Original Article

The Association for Clinical Biochemistry & Laboratory Medicine
Better Science, Better Testing, Better Care

Annals of Clinical Biochemistry
2015, Vol. 52(4) 456–461

DOI: 10.1177/0004563214562431
acb.sagepub.com
SAGE

Relationship of apelin, procalcitonin, and fetuin-A concentrations with carotid intima-media thickness in acromegaly

S Topsakal[1], F Akin[1], S Turgut[2], GF Yaylali[1], D Herek[3] and C Ayada[2]

Abstract

Background: Acromegaly is characterized by excess growth hormone and insulin-like growth factor-1 concentrations. There is conflicting evidence as to whether acromegaly is associated with an increased risk of atherosclerosis. Apelin is an adipose tissue-derived peptide that may be associated with hyperinsulinemia. Fetuin-A is a hepatocyte produced plasma glycoprotein that has an important role as a calcification inhibitor. The aim of this study was to examine apelin, fetuin-A, and procalcitonin concentrations and to assess their relationship with carotid intima medial thickness (cIMT) in subjects with acromegaly.

Methods: Apelin, fetuin-A, and procalcitonin serum concentrations were measured in 37 (20 inactive and 17 active) subjects with acromegaly and 30 control subjects, along with carotid intima medial thickness.

Results: The concentrations of apelin, fetuin-A, and procalcitonin were increased in subjects with acromegaly. There were significant correlations between apelin, fetuin-A, and procalcitonin in subjects with acromegaly. Carotid intima medial thickness values were similar between control subjects and subjects with acromegaly.

Conclusions: Carotid intima medial thickness was not increased in subjects with acromegaly. It is possible that the increased apelin and fetuin-A concentrations observed play a protective role against the development of atherosclerosis in subjects with acromegaly.

Keywords

Acromegaly, apelin, procalcitonin, fetuin-A, carotid intima media thickness

Accepted: 6th November 2014

Introduction

Acromegaly is an uncommon chronic disorder characterized by classical clinical features caused by excess growth hormone (GH) and consequent raised concentrations of insulin-like growth factor-1 (IGF-1). This condition may be associated with increased morbidity and mortality, considered to be mainly due to cardiocerebrovascular disease (although the latter is unclear).[1] In most cases, acromegaly is caused by a pituitary somatotroph adenoma that secretes excess GH, which leads to insulin resistance, glucose intolerance, and

[1]Department of Endocrinology and Metabolism, Faculty of Medicine, Pamukkale University, Denizli, Turkey
[2]Department of Physiology, Faculty of Medicine, Pamukkale University, Denizli, Turkey
[3]Department of Radiology, Faculty of Medicine, Pamukkale University, Denizli, Turkey

Corresponding author:
S Topsakal, Department of Endocrinology and Metabolism, Faculty of Medicine, Pamukkale University, Kinikli Campus, Denizli 20070, Turkey.
Email: topsakals@hotmail.com

increased prevalence rates of atherosclerosis and cardiovascular mortality.[1,2] The presence of early atherosclerotic changes may be assessed by measuring carotid intima medial thickness (cIMT) with carotid Doppler ultrasonography (USG).[3–5]

Apelin and the APJ (apelin) receptor are expressed in a wide variety of tissues, including heart, brain, kidneys, and lungs.[6–9] Apelin is a peptide growth factor that exhibits high affinity binding with the APJ receptor, which has high sequence homology with the angiotensin II type 1 receptor, but does not bind angiotensin II.[10,11] Procalcitonin and fetuin-A are proteins that are mainly secreted by the liver.[12,13] Procalcitonin secretion is closely related to inflammatory mediator concentrations,[12] while fetuin-A inhibits arterial calcium deposition *in vitro*.[13] Clinical studies have demonstrated that circulating fetuin-A concentrations are positively associated with fat accumulation in the liver, insulin resistance, and metabolic syndrome.[14–16]

Data on accelerated atherosclerosis and increased cardiovascular risk in acromegaly are somewhat conflicting and have been based for the most part on retrospective case series reports.[17,18] The aim of this study was to examine apelin, procalcitonin, and fetuin-A concentrations and assess their relationship with cIMT in subjects with acromegaly.

Material and methods

This study was approved by the institutional ethics and research committee of Pamukkale University. Informed consent was obtained from all participants. Measurements were performed in 37 acromegalic patients (20 male and 17 female) and 30 healthy controls (15 male and 15 female). The mean ages of the patient and controls were similar ($51.5\,y \pm 10.5$ and 46.4 ± 6.9, respectively, $P > 0.05$).

Height and weight were measured with participants wearing light clothes and no shoes, and body mass index (BMI) was calculated as weight (kg)/height $(m)^2$. Systolic and diastolic blood pressures were measured twice in the seated position after 5 min of rest.

Serum insulin, thyroid stimulating hormone (TSH), GH, and IGF-I concentrations were measured by chemiluminescent assay (Immulite 2000, Siemens AG, Erlangen, Germany). Serum concentrations of glucose, triglyceride, HDL-cholesterol, and LDL-cholesterol were measured on a Beckman-Coulter LX-20 analyzer (Beckman-Coulter Inc., Brea, CA, USA), with reagents supplied by the manufacturer.

Acromegaly subjects with GH $\leqslant 1\,\mu g/L$ and IGF-1 concentrations within the healthy population reference ranges appropriate for age and sex were classified as "inactive," and patients with GH $> 1\,\mu g/L$, and higher IGF-1 concentrations, were classified as having "active" acromegaly. Insulin resistance was calculated according to the homeostasis model assessment (HOMA) method, using the following formula: (fasting plasma insulin [$mIU/L \times$ fasting plasma glucose (mmol/L)]/ 22.5. A HOMA-IR cutoff value >2.7 is considered to indicate insulin resistance.

Blood samples were obtained by venepuncture between 8:00 and 10:00 am after a 12 h fast. Plasma total cholesterol, triglycerides, HDL, LDL, TSH, GH, IGF-1, IGFBP3, insulin, and glucose concentrations were measured immediately. Serum samples for apelin, procalcitonin, and fetuin-A measurement were frozen at $-80^{\circ}C$ until analysis (RayBio® Human Apelin kit, RayBiotech, Norcross, GA, USA; Booster® Human Fetuin-A kit, RayBiotech, Norcross, GA, USA; CUSABIO® Human Procalcitonin kit, CSB-E09502h, CUSABIO, Hubei, China) according to the manufacturers' instructions. The intra-assay and inter-assay coefficients of variation (%CV) varied between 10–15% (apelin), 10–12% (fetuin-A), and <8–<10% for (procalcitonin).

B-mode USG of the left and right common and internal carotid arteries was performed with measurements made at least 15 min after resting in a supine position. After bilateral, longitudinal, and transverse examination of the carotid arteries, two sets of standardized images were obtained at 5-min intervals at two different points: one at the lateral angle of the carotid artery bulb and 20 mm proximal to the bifurcation. The common cIMT was calculated as the mean of the left and right measurements, and cIMT values >0.8 mm were considered as increased thickness.

Statistical analysis was done with SPSS (Statistical Package for Social Sciences) 13.0 software (SPSS Inc, Chicago, IL, USA). Discrete variables were expressed as counts (percentage) and interquartile ranges. In the statistical evaluations, one-way analysis of variance test was used to observe any differences between control group, active acromegaly, and inactive acromegaly subject groups. In the determination of different groups, Duncan multiple comparison method was used. The Bonferroni–Dunn procedure was used to compare mean values between the groups. In addition, logistic regression and Pearson's correlation tests were used for association between parameters. All testing was two-tailed and p values less than 0.05 were considered to indicate statistical significance.

Results

The clinical and demographical findings of control, active, and inactive acromegaly subject groups are shown (Table 1). Higher apelin, procalcitonin, and fetuin-A concentrations were observed in subjects with acromegaly compared to controls. Notably, the

Table 1. Characteristics of subjects with inactive acromegaly, active acromegaly, and controls. Results given as median (interquartile range).

	Inactive (n = 20)	*P	Active (n = 17)	Controls (n = 30)	**P
Ages (years)	55.2 (48.8–63.3)[a]	NS	47.1 (37–55)[b]	46.4 (41.3–51)[b]	<0.01
Height (cm)	167.2 (158–174)	NS	168.1 (161–172)	167.4 (164–172)	NS
Weight (kg)	81.7 (75–91.3)[a]	NS	84.6 (75–90)[a]	71.5 (60.5–81.8)[b]	<0.01
BMI (kg/m^2)	29.5 (25.8–33.3)[a]	NS	29.2 (27.3–31.1)[a]	25.4 (22.5–27.7)[b]	<0.01
Systolic BP (mmHg)	136 (130–140)[a]	NS	132.4 (130–140)[a]	119.3 (100–130)[b]	<0.01
Diastolic BP (mmHg)	81.5 (80–80)[ab]	NS	82.9 (80–90)[a]	76 (70–80)[b]	<0.05
Fasting glucose (mmol/L)	6.1 (5.3–6.4)[a]	NS	6.4 (5.2–6.9)[a]	5.3 (4.9–5.5)[b]	<0.01
Creatinine (μmol/L)	61.9 (54.8–69)[ab]	NS	57.5 (46.9–67.2)[a]	69.8 (59.2–84)[b]	<0.05
Total cholesterol (mmol/L)	4.8 (3.2–5.6)	NS	4.9 (4.2–5.4)	5.2 (4.6–5.6)	NS
Triglyceride (mmol/L)	1.1 (0.7–1.4)[a]	<0.01	1.7 (0.9–2.4)[b]	1.4 (0.8–1.7)[ab]	<0.05
HDL (mmol/L)	1.5 (1.2–1.7)	NS	1.4 (1.2–1.5)	1.4 (1.1–1.7)	NS
LDL (mmol/L)	2.8 (2.1–3.4)	NS	2.8 (2.0–3.3)	3.2 (2.6–3.7)	NS
GH (μg/L)	0.8 (0.5–0.9)[a]	<0.01	2 (1.3–2.3)[b]	0.4 (0.1–0.2)[c]	<0.001
IGF1 (ug/L)	216.1 (162–278.3)[a]	<0.05	414.4 (318–500)[b]	151.4 (117–182.3)[c]	<0.001
IGFBP3 (mg/L)	4.5 (4.1–5.4)[a]	<0.05	5.6 (4.9–6.5)[b]	4.2 (3.6–4.7)[a]	<0.01
Insulin (pmol/L)	41 (21.3–68.6)	NS	56.7 (35.8–84.2)	81.1 (45.3–70.1)	NS
Right cIMT (mm)	0.7 (0.7–0.8)	NS	0.7 (0.7–0.8)	0.8 (0.6–0.8)	NS
Left cIMT (mm)	0.8 (0.7–0.9)	NS	0.8 (0.7–0.9)	0.8 (0.6–0.8)	NS
Apelin (nug/L)	121.5 (95.1–149.2)[a]	NS	116.5 (94.1–132.3)[a]	99.6 (88–113.7)[b]	<0.05
Fetuin-a (ug/L)	1.9 (1–2)[a]	NS	2.6 (1.2–4.2)[a]	1.1 (0.6–1.3)[b]	<0.001
Procalcitonin (ug/L)	79.5 (36.5–117.1)[a]	<0.05	59.1 (39.6–85.1)[a]	10.6 (–1.8–22.2)[b]	<0.001
HOMA-IR	1.7 (0.6–1.9)	NS	2.2 (1.2–2.7)	2.6 (1.4–2)	NS

*P value (Bonferroni–Dunn Test) between inactive and active and acromegalic subjects.
**P value for one-way ANOVA of results from inactive and active acromegaly subjects and control subjects.
[a]Significant with respect to[b] and/or[c].
[b]Significant with respect to[a] and/or[c].
[c]Significant with respect to[a] and/or[b].

procalcitonin concentrations in subjects with acromegaly were found to be almost sevenfold higher than controls ($P < 0.0001$). There were no differences in apelin, fetuin-A, or procalcitonin concentrations between the active and inactive acromegaly groups, and both groups exhibited similar cIMT measurements.

Statistically significant correlations were observed for apelin, fetuin-A, and procalcitonin concentrations in subjects with acromegaly (Table 2). In particular, positive correlations were found between the concentrations of apelin and GH, fetuin-A and IGF-1, and procalcitonin and BMI. There were no significant associations of apelin, fetuin-A, or procalcitonin with HOMA or with IGFBP3, triglyceride, LDL, HDL, or total cholesterol concentrations.

Discussion

The physiological importance of fetuin-A, procalcitonin, and apelin concentrations in acromegaly has been unclear. The present study found higher concentrations of fetuin-A, procalcitonin, and apelin in subjects with acromegaly but no increase in cIMT.

Acromegaly-related symptoms are usually associated with metabolic and cardiovascular complications, such as obesity, hypertriglyceridemia, diabetes mellitus, and hypertension, all of which may confer increased risk of atherosclerosis. Studies of acromegaly have reported differing findings regarding the relationship with atherosclerosis.[19–21] Fetuin-A, a liver-derived inhibitor of calcification, has been inversely associated with arterial stiffness and cardiovascular morbidity and mortality.[22] Prospective studies have suggested that low serum fetuin-A concentrations may be a predictor of coronary artery disease incidence, severity, and related mortality.[23–25] The cardioprotective role of fetuin-A has been supported by low circulating fetuin-A concentration as a negative predictor of acute coronary disease evolution.[25] Insulin resistance in acromegaly causes impaired glucose tolerance and type 2 diabetes in 60 and 25% of patients, respectively.[26] Studies performed in laboratory animals and humans suggested that

Table 2. Correlations between apelin, fetuin-A, procalcitonin, GH, IGF-1 concentrations and BMI in subjects with acromegaly.

	Apelin	Fetuin-a	Procalcitonin
Apelin (ug/L)			
r	1	0.337	0.507
p		0.006**	0.000**
Fetuin-a (ug/L)			
r	0.337	1	0.548
p	0.006**		0.000**
Procalcitonin (ug/L)			
r	0.507	0.548	1
p	0.000**	0.000**	
GH (μg/L)			
r	0.307	0.242	0.155
p	0.012*	0.052	0.219
IGF-1 (ug/L)			
r	0.074	0.294	0.199
p	0.550	0.017*	0.109
BMI (kg/m^2)			
r	0.006	0.170	0.367
p	0.963	0.172	0.002**

*Correlation is significant at the 0.05 concentration.
**Correlation is significant at the 0.01 concentration.

fetuin-A induces insulin resistance,[27–30] which supports the hypothesis that fetuin-A may also play a role in the pathophysiology of acromegaly. However, the relationship of fetuin-A to insulin resistance is still a subject of debate and the physiological importance of fetuin-A in acromegaly remains unclear. Our results show that although fetuin-A concentration was increased in subjects with acromegaly there was no correlation between fetuin-A concentration and insulin resistance or cIMT. This finding supports the suggestion that high serum fetuin-A concentration may have a protective effect against artherosclerosis. The putative protective action of fetuin-A may act through a direct antiatherogenic effect or through an anti-inflammatory action. To our knowledge, this is the first study for to examine serum fetuin-A concentrations in acromegaly. A limitation of our study is the relatively small number of subjects with acromegaly included and therefore the findings need to be confirmed in a larger study.

The functions of apelin and its receptor are not fully understood. Various studies have suggested that apelin is involved in body fluid homeostasis[31] and cardiovascular system regulation.[32,33] It is well known that bone mineral disorders and the related vascular calcification plays an important role in the pathogenesis of cardiovascular disease. It has been proposed that apelin is protective against vascular calcification through inhibition of osteoblastic differentiation of vascular smooth muscle cells.[34] However, the role of the apelin–APJ system in cardiovascular function and its relationships to other neuroendocrine pathways remain unclear.[35] Apelin injection resulted in improved cardiac function and reduced cardiac loading *in vivo*.[36] Serum apelin concentrations were found to be lower in uremic patients with dilated cardiomyopathy.[37] Lower apelin concentrations in patients with both chronic kidney disease and heart disease than those with chronic kidney disease without heart disease have been reported.[37,38] In the present study, we found higher apelin concentrations in subjects with acromegaly than in controls and a significant correlation with GH concentration in these subjects. There was no correlation with between apelin concentration and cIMT. One possible explanation for these associations is that high apelin concentrations may play a protective role against the development of atherosclerosis.

There is conflicting evidence as to whether subjects with acromegaly are at increased risk of accelerated atherosclerosis. Cannavo et al.[39] reported that 41% of subjects with acromegaly were at risk of coronary atherosclerosis and furthermore Ozkan et al.[40] found that procalcitonin can be used as a marker of premature atherosclerosis. In contrast, Bogazzi et al.[41] showed that coronary heart disease risk of in acromegaly was lower than that in subjects without acromegaly. Although our study confirms the finding of increased procalcitonin concentration there was no correlation with cIMT.

GH increases glucose production and inhibits hepatic gluconeogenesis, and excessive GH production leads to compensatory hyperinsulinemia.[42] In the present study, we noted statistically significant differences between subjects with acromegaly and controls for body weight, systolic and diastolic blood pressures, fasting glucose, and LDL concentrations (Table 1).

In conclusion, we found increased serum concentrations of fetuin-a, procalcitonin, and apelin in subjects with acromegaly and positive correlations between apelin and GH, fetuin-A and IGF-1, and procalcitonin and BMI. cIMT was not increased in the subjects with acromegaly despite having higher procalcitonin. We speculate that the higher concentrations of fetuin-A and apelin may play a protective role against cardiovascular disease in subjects with acromegaly.

Acknowledgement

The authors thank Scientific Projects Commission of the Pamukkale University for support.

Declaration of conflicting interests

None declared.

Funding

This study was supported by the Scientific Projects Commission of the Pamukkale University (Grant number: 2011-TPF-045).

Ethical approval

This study was approved by the institutional ethics and research committee of Pamukkale University (2011-034).

Guarantor

ST.

Contributorship

ST: Planning, evaluating, and writing
FA: Planning, evaluating
ST: Hematological observations
GFY: Planning
DH: Radiological analysis
CA: Hematological examinations

References

1. Colao A, Baldelli R, Marzullo P, et al. Systemic hypertension and impaired glucose tolerance are independently correlated to the severity of the acromegalic cardiomyopathy. *J Clin Endocrinol Metab* 2000; 85: 193–199.
2. Taboada GF, Van Haute FR, Correa LL, et al. Etiologic aspects and management of acromegaly. *Arquivos Brasil Endocrinol Metab* 2005; 49: 626–640.
3. Pignoli P, Tremoli E, Poli A, et al. Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. *Circulation* 1986; 74: 1399–1406.
4. Mukherjee D and Yadav JS. Carotid artery intimal-medial thickness: indicator of atherosclerotic burden and response to risk factor modification. *Am Heart J* 2002; 144: 753–759.
5. Salonen JT and Salonen R. Ultrasound B-mode imaging in observational studies of atherosclerotic progression. *Circulation* 1993; 87: 1156–1165.
6. O'Carroll AM, Selby TL, Palkovits M, et al. Distribution of mRNA encoding B78/apj, the rat homologue of the human APJ receptor, and its endogenous ligand apelin in brain and peripheral tissues. *Biochim Biophys Acta* 2000; 1492: 72–80.
7. Kawamata Y, Habata Y, Fukusumi S, et al. Molecular properties of apelin: tissue distribution and receptor binding. *Biochim Biophys Acta* 2001; 1538: 162–171.
8. Medhurst AD, Jennings CA, Robbins MJ, et al. Pharmacological and immunohistochemical characterization of the APJ receptor and its endogenous ligand apelin. *J Neurochem* 2003; 84: 1162–1172.
9. Kleinz MJ, Skepper JN and Davenport AP. Immunocytochemical localisation of the apelin receptor, APJ, to human cardiomyocytes, vascular smooth muscle and endothelial cells. *Regul Pept* 2005; 126: 233–240.
10. O'Dowd BF, Heiber M, Chan A, et al. A human gene that shows identity with the gene encoding the angiotensin receptor is located on chromosome 11. *Gene* 1993; 136: 355–360.
11. Tatemoto K, Hosoya M, Habata Y, et al. Isolation and characterization of a novel endogenous peptide ligand for the human APJ receptor. *Biochem Biophys Res Commun* 1998; 251: 471–476.
12. Carrol ED, Thomson AP and Hart CA. Procalcitonin as a marker of sepsis. *Int J Antimicrob Agents* 2002; 20: 1–9.
13. Price PA and Lim JE. The inhibition of calcium phosphate precipitation by fetuin is accompanied by the formation of a fetuin-mineral complex. *J Biol Chem* 2003; 278: 22144–22152.
14. Stefan N, Hennige AM and Staiger H. Alpha2-Heremans-Schmid glycoprotein/fetuin-A is associated with insulin resistance and fat accumulation in the liver in humans. *Diabetes Care* 2006; 29: 853–857.
15. Mori K, Emoto M and Yokoyama H. Association of serum fetuin-A with insulin resistance in type 2 diabetic and nondiabetic subjects. *Diabetes Care* 2006; 29: 468.
16. Ix JH, Shlipak MG and Brandenburg VM. Association between human fetuin-A and the metabolic syndrome: data from the Heart and Soul Study. *Circulation* 2006; 113: 1760–1767.
17. Goldberg MB and Lisser H. Acromegaly: a consideration of its course and treatment. Report of four cases with autopsies. *J Clin Endocrinol Metab* 1942; 2: 477–501.
18. Hejtmancik MR, Bradfield JY and Herrmann GR. Acromegaly and heart: a clinical and pathologic study. *Ann Intern Med* 1950; 34: 1445–1456.
19. Cannavo S, Almoto B, Cavalli GG, et al. Acromegaly and coronary disease: an integrated evaluation of conventional coronary risk factors and coronary calcifications detected by computed tomography. *J Clin Endocrinol Metab* 2006; 91: 3766–3772.
20. Berg C, Petersenn S, Lahner H, et al. Cardiovascular risk factors in patients with uncontrolled and long-term acromegaly: comparison with matched data from the general population and the effect of disease control. *J Clin Endocrinol Metab* 2010; 95: 3648–3656.
21. Bogazzi F, Battolla L, Spinelli C, et al. Risk factors for development of coronary heart disease in patients with acromegaly: a five-year prospective study. *J Clin Endocrinol Metab* 2007; 92: 4271–4277.
22. Pateinakis P, Papagianni A, Douma S, et al. Associations of fetuin-A and osteoprotegerin with arterial stiffness and early atherosclerosis in chronic hemodialysis patients. *BMC Nephrol* 2013; 14: 122.
23. Chen YC, Lin FY, Lin RH, et al. Relation between fetuin-a levels and fibroblast growth factor 23 with the severity of coronary artery disease measured by SYNTAX Scores. *Am J Cardiol* 2013; 112: 950–963.
24. Zhao ZW, Lin CG, Wu LZ, et al. Serum fetuin-A levels are associated with the presence and severity of coronary artery disease in patients with type 2 diabetes. *Biomarkers* 2013; 18: 160–164.
25. Kadoglou NPE, Kottas G, Lampropoulos S, et al. Serum levels of fetuin-A, osteoprotegerin and osteopontin in patients with coronary artery disease: effects of statin (HMGCoA-reductase inhibitor) therapy. *Clin Drug Investig* 2014; 34: 165–171.

26. Pereira AM, van Thiel SW, Lindner JR, et al. Increased prevalence of regurgitant valvular heart disease in acromegaly. *J Clin Endocrinol Metab* 2004; 89: 71–75.
27. Stefan N, Fritsche A, Weikert C, et al. Plasma fetuin-a levels and the risk of type 2 diabetes. *Diabetes* 2008; 57: 2762–2767.
28. Andersen G, Burgdorf KS, Sparso T, et al. Ahsg tag single nucleotide polymorphisms associate with type 2 diabetes and dyslipidemia: studies of metabolic traits in 7,683 white Danish subjects. *Diabetes* 2008; 57: 1427–1432.
29. Reinehr T and Roth CL. Fetuin-a and its relation to metabolic syndrome and fatty liver disease in obese children before and after weight loss. *J Clin Endocrinol Metab* 2008; 93: 4479–4485.
30. Ix JH, Wassel CL and Kanaya AM. Fetuin-a and incident diabetes mellitus in older persons. *JAMA* 2008; 300: 182–188.
31. Reaux A, Gallatz K and Palkovits M. Distribution of apelin-synthesizing neurons in the adult rat brain. *Neuroscience* 2002; 113: 653–662.
32. Tatemoto K, Takayama K and Zou MX. The novel peptide apelin lowers blood pressure via a nitric oxide-dependent mechanism. *Regul Pept* 2001; 99: 87–92.
33. Seyedabadi M, Goodchild AK and Pilowsky PM. Site-specific effects of apelin-13 in the rat medulla oblongata on arterial pressure and respiration. *Autonom Neurosci* 2002; 101: 32–38.
34. Shan PF, Lu Y, Cui RR, et al. Apelin attenuates the osteoblastic differentiation of vascular smooth muscle cells. *PLoS One* 2011; 18: 17938.
35. Chandrasekaran B, Dar O and McDonagh T. The role of apelin in cardiovascular function and heart failure. *Eur J Heart Fail* 2008; 10: 725–732.
36. Ashley EA, Powers J and Chen M. The endogenous peptide apelin potently improves cardiac contractility and reduces cardiac loading in vivo. *Cardiovasc Res* 2005; 65: 73–82.
37. Karadag S, Ozturk S and Gursu M. The relationship between apelin and cardiac parameters in patients on peritoneal dialysis: is there a new cardiac marker? *BMC Nephrol* 2014; 15: 18.
38. Malyszko J, Malyszko JS and Pawlak K. Apelin, a novel adipocytokine, in relation to endothelial function and inflammation in kidney allograft recipients. *Transpl Proc* 2008; 40: 3466–3469.
39. Cannavo S, Almoto B and Cavalli G. Acromegaly and coronary disease: an integrated evaluation of conventional coronary risk factors and coronary calcifications detected by computed tomography. *J Clin Endocrinol Metab* 2006; 91: 3766–3772.
40. Ozkan H, Celik O and Hatipoglu E. Procalcitonin can be used as a marker of premature atherosclerosis in acromegaly. *Pituitary* 2012; 15: 358–364.
41. Bogazzi F, Battolla L, Spinelli C, et al. Risk factors for development of coronary heart disease in patients with acromegaly: a five-year prospective study. *J Clin Endocrinol Metab* 2007; 92: 4271–4277.
42. Barkan AL, Burman P and Clemmons DR. Glucose homeostasis and safety in patients with acromegaly converted from long-acting octreotide to pegvisomant. *J Clin Endocrinol Metab* 2005; 90: 5684–5691.