differences in the severity and prevalence of SDB in acromegaly are scant and insufficient to ascertain whether they are different from that in the general population.

Malignancy

GH stimulates cellular growth and proliferation, raising concern for increased risk of cancer in patients with acromegaly (83). This has been the subject of some

Table 4 Gender differences in the prevalence or risk of diabetes in acromegaly.

Year	Reference	Country	Study	n	Measure	Female	Male
2016	Portocarrero-Ortiz <i>et al.</i> (63)	Mexico	Cohort	2057	Prevalence (%)	30.4	21.6
2012	Arosio <i>et al.</i> (21)	Italy	Cohort	1512	Prevalence (%)	12.4	16.2
2013	Vallette <i>et al.</i> (25)	Canada	Cohort	649	~	~	~
2018	Gonzalez <i>et al.</i> (60)	Mexico	Cohort, longitudinal	522*	HR (female)	1.5	
2016	Dal <i>et al.</i> (33)	Denmark	Cohort	405	Rates (per 1000 person years)	16.1	8.9
2013	Ciresi <i>et al.</i> (66)	Italy	Cohort, longitudinal	307*	Prevalence (%)	17.3	5.1

*Newly diagnosed.

debate in the literature, and a recent meta-analysis has demonstrated a slightly increased overall risk of cancer with acromegaly (84). Gender data are overall limited, although sex distribution from the same meta-analysis was approximately equal. Some studies reporting female preponderance (20, 85), some male preponderance (86) and others reporting no difference (24, 87). Thyroid cancers have a five-fold increased risk when compared with sex and age-matched controls (88), although surveillance bias cannot be excluded (84) because of female predominance of thyroid malignancies in the general population. Increased risk of colorectal cancer has been demonstrated in multiple studies, without gender dimorphism (89). Breast cancers are significantly more common in the women with acromegaly (5%) compared with the general population, although study numbers are small (88, 90). In summary, data regarding gender dimorphism in malignancy with acromegaly are scant. Larger studies are required for clinically meaningful conclusions to be drawn.

Bone health

GH and IGF-1 regulate bone growth and remodelling, promoting differentiation of osteoblasts and chondroblasts, osteoprotegerin production and bone turnover (91, 92, 93). The effects of these factors on bone mineral density are debated in the literature. Some data have demonstrated increased bone mineral density (94, 95), some decreased bone density (95, 96) and others unchanged bone density (97, 98, 99). Differential sex steroid modulation of these factors may be expected to result in gender dimorphism in bone health; however, data are limited and inconclusive. Several studies have shown increased prevalence of vertebral fractures in acromegaly, independent of bone mineral density, bone turnover and disease control (100, 101, 102, 103). Male predominance has been reported, albeit particularly in the presence of concomitant hypogonadism (101). Overall, there is insufficient evidence to ascertain whether there is a gender dimorphism in acromegalic bone disease.

Outcomes of treatment

As discussed, gender influences the relationship between GH and IGF-I across a broad spectrum of GH levels. Relative resistance to the effects of GH with regard to IGF-I response occurs in healthy women and in women

with GHD. Along with the aforementioned differences in presentation, it is possible that gender may also influence treatment outcomes in acromegaly.

Surgery

Surgery is the mainstay of therapy for acromegaly. Reported surgical cure rates are higher for microadenomas (75–90%) than macroadenomas (45–70%), with surgical expertise being a very significant determinant of outcomes (104). There are several factors that lower probability of surgical cure: younger age at diagnosis, larger tumour volume, cavernous or sphenoid sinus invasion and sparsely granulated subtype (105). A number of studies have investigated whether gender influences these factors and in turn surgical outcomes. Park *et al.* (26) performed a large retrospective study of 463 patients who underwent transsphenoidal surgery with a single operating neurosurgeon in a tertiary referral centre in South Korea. Women had lower pre-operative IGF-1, larger tumours, higher proportion of cavernous sinus invasion and were older at surgery. In particular, premenopausal women had larger and more aggressive tumours than men and post-menopausal women. Total tumour resection rate was significantly lower in women than in men (85.5% vs 92.6%) as was long-term surgical remission (76.5% vs 89.7%) (26). By contrast, several smaller retrospective studies have reported no gender difference in surgical remission rates (106, 107, 108, 109, 110). Jane *et al.* (106) reported that gender did not influence outcome in a retrospective single centre retrospective study of 60 patients. In another retrospective single centre study of 55 patients, Babu *et al.* (109) also observed that gender did not affect cure rates. Similar observation was made by Hazer *et al.* (108) in 214 patients and by Antunes *et al.* (107) in 69 patients. These studies were retrospective, heterogenous in patient groups, follow-up period and definition of cure. Several other recent studies have investigated surgical outcomes in acromegaly, without reporting specifically on gender as a predictor (111, 112, 113). In summary, data regarding gender differences in acromegaly surgical outcomes are conflicting. The single largest study investigating this directly suggests more aggressive natural history and hence worse treatment outcomes in premenopausal women (26). Further prospective age-matched data are required to elucidate whether surgical outcomes are influenced by gender.

Medical therapy

Somatostatin Analogues (SSAs)

Somatostatin analogues (SSAs) form the cornerstone of medical therapy in acromegaly. Many large clinical trials have demonstrated the comparable efficacy of first generation SSAs, octreotide and lanreotide, with normalisation of IGF-1 in 38–85% and reduction of GH to < 2.5 mcg/L in 33–75% (114, 115, 116). Second generation SSA, pasireotide LAR, is associated with higher rates of biochemical cure than those achieved with octreotide (117). Nevertheless, rates of cure with SSA therapy are sub-optimal, with response affected by patient selection, compliance, baseline IGF-1 levels, prior therapy and possibly gender. In a review of SSA resistance, Cuevos-Ramos & Fleseriu (118) proposed female gender as a positive predictor of response to SSA, attributed to oestrogen upregulation of SSTR2. However, the potential role of sex has not widely been reported in clinical trials to substantiate this. Results that are available are conflicting and inconclusive. In a large randomised, placebo-controlled multicentre study, Melmed *et al.* (119) reported on 99 unselected patients with acromegaly. Treatment was with Lanreotide Autogel or placebo, with 52 weeks open extension. In this study, 54.4% of females and 48% of males achieved GH defined biochemical control; 59.6% of females and 56% of males normalised IGF-1. By combined criteria, 45.6% of females and 36% of males achieved biochemical cure. By contrast, in a prospective study of 104 patients treated preoperatively with lanreotide SR, normalisation of IGF-1 was reported in 25% of patients, with no gender dimorphism (120). Many other prospective studies have investigated treatment efficacy of lanreotide (seven large recent studies reviewed, total $n=2275$), without reporting on gender data (121, 122, 123, 124, 125, 126, 127). Results are similarly limited for octreotide. In a large multi-centre prospective trial published in 1991, 189 patients with acromegaly were treated with octreotide (128). There was no gender difference in biochemical control following treatment. Similarly, a retrospective evaluation of 110 acromegalic patients treated with octreotide LAR for 4 years demonstrated no gender difference in outcomes (129). Numerous other studies have investigated treatment efficacy of octreotide, without reporting on gender data (six large recent studies reviewed, total $n=1348$) (117, 130, 131, 132, 133). Although a number of studies have investigated the efficacy of pasireotide, gender specific outcomes have not been reported (117, 134, 135, 136, 137, 138, 139). In summary, although there are proposed mechanistic reasons for better efficacy of SSA in female

patients, study data are conflicting. Further prospective trials should report on gender specific outcomes. Such data may help guide medication selection and titration in the future.

GH receptor antagonist

Pegvisomant, formulated from the pegylation of a GH analogue which binds to but not activate the GH receptor, has an established place in the drug management of acromegaly (115). From the principles of competitive inhibition, biochemical control is dependent on the dose and the prevailing concentration of GH in blood. Biochemical control rates vary from 60 to 90%, with lower rates reported in real-world studies, at least partly explained by lesser dose titration in the community than in clinical trials (115). There has been interest in identifying other factors determining the efficacy of pegvisomant, including that of gender.

Parkinson *et al.* (140) analysed the treatment effects between men and women in a multicentre, open-label trial of pegvisomant monotherapy in 118 patients. At baseline, mean GH levels were similar but IGF-I levels were higher in men. During treatment, there was a greater decline in IGF-1 in men, with both sexes attaining a similar level of IGF-1. Women received 20% higher weight-corrected dose of pegvisomant than in men to achieve the same concentration, indicating that the pharmacokinetics were different. In women, for an equivalent concentration of pegvisomant, the reduction in IGF-I was lower, indicating that clearance and sensitivity were lower in women. Biochemistry was measured in a centralised laboratory. In a retrospective, multicentre cross-sectional study, Marazuela *et al.* evaluated the effect of gender on pegvisomant monotherapy efficacy in a smaller group of 44 patients resistant to other treatment modalities (141). Male patients had significantly greater decline in their IGF-1 from baseline than did women. More male patients were controlled at the end of treatment than were women. The mean dose of pegvisomant was significantly higher in women than in men, although significance was lost when corrected for weight. The findings are broadly similar to the those of Parkinson *et al.* (140). Limitations of this study were its small sample size and de-centralised laboratory studies. Franck *et al.* (142) reported on a multivariable regression analysis of two retrospective cohorts developing a predictive model for pegvisomant dosing, as monotherapy ($n=83$) and in combination with long-acting SSA ($n=76$). Sex

differences in pegvisomant dosing were not confirmed in this larger study. The weaknesses of this study were the magnitude of missing data (72 in the monotherapy group and 65 in the combination group), and unlike the Parkinson study, GH was measured using different assays by different participating centres. In summary, there is limited though conflicting evidence suggesting that women require more pegvisomant than men for disease control.

Radiotherapy

Radiation therapy is generally considered as a third-line treatment in patients who have not achieved control with surgery and/or medical therapy. Mildly better biochemical remission and lesser adverse events are observed with stereotactic radiosurgery (SRS) than with conventional fractionated radiotherapy (RT) (104, 143). Nevertheless, the rates of biochemical remission with SRS are widely varied in the literature. Whether the response to radiotherapy is influenced by gender has been investigated in several studies. In a multicentre retrospective cohort, comprising of ten participating institutions, the outcome SRS in 373 patients followed for 79 months was not different between men and women (144). Another large retrospective multicentre study comprising of 14 participating centres, with 884 patients with acromegaly observed no effect of gender on the efficacy of conventional RT (145). Several further large retrospective single-centre studies have similarly observed no effect of gender on outcomes with SRS and conventional RT (total $n=367$) (146, 147, 148). Conversely, in a smaller retrospective single centre review of 40 patients, Poon *et al.* (149) evaluated factors that may predict remission of acromegaly following gamma knife surgery. Female gender and cavernous sinus invasion were identified as failed predictors, although it is unclear if these were independent of one another. In summary, there is no substantial and consistent evidence to suggest that gender does affect remission of disease following radiation therapy.

Prognosis

Studies from the United Kingdom in the 1970–80s observed mortality rates of up to three-fold higher than the background population (8, 150, 151). The mortality rate was higher in women in one study (151), in men in another study (8) and not different in the third (150). All three studies reported that cerebrovascular disease was the major cause of death in females, while CV disease and cancer also contributed to death in men. Other studies have not signalled a gender difference in increased mortality risk (30, 152).

Improvements in disease control brought about by more effective therapies have resulted in a gradual reduction in mortality. Recent studies from France (24), Italy (21) and Mexico (153) have reported that mortality rates in acromegaly are similar to those of the general population. In the French study, this occurred in parallel with progressive improvements in treatment and resultant disease control over a 30-year period of observation. In the Italian study, restoration of life expectancy from improved GH control was similar between males and females (21). Registry studies from the three Scandinavian countries have also reported that a decline of mortality rates in acromegaly but not to those (SMR: 1.3–2.7) of matched populations (23, 28, 33). In Denmark, the mortality rate was similar between males and females (33). There was a two-fold higher risk of diabetes and hypertension in women and the major cause of death was cardiovascular disease for both sexes. In Sweden, cardiovascular disease was also the major cause of death with ischaemic heart disease occurring more frequently in women (23). However, the mortality rate was similar in men and women. In Finland, the mortality rate was increased in women and not men with acromegaly compared to the general population over a 20-year period of observation (28). The female group was older, no dominant cause of death was identified and GH data was unavailable. A recent study of 718 acromegalic patients from Korea observed an increased risk of mortality in female but not male patients (20). Table 5 summarises studies that have

Table 5 Gender and standardised mortality in acromegaly.

Year	Reference	Study period	<i>n</i>	SMR	Gender comparison
1987	Nabarro (154)	1963–1983	256	1.26	F > M (1.7 vs 1.01)
1998	Abosch <i>et al.</i> (152)	1974–1992	214	1.28	F > M (1.8 vs 1.02)
2003	Beauregard <i>et al.</i> (155)	1970–1999	103	2.14	F > M (2.5 vs 1.9)
2005	Kauppinen-Makelin <i>et al.</i> (27)	1980–1999	334	1.16	F > M (1.34 vs 1.06)
2013	Bogazzi <i>et al.</i> (156)	1999–2009	438	0.7	F > M (0.88 vs 0.53)
2014	Mercado <i>et al.</i> (153)	1990–2010	442	0.76	F > M (1.04 vs 0.41)
2016	Ritvonen <i>et al.</i> (28)	1980–1999	333	1.9	F > M (2.5 vs 1.4)
2018	Esposito <i>et al.</i> (23)	1987–2013	1089	2.79	F ~ M (2.99 vs 2.60)

F, female; M, male; SMR, standard mortality ratios.

reported comparison between SMR in women and in men (23, 27, 28, 152, 153, 154, 155, 156).

In summary, mortality rate in uncontrolled acromegaly is increased but has fallen to that of the general population in parallel with attainment of disease control in both males and females. In studies where mortality rate is still increased, the risk is similar between the sexes, despite women having a higher risk of diabetes and hypertension. The collective evidence suggests no clear gender influence on mortality nor on beneficial effect of disease control.

Summary

Acromegaly is more prevalent in women than in men. There is a greater delay to diagnosis in female compared with male patients, despite experiencing symptoms for longer and seeing more doctors. QoL is more adversely affected in women than in men, predominantly due to mental health and sleep factors, and does not appear to improve as much after successful therapy. At diagnosis, women have lower IGF-I levels relative to GH status. Women present with larger, more invasive tumours in some but not all studies. The prevalence of diabetes and hypertension is increased, arguably affecting women more than men. Obstructive sleep apnoea prevalence is increased in acromegaly, with a male predominance reflecting that in the general population.

Women are equally responsive to SSAs but may require a higher dose of pegvisomant to achieve equivalent control compared to men. Surgical outcomes are similar except when tumour characteristics differ between male and female patients. The mortality rate is increased in uncontrolled acromegaly and has gradually fallen to that of the general population in both sexes through improved treatments and biochemical control. While women seem to have a higher risk of diabetes and hypertension, the improvement in life expectancy is not different between genders.

Conclusion

Gender has not been sufficiently considered as an important variable in the management of acromegaly such that a review necessitates extracting results from studies of varying quality and intent. Nevertheless, the information has allowed us to conclude from a literature survey of the epidemiology, management and treatment outcomes that acromegaly is more common in women, who also bear greater burden of disease. The biochemical

profile in women consisting of relatively higher GH, which causes insulin resistance, and lower IGF-I, which mediates anabolism, may contribute to a possible higher prevalence of hypertension, diabetes and to diagnostic delay. The mortality risk for men and women with acromegaly is increased but falls to that of the general population with treatments that cure or control disease. Although life expectancy can be restored in both sexes, the disease burden in women is greater from late diagnosis which prolongs suffering, potentially increasing the extent of complications compromising prognosis.

Gender does matter in the management of acromegaly. However, more research is required to determine the cause(s) of diagnostic delay and whether co-morbidities such as hypertension and diabetes are more prevalent in females with acromegaly. A programme of greater awareness for health practitioners and the community is required to remove gender disparity in the management of acromegaly.

Declaration of interest

K H is an Associate Editor of European Journal of Endocrinology. He was not involved in the review or editorial process of this paper, on which he is listed as an author. The other authors have nothing to disclose.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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Received 14 December 2019

Revised version received 5 February 2020

Accepted 17 February 2020