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Review article

Risk of left ventricular hypertrophy and diastolic and systolic dysfunction in Acromegaly: A meta-analysis

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ABSTRACT

Objective: To perform a meta-analysis to evaluate the exact incidence of left ventricular hypertrophy, diastolic dysfunction and systolic dysfunction in patients with treatment-naïve acromegaly.
Methods: PubMed, EMBASE, Ovid MEDLINE, the Cochrane Library, Scopus, Science Citation Index Expand and PubMed Central were searched for eligible studies. Eligible data were extracted and evaluated using a fixed- or random-effects model. The Q test, I^2 statistics for testing heterogeneity, the Newcastle-Ottawa Scale (NOS) for the retrospective appraisal of study quality, and Begg's test and Harbord's modified test for the evaluation of publication bias were used.
Results: Seven eligible studies were selected, and a total of 458 patients and 650 controls were included. Left ventricular hypertrophy was significantly more frequent in treatment-naïve acromegaly patients than in controls [odds ratio (OR) = 28.2, 95% confidence interval (CI) = 19.17–41.49] with a prevalence of 65.1%. Diastolic dysfunction was also common (50.5%) in acromegaly patients (OR = 15.62, 95% CI = 1.98–123.34). Moreover, 19.6% of patients presented abnormal systolic function with an OR of 13.1 (95% CI = 6.64–25.84).
Conclusions: Patients with treatment-naïve acromegaly are at an increased risk of developing left ventricular hypertrophy, diastolic dysfunction and systolic dysfunction than the general population.

1. Introduction

Acromegaly, a chronic neuroendocrine disease, is characterized by the excessive secretion of growth hormone (GH) and elevated levels of insulin-like growth factor 1 (IGF-1) [1–3]. Mortality is increased, and quality of life is decreased in these patients [3,4]. Specifically, in a recently published meta-analysis, acromegaly was associated with an elevated standardized mortality ratio of 1.72 [5]. The poor prognosis in acromegaly patients is primarily attributed to cardiovascular comorbidities, respiratory comorbidities and malignant neoplasms. Of these patients, 60% die from cardiovascular disease, 25% die from respiratory disease, and 15% die from malignancies [6]. Cardiomyopathy, which was identified in 1895, also arises in acromegaly and includes three main presentations, namely, left ventricular hypertrophy, diastolic dysfunction, and systolic dysfunction. These manifestations were thought to be the most important manifestations of acromegalic cardiovascular abnormality and thus had greater significance [2,7].

To the best of our knowledge, a higher risk of developing cardiomyopathy has been widely accepted; however, the risk ratio has varied between studies. A meta-analysis performed by Rokkas, Pistiolas [8] and Wolinski, Czarnywojtek [9] revealed an increased risk of thyroid nodular disease (OR = 6.9), thyroid cancer (OR = 7.9) and colon cancer (OR = 4.4) in acromegaly patients compared with the general population. In contrast, the prevalence of cardiomyopathy in acromegaly patients has not been precisely summarized. We conducted this meta-analysis to examine the pooled risk of left ventricular hypertrophy, diastolic dysfunction and systolic dysfunction in treatment-naïve acromegalic patients with the aim of elucidating and more accurately presenting the ratio of developing cardiomyopathy.

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2. Methods

2.1. Study selection

All relevant studies on the topic of cardiomyopathy in acromegaly patients were retrieved from the PubMed, EMBASE, Ovid MEDLINE, Cochrane Library, Scopus, Science Citation Index Expand and PubMed Central databases. Search keywords were confined to the following: "acromegaly" or "acromegalic" or "growth hormone-secreting pituitary adenoma" and "cardiomyopathy" or "ventricular hypertrophy" or "diastolic dysfunction" or "systolic dysfunction" or "heart failure." Other studies were identified by searching printed resources, conference papers and presentations. Articles from the references in the retrieved articles were scanned to search for other potentially eligible reports.

All results were imported into a database manager (EndNote X7, Thomson Reuters, US, Patent NO. 8082241). Duplicate studies were automatically and manually excluded. Two reviewers (XG and HF) independently strictly identified studies according to the inclusion criteria and extracted eligible data from articles. Disagreements between the two reviewers were settled by discussion. If the disagreement remained unsettled after discussion, it was resolved through a discussion with a third reviewer (BX).

2.2. Inclusion and exclusion criteria

Patients were diagnosed with acromegaly according to either elevated serum levels of GH and IGF-1 or pathology confirmation. Patients were treatment-naïve (newly diagnosed without being treated with surgery, medication or radiation) and underwent echocardiography. Age- and gender-matched acromegaly patients and control subjects were included in each of the selected studies. We enrolled studies with main outcomes of echocardiographic findings indicating at least one cardiomyopathy presentation. The odds ratio (OR) with 95% confidence interval (CI) could be directly obtained or calculated using the diagrams or tables in the articles.

Studies that did not meet the above inclusion criteria were excluded to avoid within-study bias. We also excluded case reports, reviews, letters, comments, editorials, and studies that were not written in English or that were performed *in vitro* or on animals.

2.3. Data identification and extraction

We extracted information from the eligible studies. The first author; publication year; data regarding left ventricular hypertrophy, diastolic dysfunction or systolic dysfunction; disease duration; and diagnostic criteria were collected and summarized.

2.4. Statistical analysis

We followed the PRISMA criteria for this review [10]. We calculated the OR and 95% CI using RevMan 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Forest plots were constructed for pooled data. The Newcastle-Ottawa Scale (NOS), a method for the quality assessment of retrospective studies, was used to assess the quality of pooled studies with at least six stars indicating high quality. The Z test was used to evaluate the significance of an overall effect. Because I^2 is a sample-adjusted statistical method that is thought to have sufficient power regardless of the number of studies, the Q test and I^2 statistic were both used to assess heterogeneity. The analysis was considered heterogenic if $I^2 > 50\%$, and the Q test provided a $P < .1$ (I^2: 0% represents no heterogeneity, greater values represent increasing heterogeneity, and values over 50% indicate substantial heterogeneity) [11]. If heterogeneity was found, a random-effects model was used to estimate the overall effect. In contrast, if $P > .1$ or $I^2 < 50\%$, a fixed-effects model was selected. A sensitivity analysis was performed to explore the possible causes of heterogeneity. The likelihood of publication bias was quantitatively estimated using Begg's test and Harbord's modified test and visually assessed using funnel plots obtained with STATA statistical software version 12.1 (StataCorp LP).

3. Results

3.1. Study selection

An overview of the study selection process is presented in Fig. 1. A total of 1904 articles were imported into Endnote X7 (1860 identified through seven electronic databases and 44 through printed resources and the references in retrieved articles). The initial pooled database that was established consisted of 1222 articles after duplicates were excluded. After screening the study titles, abstracts and keywords, 112 articles were considered relevant to our topic. We then excluded 58 articles for the following reasons: 29 articles were case reports (including studies with less than three patients), 26 were reviews, one was a comment, and two were studies on animals. A full-text version was retrieved for the 54 articles, and forty-seven articles were removed because they did not strictly meet the inclusion criteria. Finally, seven articles fulfilled our criteria and were included in the meta-analysis [12–18].

3.2. Study characteristics

These studies enrolled 458 patients and 650 control subjects. The characteristics of the pooled eligible articles published from 1999 to 2013 are shown in Table 1. The NOS assessment revealed that all of the pooled studies were of high quality (Supplemental Table).

3.3. Left ventricular hypertrophy

All pooled studies contained echocardiographic data of ventricular hypertrophy in treatment-naïve acromegaly patients and controls [298/458 (65.1%) vs 53/650 (8.2%), respectively]. No heterogeneity [$P = .78$, $I^2 = 0\%$, $Chi^2 = 3.23$, degrees of freedom (df) = 6] was found among these studies. Based on the fixed-effects model, the pooled OR (95% CI) was 28.20 (19.17–41.49). The Z test for the overall effect was 16.95 with $P < .001$ (Fig. 2a). Moreover, no significant publication bias was observed in the funnel plot (Fig. 3a), Begg's test (Pr = 0.548) or Harbord's modified test (Pr = 0.730).

3.4. Diastolic dysfunction

For diastolic dysfunction in treatment-naïve patients with acromegaly, the pooled OR was 15.62 with a 95% CI of 1.98–123.34 compared with the control group [163/323 (50.5%) vs 40/463 (8.6%), respectively] using the random-effects model. This result was significant according to a Z test of 2.61 and $P = .009$ (Fig. 2b). There was moderate heterogeneity among the pooled studies ($P = .07$, $I^2 = 63\%$, $Chi^2 = 5.37$, df = 2). Publication bias was not significant according to Begg's test (Pr = 1.000) and Harbord's modified test (Pr = 0.640) (Fig. 3b). Given the existence of heterogeneity, a sensitivity analysis was performed in this subgroup (Table 2). After excluding the study performed by Damjanovic SS (with a high OR of 159.26), heterogeneity was not significant ($Chi^2 = 0.02$, df = 1, $P = .89$, $I^2 = 0\%$).

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