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Original Article

Role of IGF-I, IGF-II and IGFBP-3 in lung function of males: the Caerphilly Prospective Study

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Abstract: Insulin-like growth factors are peptide hormones that have an endocrine role in the development, growth and repair of human tissues including the respiratory tract. To date, only one population study exists which found positive cross-sectional associations with IGF-I and higher lung volumes. We hypothesised that higher IGF-I, IGF-II, IGFBP-3 and IGF molar ratio would be associated with better cross-sectional and longitudinal lung function. We examined cross-sectional (n=843) and prospective associations (n=717) between IGF-I, IGF-II, IGFBP-3 and IGF molar ratio with lung function in the Caerphilly Prospective Study (CaPS) from blood samples obtained around 1986, with spirometry (forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC)) performed in the same year and around 2003. Higher IGF molar ratio was associated with improved FEV_1/FEV ratio cross-sectionally in both simple (0.007, 95% CI 0.001-0.013, P=0.02) and fully adjusted (0.001, 95% CI 0.001-0.012, P=0.03) models. With the exception of IGFBP-3 and FEV_1/FVC in the simple model (0.009, 95% CI 0.001-0.018, P=0.04) all prospective associations between IGF and spirometric measures were consistent with chance. In this study of men, higher IGF molar ratio was associated with improved cross-sectional lung function, although these findings were not replicated prospectively. Further work is required with repeat IGF sampling during follow up to see if IGF levels play any role in predicting future lung function through the life course.

Keywords: Insulin-like growth factors, cohort study, spirometry, lung function

Introduction

Insulin-like growth factors (IGF-I and IGF-II) are peptide hormones that have an endocrine role in growth and development of human tissues and their systemic activity is modulated in the serum by six binding proteins (IGFBP-1 -6) [1]. In addition to a role in cardiovascular disease, cognitive function, diabetes and malignancy [2], there is evidence that the IGF/growth hormone axis is associated with lung development and mediating pathological and cellular repair processes. One animal study showed IGF-1 stimulated lung epithelial cell proliferation and maturation [3], whilst in humans, both IGF-I and IGF-II have been detected in the fetal respiratory tract and may act on epithelial cell proliferation and stimulate the maturation of connective tissue [4]. In terms of potential associations with respiratory pathology, lower levels of IGFs are seen in patients with COPD [5-7] and cystic fibrosis [8-10], though this may reflect reverse causation. Moreover, IGFBP-3 is implicated in the development of lung fibrosis [11], is higher in the lungs of patients with acute respiratory distress syndrome [12] and is associated with endothelial cell apoptosis and inhibition of IGF mediated proliferation [13].

To our knowledge, only one cross-sectional population based study has investigated insulin-like growth factors and lung function and found a positive association with IGF-I and IGF molar ratio and higher lung volumes [14]. We explored both cross-sectional and prospective associations of IGF-I, IGF-II, IGFBP-3 and IGF molar ratio on spirometric lung function over a median follow-up of around 17 years. Our *a priori* hypothesis was that increased levels of IGF-I, IGF-II, IGFBP-3 and IGF molar ratio would be

associated with improved measures of lung function in our cohort and maintained longitudinally.

Materials and methods

Ethics statement

Ethical approval for the different phases of the study was given by the Ethics Committee of the Division of Medicine of the former South Glamorgan Area Health Authority and Gwent Research Ethics Committee and participants gave consent for access to their medical records for research purposes.

Study population

The Caerphilly Prospective Study (CaPS) is a population-based cohort of 2512 Welsh men who were recruited in 1979 with an age range between 45 and 59 years [15]. They have been followed up on four subsequent occasions during phases 2-5 which occurred during 1984-88, 1989-93, 1993-97 and 2002-2004, respectively. In this paper we are using the "reconstructed cohort" which consists of men who were screened at phase II regardless of whether they had attended phase I, as 447 men were identified at this phase who had never been invited at phase I.

Measurement of insulin-like growth factors

Serum IGF-I, IGF-II and IGFBP-3 were measured from 927 individuals where aliquots had been collected at phase 2 and stored at -80 deg C. The average coefficients of variation for intra-assay variability for IGF-I, IGF-II and IGFBP-3 were 7.0, 7.9 and 5.6%, respectively; for inter-assay variation 8.8, 9.7 and 8.8%. Details of the laboratory measurement of the IGFs have been reported previously [16].

Measurement of lung function

Pre-bronchodilator spirometry data from phases 2 and 5 was used. The forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and their ratio (FEV_1/FVC) were calculated. This has been described elsewhere [17] but in summary, for phase 2 the McDermott spirometer was used with subjects in a standing position. An acceptable result was only included if the two valid, best traces of three performed had less than 100ml variability in FEV_1 and FVC. At Phase 5, spirometry was performed using vitalograph spirometer with the same strict criteria.

Measurement of potential confounders

Data on potential confounders were collected from questionnaires administered at Phase 2. Self-reported smoking status was categorised into: never, ex-smoker >10 years, ex-smoker <10 years, cigar/pipe, current 1-24 a day and current >25 day. Adult socio-economic status was based on occupational social class and classified into 5 categories based on the individual's present or last job (I/II, professional and managerial; III skilled non-manual; III, skilled manual; IV, Partly skilled; and V unskilled/unclassified). BMI was calculated from height and weight measurements using the formula weight (kg)/height^2 (m^2). No information was collected on a pre-existing doctor diagnosis of chronic obstructive pulmonary disease (COPD), asthma or interstitial lung disease. Consequently, in an attempt to exclude either obstructive or restrictive respiratory impairment at Phase 2 we calculated FEV_1% predicted and FVC% predicted according to the Association for Respiratory Technology and Physiology (ARTP) equations [18] and created an additional variable to categorize clinically relevant respiratory impairment where either of these fell below 80%.

Statistical analysis

There was some variation in the mean IGF by laboratory batch so these were corrected for by adjusting for the date of assay (centred on the average date) and participant age. To estimate the biologically available IGF-I the molar ratio of IGF-I: IGFBP-3 was calculated based on the molecular weight [19]. The IGF values (ng/ml) were then converted to z-scores to facilitate the comparison between the different IGF values as by definition this rescales the raw values to have a mean of zero and standard deviation (SD) of 1; therefore all the regression coefficients are based on a one SD increase in IGF from the mean value. We initially did simple regression models adjusting for age, height and IGF laboratory batch. We then used multivariable linear regression with adjustment for potential confounders (smoking status, socio-economic status and BMI) to evaluate cross-sectional associations at phase 2 and then pro-

Table 1. Characteristics of study participants from phase 2 with or without lung function at phase 5

	Present at phase 5				Not present at phase 5			
	N	%	Mean	SD	N	%	Mean	SD
Exposures								
IGF-I (ng/ml)	717		155	48.5	210		151.5	45.4
IGF-II	716		719	239.3	210		702.1	249.2
IGFBP3	717		3394.1	729.9	210		3366.1	898.4
Outcomes								
FEV_1 (litres)	1043		2.25	0.64	1221		2.63	0.73
FVC (litres)	1043		3.30	0.76	1308		3.49	0.79
FEV_1/FVC	1043		0.67	0.11	1221		0.75	0.1
Potential Confounders								
Age at baseline	1043		55.9 (47-67)	4.3	1355		57.6 (48-66)	4.5
Age at phase 5	1038		72.7 (60-83)	4.1				
Smoking Status								
Never	241	23.2			190	14		
Ex >10 years	278	26.7			265	19.6		
Ex <10 years	146	14			218	16.1		
Cigar/pipe	102	9.8			120	8.8		
1-24 day	229	22			453	33.4		
>25 day	43	4			107	7.9		
BMI (kg/m^2)	1032		26.6	3.4	1330		26.2	3.8
Height (m)	1043		1.7	0.63	1334		1.7	0.06
Predicted FEV_1 or FVC <80%								
Yes	268	25.7			564	42.8		
No	775	74.3			752	57.1		

spectively between IGFs and FEV_1, FVC, FEV_1/FVC ratio at phases 2 and 5, respectively.

In addition, we conditioned for baseline spirometry results to ascertain any effect of changes in lung function from the pre-existing baseline measure and looked at changes in lung function by subtracting phase 2 from phase 5 values and repeated the models. We then undertook sensitivity analyses by controlling for our variable of FEV_1 or FVC <80% at Phase 2 and ran interaction models to test for any effect modification between smoking status (current versus ex- and never smokers) and IGF on lung function. We have expressed the beta-coefficient for the FEV_1/FVC ratio as a percentage (multiplied raw value by 100) to reduce the number of decimal places. The statistical analysis was carried out using Stata version 12.

Results

Serum IGF values with corresponding spirometry was available for 843 men at Phase 2, and again for 717 of those men at Phase 5 (median follow-up 17 years) when median age was 73 years (range 65-84 years). Summary statistics for the study participants who were present or not at Phase 5 for spirometry testing are shown in **Table 1**; individuals not present at phase 5 were older (P<0.001), of lower social class (P<0.001), heavier smokers (P<0.001) and more had predicted FEV_1 or FVC <80% (P<0.001). There was no difference in baseline IGF-I (p=0.33), IGF-II (p=0.37) and IGFBP-3 (p=0.63) for men who were or were not followed up at phase 5. There were moderate correlations between the phase 2 IGFs; IGF-I was positively correlated with IGF-II (0.30, P<0.001) and IGFBP-3 (0.31, P<0.001), and IGF-II with IGFBP-3 (0.31, P<0.001).

At phase 2, in the age, height and IGF batch adjusted model a one SD increase in the molar ratio was associated with a 0.7% increase in FEV_1/FVC ratio (95% CI 0.1-1.3%, p=0.02), which was not attenuated upon full adjustment (P=0.03). With the exception of a weaker asso-

Table 2. Simple and fully adjusted models examining association of IGF-I, IGF-II and IGF molar ratio with FEV_1, FVC & FEV_1/FVC ratio at Phase 2

Phase 2	FEV_1				FVC				FEV_1/FVC Ratio (%)			
	Coeff	95% CI		P	Coeff	95% CI		P	Coeff	95% CI		P
IGF-I												
Model 1*	0.035	-0.004	0.074	0.08	0.019	-0.024	0.062	0.39	0.6	0.0	1.2	0.05
Model 2**	0.011	-0.026	0.049	0.55	-0.001	-0.043	0.041	0.96	0.4	-0.2	1.0	0.18
Model 3***	0.021	-0.005	0.047	0.11	0.008	-0.025	0.040	0.65	0.5	-0.1	1.0	0.11
IGF-II												
Model 1*	0.007	-0.035	0.050	0.74	0.013	-0.033	0.059	0.59	-0.1	-0.8	0.5	0.70
Model 2**	-0.002	-0.042	0.038	0.93	0.011	-0.033	0.056	0.62	-0.3	-1.0	0.3	0.32
Model 3***	0.006	-0.022	0.034	0.69	0.022	-0.013	0.057	0.23	-0.3	-0.9	0.3	0.38
IGFBP3												
Model 1*	-0.002	-0.043	0.039	0.91	0.007	-0.038	0.051	0.77	-0.2	-0.8	0.4	0.54
Model 2**	-0.003	-0.042	0.035	0.86	0.011	-0.032	0.054	0.61	-0.3	-0.9	0.3	0.28
Model 3***	0.015	-0.012	0.042	0.29	0.031	-0.002	0.065	0.07	-0.2	-0.8	0.4	0.47
Molar ratio												
Model 1*	0.026	-0.014	0.066	0.21	0.000	-0.044	0.044	1.00	0.7	0.1	1.3	0.02
Model 2**	0.004	-0.034	0.042	0.85	-0.022	-0.065	0.021	0.31	0.6	0.0	1.2	0.05
Model 3***	0.007	-0.020	0.034	0.61	-0.021	-0.054	0.012	0.22	0.6	0.1	1.2	0.03

*Model 1 = adjusted for age, height and IGF laboratory batch. **Model 2 = Model 1 + adjusted for BMI, smoking and social class. ***Model 3 = Model 2 + adjusted for predicted FEV_1 or FVC <80%.

Table 3. Simple and fully adjusted models examining association of IGF-I, IGF-II and IGF molar ratio with FEV_1, FVC & FEV_1/FVC ratio at Phase 2 and 5, respectively

Phase 5	FEV_1				FVC				FEV_1/FVC Ratio (%)			
	Coeff	95% CI		P	Coeff	95% CI		P	Coeff	95% CI		P
IGF-I												
Model 1*	0.030	-0.011	0.072	0.15	0.022	-0.025	0.070	0.36	0.4	-0.4	1.2	0.33
Model 2**	0.015	-0.024	0.055	0.45	0.008	-0.039	0.054	0.75	0.3	-0.5	1.0	0.50
Model 3***	0.023	-0.011	0.058	0.18	0.014	-0.029	0.056	0.53	0.4	-0.3	1.1	0.27
IGF-II												
Model 1*	0.012	-0.031	0.056	0.58	0.015	-0.035	0.065	0.56	0.1	-0.7	1.0	0.74
Model 2**	0.007	-0.035	0.048	0.75	0.015	-0.034	0.064	0.54	0.0	-0.8	0.7	0.90
Model 3***	0.017	-0.020	0.054	0.36	0.032	-0.014	0.078	0.17	0.0	-0.8	0.8	0.95
IGFBP-3												
Model 1*	0.021	-0.024	0.066	0.37	-0.010	-0.062	0.041	0.70	0.9	0.0	1.8	0.04
Model 2**	0.013	-0.030	0.055	0.57	-0.007	-0.058	0.043	0.77	0.6	-0.3	1.4	0.19
Model 3***	0.026	-0.012	0.063	0.18	0.008	-0.038	0.054	0.74	0.7	-0.1	1.5	0.09
Molar ratio												
Model 1*	0.016	-0.027	0.060	0.45	0.028	-0.022	0.077	0.27	-0.2	-1.0	0.6	0.64
Model 2**	0.007	-0.034	0.049	0.73	0.012	-0.037	0.061	0.64	-0.1	-0.9	0.7	0.81
Model 3***	0.011	-0.025	0.047	0.56	0.010	-0.034	0.055	0.65	0.0	-0.7	0.8	0.96

*Model 1 = adjusted for age, height and IGF laboratory batch. **Model 2 = Model 1 + adjusted for BMI, smoking and social class. ***Model 3 = Model 2 + adjusted for predicted FEV_1 or FVC <80%.

ciation with IGF-I and the FEV_1/FVC ratio in the simple model (P=0.05), all other cross-sectional associations between IGF and lung function are consistent with chance (**Table 2**).

When considered prospectively, a one SD rise in IGFBP-3 at phase 2 was associated with a 1% increase FEV_1/FVC in the simple model (P=0.04), but this attenuated after full adjustment (**Table 3**). Moreover, there was no strong evidence of longitudinal associations between Phase 2 IGFs and Phase 5 spirometry when additionally adjusting for baseline spirometry or when examining changes in lung function between the phases (data not shown).

There was weak evidence of effect modification of current smokers on associations between IGFBP-3 and FEV_1 so that amongst smokers compared to ex- and never smokers there was an inverse association in the simple model (difference between coefficients -0.08, 95% CI -0.161, -0.001 *p* value for interaction 0.05) and this remained in the fully adjusted models (*p*-value for interaction=0.05) at Phase 2. However, this was not replicated with the other outcomes either cross-sectionally or prospectively.

Discussion

This the first population-based study to examine insulin-like growth factors and lung function in males both cross-sectionally and longitudinally with long term follow-up. In relation to our hypothesis, the only exposure that showed any cross-sectional association with improved lung function when fully adjusted is IGF molar ratio and FEV_1/FVC ratio. This is, in part, consistent with the only other cross-sectional population study that found higher IGF molar ratio levels were associated with higher lung volumes in men [14]. However, in addition they found a similar trend with IGF-I which we only replicated in our unadjusted model with a weaker association. This could be due to the fact that the previous study had a broader age range of subjects (25-85 years) compared to our cohort (47-67 years) and, they were able to exclude people with known respiratory pathology on the basis of previous medical history rather than using predicted lung function values to adjust for likely airway disease at baseline. That study had a larger sample size (around 600 more participants) so had greater statistical power.

In studies looking at the GH/IGF axis in endocrine abnormalities, elevated levels of IGF-1 in acromegaly were associated with higher lung volumes [20], whilst in individuals with growth hormone deficiency onset in childhood, lung volumes were reduced [21]. Furthermore, in children with cystic fibrosis exogenous GH administration raised IGF-I and IGFBP-3 levels, reversing clinical symptoms and improving lung function [22, 23]. Although these studies provide further evidence for association of higher IGF and improved lung function, this study was designed to only consider actions of IGF in a healthy population.

As IGFBP levels are known to influence the bioavailability the IGFs in the serum the IGF-I/IGFBP-3 molar ratio has been suggested to reflect changes in bioactive IGF-I [24] which may explain our findings. IGF-I has been shown to regulate post natal lung growth and alveogenesis [25], and higher unbound, or more available serum levels may improve lung function by exerting proliferative effects on lung and smooth muscle cells via receptor interactions and, in addition, by local cellular secretion of IGF-II [26].

Smoking has been shown to effect levels of circulating IGFs and their binding proteins. Current smoking is associated with suppression of the IGF axis and a reduction in serum IGF-1 and IGFBP-3, although levels normalise upon cessation [27, 28]. Smoking has also been linked to a reduction in antenatal organ size and function [29], as well as smoking-induced lung cancer through inhibition of IGFBP-3, a potent p-53 tumour suppressor [30]. We found weak evidence of effect modification of current smokers compared to ex and never smokers cross-sectionally but only with IGFBP-3 and FEV_1; this needs to be replicated and given the multiplicity of statistical tests may simply represent a type 1 error.

The only prospective association was with higher IGFBP-3 and improved FEV_1/FVC ratio in our simple model but this attenuated after full adjustment. We know that IGFBP-3 plays a paradoxical role on IGFs by both sequestering IGFs away from cell receptors thereby inhibiting activity, whilst at the same time enhancing cellular activity via different mechanisms [2, 31]. Thus, growth factor binding proteins can have an influence on pathological and cellular proliferation processes independently of IGFs [32]. There is some evidence in the literature that IGFBP-3 can have an influence on airway remodeling in allergy mediated inflammation

[33] and independent effects on endothelia cell survival [13] but explaining our results in terms of independent actions of IGFBP-3 in healthy individuals is difficult. Any potential preservative effect on lung function through the life course is likely to be a complex interaction between binding proteins, serum peptide hormones and cellular receptors that has yet to be fully elucidated. Moreover, this finding could be indicative of a type 1 error.

Although we found an absence of any association with IGF-I in middle age and spirometry values around 17 years later, one must be cautious in the interpretation. We only have blood samples from a single time point and unlike IGF-II, serum IGF-I levels vary and are strongly linked to levels of nutrition [34, 35]. Consequently, through changes in lifestyle an individual can alter their IGF-I levels through the life course which may impact on the endocrine processes at a cellular level.

Strengths and limitations

The study has a number of strengths over those previously published. It is prospective with a long latency period between our measures of the IGFs and the outcome measures making a potential reverse causation unlikely and allowing us to test whether IGFs could be used as potential biomarkers for future disease risk. We were able to adjust for a number of potential confounders in the regression models. There are also some limitations that need to be considered. There were only males in this cohort which could affect the generalisability of the finding if the effects of the IGFs differ between the sexes. A previous study found positive associations in women only above the age of 50, whereas in men it was independent of age [14]. At baseline, data on pre-existed respiratory pathology was not collected so we had to estimate those participants with underlying disease using spirometry predicted values which could either over or under estimate disease prevalence depending on an individual's age.

There was some loss to follow-up in the cohort which could have introduced bias. However, this would only be true if the association between the IGFs and future lung function differed in those who were followed up compared to those lost to follow-up. However, we failed to find any difference in IGF levels at baseline suggesting this is unlikely.

Conclusion

We found that higher IGF-I molar ratio was associated with improved FEV_1/FVC ratio cross-sectionally replicating the only other previous study in the literature, but was not reproduced with the other lung function or IGF measures. There were no prospective associations after 17 years follow up and no evidence of effect modification with smoking status. Given this study suggests only a limited impact of IGF in one domain of lung function in middle aged men, it would be pertinent for future work to investigate effects in women, as well as in younger subjects where the effect of IGF are less likely to be confounded by longer term lifestyle factors and age related changes to lung function.

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Disclosure of conflict of interest

None.

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