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ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2018;7(2):265-8

Is circulating survivin altered in acromegaly?

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Received 15 November 2017; Accepted 04 December 2017
Available online 07.12.2017 with doi: 10.5455/medscience.2017.06.8681

Abstract

Acromegaly is a chronic disorder which is characterized by growth hormone (GH) excess. In most of cases, GH hypersecretion is derived from somatotroph cell tumors. Survivin is a member of apoptosis protein family, which was recently showed to be expressed in tissue samples of different benign and malignant human tumors. This study is intended to determine circulating levels of survivin in newly diagnosed acromegaly patients with somatotroph adenomas. 19 newly diagnosed acromegaly patients with somatotroph adenomas were inclu-ded in the study. Concurrently, 19 healthy individuals were included as control group. Serum survivin levels, GH, insulin like growth factor-1 (IGF-1) and, some other biochemical parame-ters as fasting glucose, creatinine, alanine aminotransferase, cholesterol, triglyceride, high den-sity lipoprotein cholesterol, low density lipoprotein cholesterol were measured in each subject. Correlation analysis was performed between survivin and GH, IGF-1. Serum survivin levels tended to be higher in acromegaly group, but this was not reach statistical significance ($p>0.05$). Serum survivin levels were comparable among acromegaly patients and controls. Neither GH nor IGF-1 correlated with serum survivin. Larger scale studies are needed concerning the circulating levels of survivin in patients with acromegaly.

Keywords: Acromegaly, survivin, apoptosis protein family

Introduction

Pituitary tumorigenesis is promoted by increased transforming gene expression, silencing of tumor suppressor genes (TSGs), pituitary and hypothalamic hormonal dysfunction. Environmental factors and mutagenic stimuli are the other causal factors underlying pituitary tumor formation [1]. Acromegaly is a chronic disorder of increased growth hormon secretion and elevated insulin like factor- 1 (IGF-1). In most cases of acromegaly, GH hypersecretion is de-rived from somatotroph cell adenomas. GH secreting tumor formation depends on uncon-trolled somatotroph proliferation associated with intrinsic cell cyle dysfunction. Although some genetic and epigenetic mechanisms were proposed about somatotroph adenoma for-mation, causes underlying different behaviours of these tumors are poorly understood [2].

Survivin, which is a promising tumor marker, have mitogenic and angiogenic roles in cancer formation.

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It is the smallest member of the apoptosis protein (IAP) family, a group of proteins that specifically inhibit caspase 3, 7 and 9. It consists of 142 amino acid residues and has a molecular mass of 16.5 kDa. Survivin supresses programmed cell death, stimulates cell divi-sion and enhances angiogenesis. It is expressed in fetal and embryonic cells but rarely expres-sed in terminally differentiated adult tissues like thymus, plasenta, basal colonic epithelium, hematopoietic progenitor cell, kidney tubuli cells, endotheliel cell, basal keratocyte cells [3]. Survivin expression has been described to be cell cycle-dependent and restricted to the G2-M checkpoint, where it inhibits apoptosis in proliferating cells. Four alternative splice variants of survivin; deltaEx3, 3 Beta, 2Beta, 2alfa have been described which play different roles in the cell-cycle [4].

A number of studies showed overexpression of survivin in common human malignancies inc-luding lung, breast, pancreatic and colon carcinoma, soft tissue sarcoma, heamatologic malignancies, melanoma, brain tumor, and neuroblastoma [5-14). In addition to studies investiga-ting expression of survivin in various human tumors, there are also some researches investiga-ting survivin expression in somatotroph adenomas to demonstrate its involvement in pituitary tumorigenesis [1,15-18]. Hovewer, no

data are available concerning circulating levels of the survivin in patients with pituitary adenomas. The aim of the present study was to investigate whether the circulating levels of survivin are altered in newly diagnosed acromegaly patients with somatotroph adenomas and, assess the relationship of survivin with several parameters in these subjects.

Material and Methods

The study group was composed of 19 patients (12 female and 7 male, mean age 40.0±11,3 years) who were presented to outpatient clinic of Endocrinology Department and newly diagnosed with acromegaly. 2 of them were being followed by Department of Physical Medicine and Rehabilitation because of arthropathy. The diagnosis of acromegaly based on the presence of clinical features, elevated age-adjusted serum IGF-1 levels, insufficient suppression of GH levels below 1 ng/ml during 2-h oral glucose (75gr) tolerance test (OGTT) and the presence of pituitary adenoma on magnetic resonance imaging. Concurrently, 19 volunteers (12 female and 7 male, mean age 36,8±11,0 years) were included in the study as control group. We recorded the tumour size and calculated the body mass index (BMI) (BMI: body weight (kg)/square height (m^2) at the time of diagnosis in all individuals. 16 patients with acromegaly had macroadenoma while 3 of them had microadenoma. Exclusion criteria for the study was malignancy, diabetes mellitus, hypertension, hyperlipidemia, coronary artery dis-ease, chronic liver or kidney diseases, collagen tissue disease, thyroid disease, other function-al or nonfunctional pituitary tumors. None of the patients were smoking or receiving any medical treatment. The study was approved by the local ethics commitee and a written informed consent obtained from all participants.

Blood sampling was conducted in the morning following one night of fasting. Serum glucose, creatinine, alanine aminotransferase (ALT), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglyceride (TG), total cholesterol (TOTAL-C), growth hormone (GH) and, insulin like growth factor-1 (IGF-1) levels were measured and a standard of 2-h OGTT was performed using 75 g of glucose in all participants. Serum glu-cose levels were measured using a hexokinase enzymatic method (Architect c8000 Chemistry Analyzer, Abbott Diagnostics, North Chicago, Illinois, USA) according to the manufacturer's instructions. Serum GH was assed by electrochemiluminescence immunoassay (human GH kit, Architect c8000 Chemistry Analyzer, Abbott Diagnostics). Serum IGF-1was assed by immunometric chemiluminescence assay (IMMULITE 2000, Siemens, Washington, DC, USA). The samples were centrifuged immediately and the serums were stored at -80ºC until the time of analysis for survivin. Survivin was measured manually by EIA technique using Quantikine brand kits (Quantikine® Survivin Elisa kit, R&D Systems, Minneapolis, Minn.).

Body mass index (BMI) was calculated for each subject as weight divided by squared height. All data were analyzed statistically using SPSS Statistics version 17 (IBM). Mann Whitney U test was used to compare the means between the two groups. The values were pre-sented as mean ± standard deviation and minimum-maximum values [(min-max)]. The correla-tion of survivin with other variables was analyzed by the Spearman's rank test. A p value less than 0.05 was considered to be statistically significant.

Results

Demographical characteristics and biochemical values of all individuals are shown in Table-1. The participants with acromegaly and the control group were similar in terms of gen-der and mean age (12 female and 7 male, mean age 40.0±11,3 vs 36,8±11,0 years respectively) ($p > 0.05$). BMI and serum creatinine, ALT, LDL-C, HDL-C, TG, TOTAL-C and, GH levels were similar both in acromegaly and control groups. Serum IGF-1 concentrations were signifi-cantly higher in the acromegaly group compared with the control group ($p< 0.05$). Serum sur-vivin levels tended to be higher in acromegaly group but no statistical significant was found (26.79 ± 26.48 vs 20.21 ± 23.88) ($p > 0.05$). There was not any correlation between survivin and BMI, GH, IGF-1 and other biochemical parameters (Table 2).

Table 1. Demographical characteristics and biochemical values of controls and patients with acromegaly

	Acromegaly (n=19)	Controls (n=19)
Age (year)	40.06 ± 11.36	36.89 ± 11.09
BMI (kg/m2)	31.03 ± 4.74	28.87 ± 7.14
FBG (mmol/L)	102.42 ± 13.9	89.16 ± 9.05
Creatinin (mg/dl)ALT (U/L)	0.81 ± 0.22 16.26 ± 7.51 14 (9-36)	0.88 ± 0.16 24.41 ± 17.80 17.50 (8-71)
Total cholesterol (mmol/L)	200.76 ± 52.80	197.45 ± 40.89
Triglyceride (mmol/L)	106.52 ± 41.89	131.36 ± 58.30
HDL- cholesterol (mmol/L) LDL- cholesterol (mmol/L)	52.60 ± 10.70 133.93 ± 43.22	44.20 ± 8.37 115.95 ± 50.69
Survivin (pg/mL)	26.79 ± 26.48 21 (4.4-71.6)	20.21 ± 23.88 13 (4.40-94.60)
GH (ng/mL)	3.55 ± 4.30 1.5 (0.44-18.1)	1.30 ± 2.06 0.1 (0-6.4)
IGF-1 (ng/mL)	341.91 ± 235.26* 306 (6.4-750)	159.04 ± 63.43* 163 (79-268)

*, $p <0.05$, between acromegaly and controls. The results of statistical analysis were expressed as mean ± standard deviation (X±SD), median and minimum–maximum values [M (min–max)].,BMI; body mass index, FBG; fasting blood glucose, GH; growth hormone, IGF-1; insulin like growth factor-1.

Table 2. The correlation analysis of survivin with some parameters in patients with acromegaly

Parameters	p value	r value
FBG	0.67	0.08
BMI	0.90	0.02
Creatinin	0.08	0.84
ALT	0.36	-0.11
IGF-1	0.90	0.40
GH	0.30	-0.16

FBG; fasting blood glucose, **BMI;** body mass index, **GH**; growth hormone, **IGF-1**; insulin like growth factor-1.

Discussion

Taking account the fact that survivin is detected in many human tumors, can inhibit apoptosis and promote both cell proliferation and angiogenesis, it would be expected that it may play some role in pituitary carcinogenesis [3]. In the light of this fact, we aimed o

investi-gate serum levels of survivin in patients newly diagnosed with acromegaly in our study. Serum levels were found to be similiar among patients with acromegaly and control group.

There are conflicting data concerning the survivin expression in pituitary tumors and its involvement in pituitary tumorigenesis. In a recent research, survivin and its splice variants deltaEx3 and 2Beta were found to be expressed in different types of functional and non-functional pituitary adenomas, and normal pituitary tissue. However, it was reported that lev-els of survivin expression were similar in pituitary tumors and in normal pituitary tissue as well as in invasive and non-invasive tumors [18]. The authors suggested that survivin does not play a significant role in pituitary tumorogenesis. Similiarly, although our study was not based on evaluation of survivin expression in samples obtained during surgical removal of pituitary tu-mors, we would like to point that we found comparable levels of survivin in samples obtained from serum of patients with acromegaly and controls. In another study, Formosa's group exam-ined the expression of survivin in 47 tissue samples of pituitary adenomas consisting of 35 non-fuctional, 7 GH-secreting, 3 prolactin and 2 adrenocorticotropin hormone-secreting tu-mour. Survivin expression was found to be extremely low in tumors and absent in normal con-trols [15]. In contrary to these results, Jankowska et al reported that survivin mRNA expression was 6 fold higher in patients with pituitary adenomas than in controls in one of their study. Moreover, there was not any statistically significance in survivin expression between invasive and non-invasive pituitary adenomas [16]. In agreement with this study, Wasko et al. showed the presence of active survivin gene in tissue samples obtained during surgical removal of the 12 patients with diagnosed: acromegaly in 7 cases, non-functioning pituitary tumours in 4 cases and prolactinoma in 1 case [14]. They concluded that the estimation of survivin expression in human pituitary tumours may help predict tumour growth and prognosis. In another study of Wasko et al, co-expression of survivin and proliferating cell nuclear antigen (PCNA) was eval-uated in 43 cases involving different types of pituitary adenomas; 22 with somatotroph adeno-mas, 16 with non-functioning adenomas, 4 with lactotroph adenomas, and 1 with corticotroph adenoma. They demonstrated the presence of survivin in all tumors as well as in normal pitui-tary tissue and pointed that immunhistochemical staining was significantly weaker limited to single cells of the tissue in normal pituitary. It was concluded that the increased accumulation of survivin in tumor cells suggest that survivin protein is one of the factors involved in neoplastic transformation of pituitary [20].

In recent years, various studies have investigated serum survivin levels in many cancer types and revealed conflicting data. A study examining circulating survivin in pancreatic duc-tal adenocarcinoma (PDCA) demonstrated increased survivin levels in patients with PDCA comparing to controls. Immunohistochemical staining for survivin in tissue samples from PDAC were also performed and survivin expression was found to be positive. Moreover, it was shown that high serum survivin levels were significantly associated with perineural invasion, venous invasion, lymph node status, cell differentiation, and recurrence [21]. Ren et al also fo-und increased serum survivin levels in patients with PDCA in addition to higher serum survivin levels in patients with advanced stages and poor differentiation [22]. In disagreement with these studies, Guney et al. showed similar serum survivin levels in patients with breast cancer com-pared to controls. But, it was remarkable that serum survivin levels were significantly higher in the patients with nodal involvement compared with node negatives [23]. Similiarly, in another study, Goksel et al also showed no difference in survivin levels between the early-stage breast cancer patients and the control group [24]. In agreement with this study, comparable circulating survivin levels between controls and patients diagnosed with melanom, and non-small cell lung cancer, respectively were reported in different researches [25,26]. We also found similar survi-vin levels between patients diagnosed with somatotroph adenomas and control group.

Unfortunately, little is still known about circulating survivin in the literature. It is un-clear whether survivin in serum exists in a free form or complexed with serum proteins. One of the most important factors concerning survivin is to develop and validate an assay for measur-ing survivin levels in serum which is simplified, quantitative and reproducible [3]. We think that different assay systems may be one of the factors involved at conflicting results in circula-ting survivin levels in different tumors reported in the literature.

Many studies revealed that survivin expression in a variety of cancers correlates with poor diagnosis. For instance, Goricar et al showed that higher serum survivin levels before chemotherapy were associated with a progressive disease in patients with malign mesothelio-ma [27]. They suggested that serum survivin levels before and during chemotherapy could ser-ve as a biomarker predicting malign mesothelioma. In a recent study, it was shown that survi-vin mRNA level in blood from stage IIIA-N2 non-small cell lung cancer patients receiving neo-adjuvant chemotherapy was predictive of cancer outcome [28]. On the contrary, Tas et al did not demonstrate any correlation between survivin and prognostic parameters analysed in pati-ents diagnosed with melanom. Similiarly, Naumnik et al revealed that survivin levels had no clinical significance in the prognosis of patients with non-lung cancer [25,26]. In acromegaly, the literature reports that both GH and IGF-I levels correlate with mortality, and mortality is si-miliar with the general population when GH and serum IGF-I are controlled [29]. Our study did not reveal any correlation between survivin levels and either GH or IGF-1 in agreement with the studies of Naumik et al and Tas et al.

Although the presence of many studies concerning survivin expression in tissue sam-ples of different types of benign and malign tumors, there are limited data about circulating levels of survivin in various tumors. To the best of our knowledge, there are no data on the serum levels of survivin in patients with pituitary adenomas. Therefore, this is the first report on the serum levels of survivin in patients with pituitary adenomas who were newly diagnosed with acromegaly. We demonstrated comparable circulating survivin levels between control group and acromegaly patients with somatotroph adenomas. One of the most limitation of our study is the small number of the patients. Larger prospective studies targeting circulating sur-vivin with implified, quantitative, and reproducible assays in serum may help to understand the role of this protein in pituitary tumor formation and progression.

Competing interests
The authors declare that they have no competing interest.

Financial Disclosure
The financial support for this study was provided by the investigators themselves.

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