ORIGINAL ARTICLE

Elevated IGF1 in clinical opiate dependence

Albert Stuart Reece

School of Psychiatry and Clinical Neurosciences, University of Western Australia, Australia

Correspondence to: Albert Stuart Reece
School of Psychiatry and Clinical Neurosciences, University of Western Australia
39 Gladstone Rd., Highgate Hill, Brisbane, Queensland, Australia.
TEL: +(617) 3844-4000; FAX: +(617) 3844-4015; E-MAIL: sreece@bigpond.net.au

Submitted: 2012-07-22 Accepted: 2013-01-05 Published online: 2013-02-25

Key words: **opiates; age; aging; heroin; age related decline; toxicology**

Neuroendocrinol Lett 2013; **34**(1):18–26 **PMID:** 23524620 NEL340113A03

Abstract

OBJECTIVE: To compare IGF1 levels in opiate dependent and general patients both absolutely and by age.
DESIGN: A naturalistic observational study was undertaken of opiate dependent and general medical patients.
SETTING: Primary care.
PATIENTS: 74 opiate substance use dependent (SUD) patients were compared with 262 non-SUD (NSUD) patients.
RESULTS: (1) Comparative IGF1 levels; (2) age and sex corrected IGF1 levels; (3) IGF1 levels corrected for age, sex, and hepatic and immune biomarkers.
MAIN FINDINGS: The SUD patients were younger (32.60+0.89 vs. 42.49+0.96 years, mean+S.E.M., $p<0.0001$) and had more males (72.9% and 39.3%, $p<0.0001$) than the NSUD patients. Restriction of the age range to 15–45 years (70 vs. 153 patients) made the difference in ages non-significant (31.27+0.71 vs. 32.32+0.61 years, $p=0.47$) but IGF1 remained elevated in SUD (26.56+1.21 vs. 22.65+0.57nmol/L, $p=0.0039$). When multiple regression was used to correct for the age and sex disparities, the age: addiction interaction remained significantly elevated ($p=0.0003$). In an additive model opiate dependence showed a 23.8% elevation in IGF1. When the interactive model was further adjusted by the inclusion of ALT and CRP as indices of hepatic inflammation and immune activation respectively, addictive status remained significant both alone ($p=0.0134$) and in 2-, 3- and 4-way interactions with age, male sex, and ALT (all $p<0.0255$).
CONCLUSION: These data demonstrate that serum IGF1 is elevated in opiate dependence both absolutely and after adjustment for age, sex, and markers of immune and hepatic activation.

INTRODUCTION

Opiate dependency, arising by way of chronic pain management, recreational drug use, and the treatment of clinical opiate dependency, is an increasing public health problem associated with the spread of blood borne viruses including HIV, and with prescription and street opiate overdose. Opiates are known to be associated with various endocrinopathies including diabetes and hyperglycaemia (Bernard 1877; Ceriello *et al.* 1987), hyperprolactinaemia (Brunton *et al.* 2006), hypogonadotrophic hypogonadism (Brunton *et al.* 2006), weight gain (Kolarzyk *et al.* 2005) and low bone density (Kim *et al.* 2006). Opiates also stimulate hedonic drives for foods high in carbohydrates and fats by an action in the arcuate nucleus of the hypothalamus (Cowley *et al.* 2001). Despite the fact that it has been known for about 30 years that opiates stimulate GH release (Morley 1981) few studies have

been done of IGF1 in opiate addiction. Most of those which were done were performed some time ago and focussed primarily on GH (Cushman 1972; Passariello *et al.* 1983; Gerra *et al.* 2001). Furthermore there are no published studies which describe and contrast the age associated decline of IGF1 in opiate dependent patients compared to control groups.

The sequence of events in the Growth Hormone (GH) signalling pathway is that hypothalamic Growth Hormone Releasing Hormone (GHRH) releases growth hormone (GH) from the anterior pituitary gland, which then circulates to the liver to stimulate Insulin-like growth factor 1 (IGF1) release from the liver. Circulating IGF1 is largely bound to various plasma proteins including IGF1 Binding Proteins 1, 2 and 3 (IGFBP1-3). IGF1 signals via a cell membrane limited tyrosine kinase receptor through the anabolic Akt pathway to stimulate cell growth, protein synthesis and other anabolic responses (Kronenberg *et al.* 2007). It is also a potent pro-survival and anti-apoptotic signal to cells (Svensson *et al.* 2008), and has been widely implicated as an important mechanism contributing to cancer pathogenesis (Clemmons 2007), particularly in obesity (Onuma *et al.* 2003) and the syndrome of GH excess known as acromegaly, where significant rates of colonic polyposis and other oncogenesis mandate on-going clinical monitoring (Kronenberg *et al.* 2007; Melmed 2009). Importantly the insulin – IGF1 signalling (IIS) pathway is one of the major pathways implicated experimentally in the ageing process, in lower organisms, rodents and monkeys (Guarente & Picard 2005).

Clinical opiate addiction has been noted to be associated with a wide range of pathologies including many neuropsychiatric disorders (Weizman *et al.* 2003), elevated rates of atherosclerosis (Sadeghian *et al.* 2007), osteoporosis (Kim *et al.* 2006), aggressive periodontitis (Reece 2007a; 2009), hair greying (Reece 2007c), a relative deficiency of circulating endothelial progenitor stem cells (Reece & Davidson 2007) and elevated rates of several cancers (Behmard *et al.* 1981; Mousavi *et al.* 2003), all of which are degenerative or age related disorders which are usually seen in much older aged cohorts. Indeed some authors have suggested that opiate dependent patients surviving to the age of 50 years need facilitated access to geriatric services to handle their multisystem disease (Rosen *et al.* 2008). Many other disorders have also been described in opiate dependent patients (Gottshcalk L.A. *et al.* 1979). Indeed this concatenation of age related pathologies has led some workers to suggest that the ageing process may actually be speeded up in such patients (Reece 2007b; 2010).

Given the known secretagogue activity of opiates on GH and the proximate association of IGF1 with many major pathologies all of which are well described in this patient group, it appeared to be important to document formally and carefully the age related associations of IGF1 in clinical populations, and to compare the known age dependent decline in IGF1 in opiate dependent and opiate naive patient cohorts. Whilst a number of endocrinopathies have been described in opiate addiction (Pfeiffer & Herz 1984), the importance of the IGF1-IIS pathway to many central processes both within the cell and in disease pathogenesis, suggested that a detailed profiling of its age dependent decline in our patient populations would be not only interesting, but pathophysiologically important.

The hypothesis which this study was designed to test was that opiate dependence would be associated with an elevated serum IGF1 in direct age matched comparison with control groups, and after correction for age by multiple regression. As this clinic sees both opiate dependent and general medical patients, it presented in ideal opportunity from which to compare the two groups. The present report constitutes a signficant extension of an earlier report related on this subject from this clinic (Reece 2007b).

METHODS

Patient recruitment and sampling

This study was performed in the form of a clinical audit of our pathology results in the period 1995–2010. This clinic is a family medical practice which sees both general medical and drug dependent patients. Patients were divided into substance use disorder (SUD) and non-substance use disorder (NSUD) groups. SUD patients were addicted principally to opiates. Treatment of the opiate addiction was with the combination buprenorphine / naloxone sublingual tablet ("Suboxone"). Patients were not subject to restrictions prior to blood sampling in relation to either food or tobacco intake. Patients with a diagnosed acromegalic tumour or under investigation for this condition were excluded from consideration.

Laboratory analysis

All pathology results in the period 2005–2010 were accessed. IGF1 assays were performed using the fully automated Siemens Immulite 2000 immunoassay system at the clinical pathology laboratories of Queensland Medical Laboratories (QML). The coefficient of variation for this assay was 3%. Hepatitis C serology was determined initially by running the sample through an Architect I-2000 system, and results were validated by an Advia Centaur 5100 assay. Other laboratory techniques are standardized to clinical pathology laboratories across the world. Hepatitis C serology is ordered virtually only in parenteral drug using patients, so that the presence of this test was used to indicate that the patient was a parenteral drug user. This status assignment was supplemented by knowledge of our clinical database. QML is nationally accredited with the National Association of Testing Authorities (NATA) and operates the present Australian medical testing standards (AS-15189). It is also compliant with, and adherent to ISO 9001 the international clinical labora-

tory standard. Data was exported from the pathology databank as a Microsoft Excel spreadsheet.

Statistical analysis

Results are presented as mean ± S.E.M. unless otherwise indicated. Summary statistics of all parametric data were prepared using Statsoft's "Statistica" program from Tulsa Oklahoma. Chi-squared tests of categorical data were performed using EpiInfo Version 3.5.1 from the Centres for Disease control in Atlanta Georgia. Multiple regression was performed using "R" version 2.13.1 obtained from the University of Melbourne Central "R" Archive Network (CRAN) mirror. Continuous data were log transformed in the interests of normality assumptions. Simple quantitative data were compared in a bivariate comparisons in Statistica using Student's t-test, using separate variances where Levene's test was significant. All *p*-tests were two-tailed. Graphs were drawn with Ggplot2 in "R". "R" was used to calculate multivariate statistics, and particularly for study of the effect of age on the parameter of interest, IGF1, for examining interactions between independent variables, for comparing the comparative power of statistical models, and for the analysis of co-variance. $p<0.05$ was considered significant.

Ethical review

Treatment of research subjects was consistent with the Declaration of Helsinki. The Southcity Medical Centre Human Ethics Research Committee (HREC) reviewed and approved all the studies performed in this report. This HREC is nationally accredited with the Australian national body, the National Health and Medical Research Council (NHMRC) in Canberra, Australia.

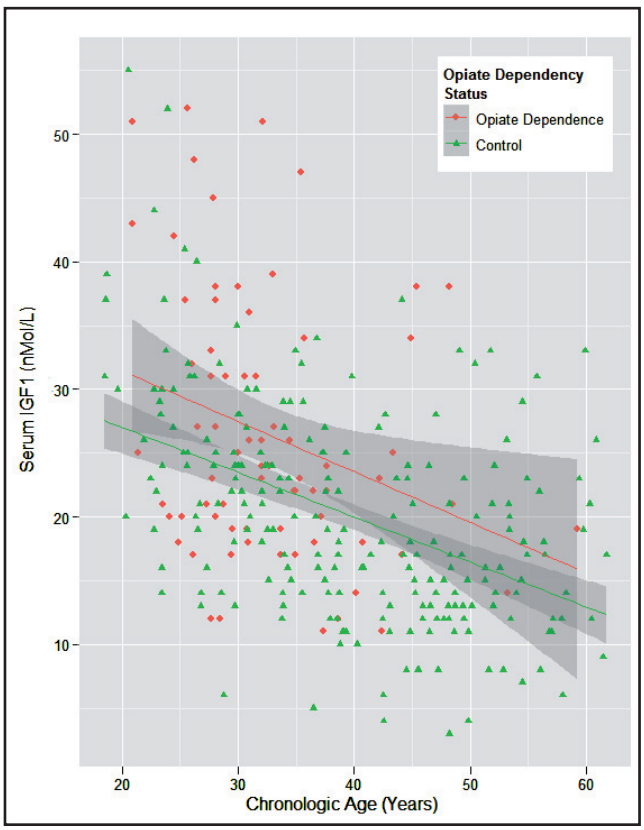

Fig. 1. IGF1 by addictive status by age.

Funding

There was no external source of funding provided for any aspect of this study.

RESULTS

The sample size was 262 the NSUD group and 74 in the SUD group, a total of 336 samples. The mean (±S.D.) ages were 42.49±0.96 and 32.60±0.89 years in the two groups respectively (Student's t separate variances=6.06, dF=212.23, $p<0.0001$, analysis on log transformed data). The sex ratio was 39.3% and 73.0% male in the two groups (103 and 54 males respectively, Chi Squ.=24.92, $p<0.0001$). Drug use in this patient cohort has been previously published (Reece 2007a,d). All SUD patients were opiate dependent, fulfilled the DSM-IV criteria for opiate dependence, and presented clinically for management of their drug dependence. The SUD group were noted to be dependent primarily on opiates. The mean amount of heroin used was 0.57±0.07 g/day and the mean duration for which it was used was 8.97±0.45 years. The mean IGF1 in both groups was 19.67±0.57 and 26.52±1.20 vs. nmol/L respectively (Student's t=6.21, dF =145.17, $p<0.0001$ on log transformed data).

Because of the significant age differences between the two groups with the SUD group being significantly younger, the age range for consideration was restricted to 15–45 years for the purposes of bivariate comparison. When this restricted age range was used and 153 NSUD patients were compared with 70 SUD patients, a total of 223 patients. The ages were then no longer significantly different being 32.32±0.62 and 31.27±0.71 years in the NSUD and SUD groups respectively (t sep. var.=0.72, dF=168.57, $p=0.47$ for log transformed data). The sex ratio was 28.6% and 70.6% male in the two groups (45 and 50 males respectively, Chi Squ.=34.67, dF=1, $p<0.0001$). The IGF1 was significantly different being 22.67±0.57 and 26.56±1.21 nmol/L in the NSUD and SUD groups respectively (t=2.93, dF=150.36, $p=0.0039$, log transformed). Bivariate (logarithmic) comparisons for other measures of hepatic and immunologic activity are also given by sex in Table 1.

Figure 1 shows a scatterplot with lines of best fit for the IGF1 results by age in the two groups. Formal comparison of the regression lines for the SUD and NSUD groups in "R" demonstrates that that the age dependent trajectory of IGF1 in the two groups is significantly different (est.=0.2135±0.0569, t=3.749, $p=0.0002$, model F=59.21, Adj. $R^2=0.2579$, dF=2,333, $p<10^{-15}$). The exponential of the parameter estimate is 1.238, consistent with a 23.8% elevation of serum IGF1 by the opiate dependent state.

Tab. 1. Bivariate comparisons by sex, sges 15–45 years.

	No. SUD	No. NSUD	SUD*	NSUD*	t-value	df	*p*-value
Males							
Chronologic Age	50	45	31.52 (5.83)	33.03 (7.90)	0.6810	79.64	0.4979
ESR (mm/hr)	33	13	14.18 (25.32)	9.31 (11.75)	1.0296	44.00	0.3088
CRP (mg/L)	33	13	20.43 (57.32)	5.27 (7.52)	3.0847	81.59	0.0028
ALT (IU/L)	50	30	76.94 (185.48)	60.37 (71.80)	0.3579	78.00	0.7214
AST (IU/L)	50	30	48.36 (93.03)	41.63 (45.91)	0.0991	78.00	0.9213
Globulins (g/L)	50	30	30.46 (4.39)	29.67 (3.18)	0.7175	78.00	0.4752
IGF1 (nmol/l)	50	45	26.54 (10.79)	23.09 (8.85)	2.0463	93.00	0.0436
Females							
Chronologic Age	20	108	31.36 (6.86)	33.01 (7.79)	0.7150	126.00	0.4760
ESR (mm/hr)	14	32	19.14 (19.65)	10.5 (10.26)	2.0879	44.00	0.0426
CRP (mg/L)	15	37	7.64 (9.19)	3.9 (4.70)	2.3523	21.74	0.0281
ALT (IU/L)	20	79	23.55 (15.59)	34.34 (44.4)	0.8752	97.00	0.3836
AST (IU/L)	20	79	24.3 (11.11)	28.87 (27.55)	0.3414	97.00	0.7336
Globulins (g/L)	20	79	31.1 (4.33)	29.78 (4.23)	1.2363	97.00	0.2193
IGF1 (nmol/l)	20	108	26.63 (9.60)	22.47 (9.41)	2.2647	126.00	0.0252
All Patients							
Chronologic Age	70	153	31.48 (6.09)	33.02 (7.79)	1.1546	170.61	0.2498
ESR (mm/hr)	47	45	15.66 (23.67)	10.16 (10.59)	1.5360	90.00	0.1280
CRP (mg/L)	48	50	16.43 (47.94)	4.26 (5.52)	4.0088	92.28	0.0001
ALT (IU/L)	70	109	61.69 (158.40)	41.5 (54.26)	0.9881	177.00	0.3244
AST (IU/L)	70	109	41.49 (79.37)	32.39 (33.87)	1.3792	177.00	0.1696
Globulins (g/L)	70	109	30.64 (4.35)	29.75 (3.95)	1.3492	177.00	0.1790
IGF1 (nmol/l)	70	153	26.56 (10.41)	22.65 (9.22)	2.9311	150.35	0.0039

All parameters log transformed for statistical analysis. CRP asinh transformed for statistical analysis. * - Data sown as Mean (+ S.D.)

Figure 2 shows various parameters of interest by sex. Table 2 gives the output of additive multivariate regression models with age for all patients and for each sex separately. The additive status is shown to be significant in each group. When sex is included in the interactive multivariate model the age: addiction interaction remains significant (est.=0.0625±0.01711, t=3.653, p=0.0003, model Adj. R^2 =0.2779, F=33.23, dF=4,331, $p<10^{-15}$).

Table 3 shows the outcomes of interactive models of the various parameters of interest with age. Most variables studied are found to be signficant in both sexes and in all patients considered together.

Table 4 presents the final multivariate model where (log) IGF1 is regressed against chronologic age, Sex, ALT, CRP and addictive status. The model parameters are Adj. R^2=0.2566, F=3.934, dF=16,120, $p=6.45\times10^{-6}$. Addictive status is noted to be significant in its own right (p=0.0134), and to be included in a further seven interactive terms with second, third and fourth order interactions with age, male sex and ALT.

DISCUSSION

Together these results demonstrate that the age dependent trajectory of IGF1 in the opiate dependent SUD group is significantly higher than that in the NSUD group ($p<0.004$). When the analysis is restricted to the 15–45 year age group and the mean ages were not significantly different (p=0.47), the (log) IGF1 in the SUD group is significantly higher than that in the NSUD group by 34.87% (26.53±1.21 vs. 19.67±0.57 IU/l, p=0.0039). Graphical display of the results shows that the IGF1 regression line in SUD is significantly higher than that in the NSUD group, and formal testing demonstrates that whilst the regression lines of best fit in the SUD group is significantly displaced upwards (p=0.0002). When sex was included as an independent variable there was a significant interaction with age (p=0.0003). Hepatitis C serostatus was also shown to be a significantly positively associated with IGF1 level both as a main effect and in interactions. Hepatic inflammation was also shown at multiple regression on various

Tab. 2. Additive multivariate comparisons.

Index	Parameter	Estimate	Std. Error	Adj'd R Squ.	t-value	*p*-value
All Patients						
Addictive Status	Addicted *	0.2135	0.0570	0.2579	3.7490	0.0002
HCV-	HCVNegative	0.2040	0.0774	0.2557	2.6360	0.0088
HCV+	HCVPositive	0.2218	0.0731	0.2557	3.0350	0.0026
ALT	log(ALT)	–0.0427	0.0317	0.1689	–1.3470	0.1790
AST	log(AST)	–0.0115	0.0455	0.1631	–0.2540	0.8000
Globulin	log(Globulin)	–0.2555	0.1830	0.1693	–1.3960	0.1640
CRP	asinh(CRP)	–0.0151	0.0284	0.1738	–0.5310	0.5970
ESR	asinh(ESR)	0.0005	0.0299	0.2232	0.0160	0.9870
Males						
Addictive Status	Addicted	0.2192	0.0767	0.1771	2.8570	0.0049
HCV-	HCVNegative	0.2173	0.1016	0.1718	2.1380	0.0341
HCV+	HCVPositive	0.2207	0.0922	0.1718	2.3940	0.0179
ALT	log(ALT)	0.0010	0.0461	0.0642	0.0220	0.9827
AST	log(AST)	0.0269	0.0654	0.0655	0.4110	0.6820
Globulin	log(Globulin)	–0.2873	0.2838	0.0720	–1.0120	0.3134
CRP	asinh(CRP)	0.0217	0.0303	0.1731	0.7160	0.4765
ESR	asinh(ESR)	0.0583	0.0405	0.1861	1.4380	0.1551
Females						
Addictive Status	Addicted	0.2252	0.0974	0.3508	2.3110	0.0220
HCV-	HCVNegative	0.2000	0.1282	0.3475	1.5600	0.1205
HCV+	HCVPositive	0.2555	0.1396	0.3475	1.8310	0.0689
ALT	log(ALT)	–0.1337	0.0466	0.3319	–2.8690	0.0048
AST	log(AST)	–0.0839	0.0669	0.2979	–1.2550	0.2120
Globulin	log(Globulin)	–0.2686	0.2311	0.2967	–1.1620	0.2470
CRP	asinh(CRP)	–0.0988	0.0361	0.3080	–2.7340	0.0080
ESR	asinh(ESR)	–0.0670	0.0453	0.2978	–1.4790	0.1440

* - "Addicted" = Opiate Dependent

tests to be significant predictor of IGF1. These results extend the single previous report of such data which was from this clinic both in breadth and in depth, by substantially increasing the sample size, by extending the number of independent variables, by the application of multivariate statistical analysis to these data, by detailed significance testing, by formal comparison of regression lines and by detailed age comparison calculations (Reece 2007b).

The present results then, demonstrate on both bivariate and multivariate age related testing, that over most of the period of active addiction, the IGF1 level appears to be elevated. In these studies the significance both of addictive status, and of the interaction of addiction with age is of interest. Such modelling demonstrates that addiction *per se,* and also by virtue of its effects over time an its interaction with sex, is likely to impact on the IGF1 level, and may also be presumed to be of relevance to systemic pathophysiological processes.

The contribution of Hepatitis C seropositivity to these changes is also of note. Clearly HCV seropositivity does not appear to account for most of the effects of SUD. These results make an interesting empirical contribution to the field. Since the liver is the major source of circulating IGF1, there are theoretical grounds for supposing that chronic hepatic inflammation might either increase or reduce the level of circulating IGF1. Moreover the liver is the source of most of the IGF binding proteins (IGFBP1-3) in the serum. Again hepatic inflammation may be hypothesized to either increase or reduce these levels. As they were not measured in the present study the influence of the opiate dependent milieu on the more detailed IGF and growth hormone physiology remains to be determined by fur-

Tab. 3. Interactive multivariate comparisons.

Index	Parameter	Estimate	Std. Error	Adj'd R Squ.	t-value	*p*-value
All Patients						
Addictive Status	Addicted	0.2226	0.7947	0.2557	0.2800	0.7800
Addictive Status	log(Age):Addicted	–0.0026	0.2280	0.2557	–0.0120	0.9900
HCV-	log(Age):HCVNegative	0.0600	0.0225	0.2555	2.6680	0.0080
HCV+	log(Age):HCVPositive	0.0620	0.0208	0.2555	2.9750	0.0032
ALT	log(ALT)	0.4864	0.0792	0.1786	6.1390	<0.0001
ALT	log(Age):log(ALT)	–0.1515	0.0204	0.1786	–7.4100	<0.0001
AST	log(AST)	0.5273	0.0878	0.1677	6.0080	<0.0001
AST	log(Age):log(AST)	–0.1541	0.0211	0.1677	–7.3050	<0.0001
Globulin	log(Age):log(Globulin)	–0.1346	0.0186	0.1675	–7.2470	<0.0001
CRP	asinh(CRP)	0.7923	0.1609	0.1812	4.9250	<0.0001
CRP	log(Age):asinh(CRP)	–0.2228	0.0446	0.1812	–5.0010	<0.0001
Males						
HCV+	log(Age):HCVPositive	–1.1396	0.4256	0.1989	–2.6770	0.0082
ALT	log(ALT)	0.3699	0.1079	0.0844	3.4290	0.0008
ALT	log(Age):log(ALT)	–0.1061	0.0290	0.0844	–3.6550	0.0004
AST	log(AST)	0.3973	0.1211	0.0775	3.2820	0.0013
AST	log(Age):log(AST)	–0.1068	0.0309	0.0775	–3.4590	0.0007
Globulin	log(Age):log(Globulin)	–0.0957	0.0279	0.0798	–3.4280	0.0008
CRP	log(Age)	–0.5654	0.1412	0.1732	–4.0040	0.0002
CRP	log(Age):asinh(CRP)	0.0061	0.0084	0.1732	0.7240	0.4718
Females						
Addictive Status	log(Age)	–0.7558	0.0825	0.3528	–9.1570	<0.0001
Addictive Status	log(Age):Addicted	0.0687	0.0283	0.3528	2.4280	0.0162
HCV-	log(Age):HCVNegative	0.0603	0.0378	0.3495	1.5950	0.1124
HCV+	log(Age):HCVPositive	0.0781	0.0399	0.3495	1.9580	0.0519
ALT	log(ALT)	0.6068	0.1144	0.3423	5.3040	<0.0001
ALT	log(Age):log(ALT)	–0.2098	0.0281	0.3423	–7.4590	<0.0001
AST	log(AST)	0.6584	0.1271	0.2996	5.1810	<0.0001
AST	log(Age):log(AST)	–0.2095	0.0286	0.2996	–7.3360	<0.0001
Globulin	log(Age):log(Globulin)	–0.1781	0.0243	0.2868	–7.3270	<0.0001
CRP	asinh(CRP)	1.0629	0.1917	0.3602	5.5440	<0.0001
CRP	log(Age):asinh(CRP)	–0.3274	0.0543	0.3602	–6.0250	<0.0001

ther studies. It is possible that the present results could be materially altered by unusual patterns of serum IGFBP, although this is felt to be not particularly likely. Since various sometimes subtle endocrinopathies are well described in opiate addiction, these changes could have many sources including stress, pituitary, hepatic, dietary or immune bases.

In view of the pleiotropic effects of GH-IGF1 axis these findings are conceptually very provocative. As mentioned above GH-IGF1 has important described effects in several major pathways including ageing, clinical carcinogenesis, elevation of blood sugar and the stress response (Kronenberg *et al.* 2007). Its documented elevation in clinical opiate dependence strongly suggests that this process may not be metabolically benign. The well described association of elevated levels of GH with several major pathologies, and the occurrence of those pathologies in opiate addiction suggests an important pathophysiological link which would appear to have been largely overlooked by extant research. This in turn bears importantly on issues such as the long term safety of opiate agonist treatments,

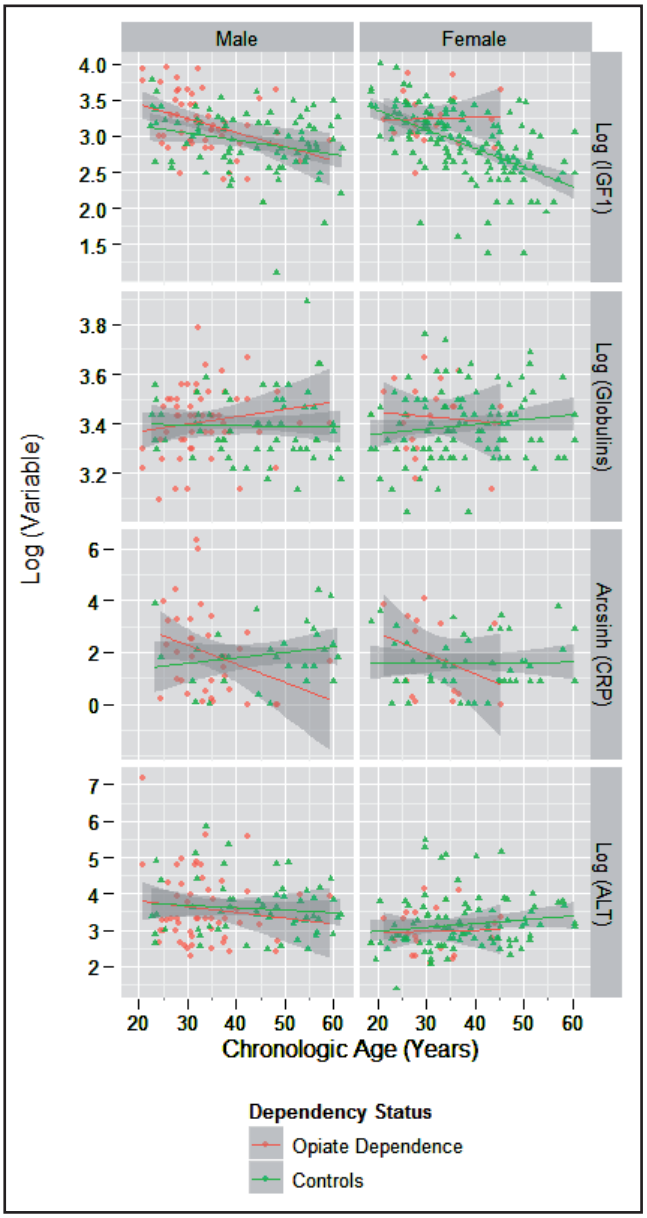

Fig. 2. Selected parameters by addiction status by age.

Tab. 4. Final multivariate model.

Parameter	Estimate	Std. Error	t-value	Pr(>|t|)
Age:CRP	–0.7426	0.2414	–3.076	0.0026
CRP	2.5818	0.8569	3.013	0.0032
Age:ALT:CRP:Male.Sex	0.0111	0.0037	3.004	0.0032
Age:Addicted	9.0451	3.5764	2.529	0.0127
Age:Male.Sex:Addicted	–9.2740	3.6878	–2.515	0.0132
Addicted	–31.0675	12.3753	–2.510	0.0134
Male.Sex:Addicted	31.7746	12.7516	2.492	0.0141
Age:ALT:Addicted	–2.7258	1.1166	–2.441	0.0161
ALT:Addicted	9.4120	3.8703	2.432	0.0165
Age:ALT:Male.Sex:Addicted	2.6046	1.1463	2.272	0.0249
ALT:Male.Sex:Addicted	–8.9902	3.9690	–2.265	0.0253
ALT:CRP	–0.5765	0.2801	–2.058	0.0417
Age:ALT:CRP	0.1568	0.0776	2.019	0.0457

which is becoming of increasing public importance with rising numbers of chronic pain patients in many western nations, together with serious calls for the wider availability of strong narcotic medications to improve treatment for this group (Wodak *et al.* 2009).

It should be noted *en passant* that there is also evidence for elevation of fasting serum insulin in opiate dependent patients maintained on both heroin and methadone together with relative insulin resistance after glucose loading (Passariello *et al.* 1983; Ceriello *et al.* 1987). Peripheral insulin resistance is induced in part by opiate induced inhibition of cell membrane receptor signalling through insulin receptor substrates 1 and 2 (Li *et al.* 2003; Russo *et al.* 2007) . Adverse effects on appetite (Cowley *et al.* 2001), body weight (Kolarzyk *et al.* 2005), lipid profile (Cooper *et al.* 2003) and hypertension (Rosen *et al.* 2008) have also been reported. Suppressive central and peripheral neuroendocrine effects of opiates on the hypothalamic – pituitary – gonadal axis are also well described (Kronenberg *et al.* 2007). Opiates have also been found to exert a potent pro-inflammatory action (Hutchinson *et al.* 2011). It is likely that these associated changes will exacerbate and compound the IGF1 perturbation described herein.

IGF1 has been shown to be an important neurotrophic factor regulating brain neurogenesis both in neurogenic zones and *in vitro*. SUD patients are known to have very high rates of psychiatric disorders, particularly anxiety, depression, and reduced cerebral processing capacity such as impaired memory formation and increased memory latency and thought processing times. In this context the demonstration that circulating IGF1 regulates the levels of brain IGF1 during key developmental stages is of particular importance (Yan *et al.* 2011).

Some authors have noted that the profile of organic pathology in patients maintained on longer acting opiate agonists such as methadone is very significantly worse than that or patients maintained no shorter acting opiate agonists such as heroin (Darke *et al.* 2009). Such workers feel that the preponderant difference may not be causal, based solely on a supposed lack of pathophysiological mechanism to account for it. Studies such as the present one, which clearly document real differences in the IGF1 pathway, demonstrate that well described pathways indeed exist. Further differential mechanisms such as on stem cell activity (Reece & Davidson 2007) or immune stimulation (Hutchinson *et al.* 2011) which likely interact (Anderson 2000), and effects on mitogen activated protein kinase (Singhal *et al.* 2002), phosphoinositide 3-kinase (Yin *et al.* 2006),

nitrergic (Hutchinson *et al.* 2011), and transforming growth factor-β (Chao *et al.* 1992) -dependent pathways also exist.

A number of limitations exist on the present research. As it is structured as a clinical audit of our pathology records detailed substance use and other demographic data is not available. Nor is it retrievable from archival records as the data series goes back so far. Such data has been supplied in detail for this patient group however on several previous occasions (Reece 2007a,d) and it has been found to be quite comparable with other such clinical populations in this country. Moreover the milieu of the opiate dependent patient is complex, particularly where the dependency is related to the use of street drugs. The use of other agents, a usually unhealthy diet, imprisonment, and the stresses of illegal drug use amongst others may all impinge on data interpretation. As the study is not of a molecular nature, and has not been conducted prospectively, issues of causality are not able to be addressed. Moreover an elevated level of IGF1 is only one of the alterations occurring in such patients, and it is not possible from this preliminary study to attribute a relative importance to any IIS related pathways in comparison to alternate metabolic or molecular processes. As such opiate dependency forms an interesting if highly complex clinical state in which to assess such long term hormonal perturbations. Further refinements to the present studies mentioned in the above discussion include the linking of BMI records, the serial measurement of GH, and the measurement of IGFBP1-3.

In conclusion this study has documented the age related elevation of serum IGF1 levels in opiate dependent patients compared to opiate naive control medical patients at a high level of statistical significance. As such it invites further detailed longitudinal, molecular and causational studies to determine the significance of such observed changes in possibly contributing to the host of well described ageing and degenerative disorders seen in chronic opiate dependent cohorts. This work also provides one possible mechanistic perspective to account for the frequently under-recognized rates of pathology seen in such patients, and suggests that earlier accounts which trivialized GH alterations in this group may have failed to take full cognizance of signficant endocrinologic-metabolic distortions.

REFERENCES

1 Anderson JE (2000). A role for nitric oxide in muscle repair: nitric oxide-mediated activation of muscle satellite cells. Mol Biol Cell **11**: 1859–74.
2 Behmard S, Sadeghi A, Mohareri MR, Kadivar R (1981). Positive association of opium addiction and cancer of the bladder. Results of urine cytology in 3,500 opium addicts. Acta Cytol **25**: 142–6.
3 Bernard CM (1877). Lecons Sur Le Diabete et la Glycogenese Animale. Paris: Cours de Medecine.
4 Brunton LL, Lazo JS, Parker KL, Eds. (2006). Goodman and Gilman's the Pharmacologic Basis of Therapeutics. New York, McGraw Hill.
5 Ceriello A, Giugliano D, Passariello N, Quatraro A, Dello Russo P, Torella R, *et al.* (1987). Impaired glucose metabolism in heroin and methadone users. Horm Metab Res **19**: 430–3.
6 Chao CC, Hu S, Molitor TW, Zhou Y, Murtaugh MP, Tsang M, *et al.* (1992). Morphine potentiates transforming growth factor-beta release from human peripheral blood mononuclear cell cultures. J Pharmacol Exp Ther **262**: 19–24.
7 Clemmons DR (2007). Modifying IGF1 activity: an approach to treat endocrine disorders, atherosclerosis and cancer. Nat Rev Drug Discov **6**: 821–33.
8 Cooper OB, Brown TT, Dobs AS (2003). Opiate drug use: a potential contributor to the endocrine and metabolic complications in human immunodeficiency virus disease. Clin Infect Dis **37 Suppl 2**: S132–6.
9 Cowley MA, Smart JL, Rubinstein M, Cerdan MG, Diano S, Horvath TL, *et al.* (2001). Leptin activates anorexigenic POMC neurons through a neural network in the arcuate nucleus. Nature **411**: 480–4.
10 Cushman P, Jr. (1972). Growth hormone in narcotic addiction. J Clin Endocrinol Metab **35**: 352–8.
11 Darke S, Duflou J, Torok M (2009). The comparative toxicology and major organ pathology of fatal methadone and heroin toxicity cases. Drug Alcohol Depend.
12 Gerra G, Zaimovic A, Raggi MA, Giusti F, Delsignore R, Bertacca S, *et al.* (2001). Aggressive responding of male heroin addicts under methadone treatment: psychometric and neuroendocrine correlates. Drug Alcohol Depend **65**: 85–95.
13 Gottshcalk L.A, McGuire F.L., Heiser J.F., Dinovo E.C., H. B (1979). Drug abuse deaths in nine cities: A survey report. National Institute of Drug Abuse. Bethesda, Maryland, USA, National Institutes of Health. **29, NIDA Research Monograph:** 1–189.
14 Guarente L, Picard F (2005). Calorie restriction--the SIR2 connection. Cell **120**: 473–82.
15 Hutchinson MR, Shavit Y, Grace PM, Rice KC, Maier SF, Watkins LR (2011). Exploring the neuroimmunopharmacology of opioids: an integrative review of mechanisms of central immune signaling and their implications for opioid analgesia. Pharmacol Rev **63**: 772–810.
16 Kim TW, Alford DP, Malabanan A, Holick MF, Samet JH (2006). Low bone density in patients receiving methadone maintenance treatment. Drug Alcohol Depend **85**: 258–62.
17 Kolarzyk E, Pach D, Wojtowicz B, Szpanowska-Wohn A, Szurkowska M (2005). Nutritional status of the opiate dependent persons after 4 years of methadone maintenance treatment. Przegl Lek **62**: 373–7.
18 Kronenberg HM., Melmed S, Polonsky KS, Larsen PR (2007). Williams Textbook of Endocrinology. New York: Saunders Elsevier.
19 Li Y, Eitan S, Wu J, Evans CJ, Kieffer B, Sun X, *et al.* (2003). Morphine induces desensitization of insulin receptor signaling. Mol Cell Biol **23**: 6255–66.
20 Melmed S (2009). Acromegaly pathogenesis and treatment. J Clin Invest **119**: 3189–202.
21 Morley JE (1981). The endocrinology of the opiates and opioid peptides. Metabolism **30**: 195–209.
22 Mousavi MR, Damghani MA, Haghdoust AA, Khamesipour A (2003). Opium and risk of laryngeal cancer. Laryngoscope **113**: 1939–43.
23 Onuma M, Bub JD, Rummel TL, Iwamoto Y (2003). Prostate cancer cell-adipocyte interaction: leptin mediates androgen-independent prostate cancer cell proliferation through c-Jun NH2-terminal kinase. J Biol Chem **278**: 42660–7.
24 Passariello N, Giugliano D, Quatraro A, Consoli G, Sgambato S, Torella R, *et al.* (1983). Glucose tolerance and hormonal responses in heroin addicts. A possible role for endogenous opiates in the pathogenesis of non-insulin-dependent diabetes. Metabolism **32**: 1163–5.
25 Pfeiffer A, Herz A (1984). Endocrine actions of opioids. Horm Metab Res **16**: 386–97.

26 Reece AS (2010). Favourable Mortality Profile of Naltrexone Implants for Opiate Addiction. Journal of Addictive Diseases **29**: 30–50.
27 Reece AS (2009). Multivariate Analysis of Dentition in Addiction. Aust Dent J **In Press**.
28 Reece AS (2007a). Dentition of addiction in Queensland: poor dental status and major contributing drugs. Aust Dent J **52**: 144–9.
29 Reece AS (2007b). Evidence of Accelerated Ageing in Clinical Drug Addiction from Immune, Hepatic and Metabolic Biomarkers. Immun Ageing **4**: 6–15.
30 Reece AS (2007c). Hair graying in substance addiction. Arch Dermatol **143**: 116–8.
31 Reece AS (2007d). Psychosocial and treatment correlates of opiate free success in a clinical review of a naltrexone implant program. Subst Abuse Treat Prev Policy **2**: 35–49.
32 Reece AS, Davidson P (2007). Deficit of circulating stem--progenitor cells in opiate addiction: a pilot study. Subst Abuse Treat Prev Policy **2**: 19–28.
33 Rosen D, Smith ML, Reynolds CF, 3rd (2008). The prevalence of mental and physical health disorders among older methadone patients. Am J Geriatr Psychiatry **16**: 488–97.
34 Russo SJ, Bolanos CA, Theobald DE, DeCarolis NA, Renthal W, Kumar A, *et al.* (2007). IRS2-Akt pathway in midbrain dopamine neurons regulates behavioral and cellular responses to opiates. Nat Neurosci **10**: 93–9.
35 Sadeghian S, Darvish S, Davoodi G, Salarifar M, Mahmoodian M, Fallah N, *et al.* (2007). The association of opium with coronary artery disease. Eur J Cardiovasc Prev Rehabil **14**: 715–7.
36 Singhal PC, Bhaskaran M, Patel J, Patel K, Kasinath BS, Duraisamy S, *et al.* (2002). Role of p38 mitogen-activated protein kinase phosphorylation and Fas-Fas ligand interaction in morphine-induced macrophage apoptosis. J Immunol **168**: 4025–33.
37 Svensson AL, Bucht N, Hallberg M, Nyberg F (2008). Reversal of opiate-induced apoptosis by human recombinant growth hormone in murine foetus primary hippocampal neuronal cell cultures. Proc Natl Acad Sci U S A **105**: 7304–8.
38 Weizman T, Gelkopf M, Melamed Y, Adelson M, Bleich A (2003). Treatment of benzodiazepine dependence in methadone maintenance treatment patients: a comparison of two therapeutic modalities and the role of psychiatric comorbidity. Aust N Z J Psychiatry **37**: 458–63.
39 Wodak AD, Cohen ML, Dobbin MD, Hallinan RA, Osborn M (2009). Improving the management of chronic non-malignant pain and reducing problems associated with prescription opioids. Med J Aust **191**: 302–3.
40 Yan H, Mitschelen M, Bixler GV, Brucklacher RM, Farley JA, Han S, *et al.* (2011). Circulating IGF1 regulates hippocampal IGF1 levels and brain gene expression during adolescence. J Endocrinol **211**: 27–37.
41 Yin D, Woodruff M, Zhang Y, Whaley S, Miao J, Ferslew K, *et al.* (2006). Morphine promotes Jurkat cell apoptosis through pro-apoptotic FADD/P53 and anti-apoptotic PI3K/Akt/NF-kappaB pathways. J Neuroimmunol **174**: 101–7.