Plasma Ghrelin Levels For The Patients With Acute Myelocytic Leukaemia (AML)

Oktay Sari[1], Umit Aydogan[1], Oral Nevruz[2], Inci Celikkol[1], Ali Ugur Ural[2], Kurtulus Ongel[3] Kenan Saglam[1]

[1] Gulhane Military Medical Academy, Department of Family Medicine, Ankara, Turkey
[2] Gulhane Military Medical Academy, Department of Hematology, Ankara, Turkey
[3] Tepecik Research and Implamentation Hospital, Department of Family Medicine, Izmir, Turkey

Abstract

Objective: Aim of the study is to determine the ghrelin level differences between the patients with Acute Myelocytic Leukaemia (AML) and the control group.

Methods: On June 16-30, 2009 in Ankara Military Hospital, 17 patients with AML and a control group of 30 induviduals were enrolled to the study. Demographic data such as gender, age, were evaluated together with body mass index (BMI) and plasma ghrelin levels. Data were analysed with SPSS 10.0 statistics program.

Results: In the study; average age of the patient group was 38.7±16.7. Of the participants 35.3% were female and %64.7 were male. For the control group 53.3% of the induviduals were female and 46.7% were male. The mean ghrelin value was detected as 906.4±674.8 ng/L for the patient group and 478.0±254.3 ng/L for the control group. The mean ghrelin value differences between the patient group and the control group was found to be statistically significant (p=0.003). In the patient group there was no significant difference between ghrelin values and the BMI. In the patient group the mean ghrelin value was documented as 1301.5 ng/L for females and 690.9 ng/L for males. Additionaly no significant difference of ghrelin values due to age groups were obtained.

Conclusion: The previous studies conclude that ghrelin values increase due to malnutrition at malignant diseases. The cachexia, seen in malignant disease is thought to increase the ghrelin release. In our study the high ghrelin values at the patient group is considered to be the result of this mechanism. Determining no significant difference between BMI and ghrelin values may be due to the small number of the study group.

Key words: Ghrelin, AML, BMI

Sarı O, Aydogan U, Nevruz O, Celikkol I, Ural AU, Ongel K, Saglam K. Plasma Ghrelin Levels For The Patients With Acute Myelocytic Leukaemia (AML). TJFMPC, 2011; 5:32-36.

Introduction

Ghrelin is a hormone that takes place in energy regulation and a role in the regulation of growth up.[1] It is a recently identified hormon that composed of 28 aminoacides (aa). N-octanoly group in a permutation provides its biological effects.

In most of the researches, it is determined in different tissues[2] and Ghrelin mRNA exists almost in all tissues.[3] Ghrelin is mainly produced in stomach but it is also found in several other tissues such as heart, brain, pancreas, kidney, parathyroid gland and plasenta.[2,4,5] Postgastrectomic ghrelin reduce showes that the octcyntic mucosa of stomach is the base source of ghrelin.[6]

Ghrelin hormone has many physiological effects [1,7] (Table-1). One of the most important physiological effects of ghrelin is its' potent growth hormone (GH) secretagogue activity. This activity is demonstrated in studies with human and rats. 20-30 minutes after administration of ghrelin, GH level makes a peak. GH releasing peptid is necessary for the ghrelin activity. Effect of the activity is enhanced with both releasing.[8] The existence of ghrelin in placenta demonstrates that efficacy of ghrelin is important on intrauterin maturation.[9] Recently; studies about the role of ghrelin in regulating energy metabolism and the appetite gained more importance than the GH releasing activity. Ghrelin stimulates the pituitary secretion of GH and regulates the food intake and improves the energy metabolism.[10] It has a role in stimulating the food intake and energy enhance. Because of the regulator effects on energy balance, ghrelin prevents cachexia and stimulates the appetite by increasing before food intake.[11]

Ghrelin is detected in normal tissues but also in hypophyseal adenoma, thyroid cancer, pancreas and lung cancers. But in one of the study; ghrelin couldn't been determined in gastric adenocarsinoma and salivary gland

Corresponding Adress:
Oktay Sarı
Gulhane Military Medical Academy, Department of Family Medicine, Etlik 06018, Ankara, Turkey
Tel: 0 532 3252792
E-mail: okitaysari72@yahoo.com
Recieved date:24.06.2011
Accepted date:19.10.2011

mucoepidermoid cancer; this situation is explained as the cause of appetite deficiency in patients with cancers.[12] In the studies, it has been determined that patients with cancer and appetite deficient have much more ghrelin levels than normal individuals. This is based on cachexia, which occurs in cancer and diagnosed with poor prognosis in cancer, enhances the secretion of ghrelin.[13] In a study which examined gastric and esophagus adenocarsinoma patients, there were opinions that high ghrelin levels are caused by non-neoplastic mucosa, not adenocarsinoma cells.[14]

Table-1: Effects of Ghrelin / GHSs

Effects of Ghrelin	Inhibitation	Stimulation
Gastric	Insulin Somatostatin GLP-1 Gastrin Cholecystokinin Glucose Fat (long chain) Amino acids Histamine-2 receptor IGF-I treatment Glucagon Leptin	Vagus nerve Acetylcholine Fasting Estrogen Hypoglycemia Cachexia Endotoxin Deep sleep
Cardiovascular	Mean arterial pressure Lusitrophy (tension relaxation) Ventricular end-systolic pressure Cardiomyocyte apoptosis Endothelial apoptosis Pulmonary hypertension Oxygen consumption Cardiac sympathetic drive	Inotropy (myocardial tension generation) Renal perfusion Coronary perfusion pressure Left-ventricular ejection fraction
Diabetogenic	Stimulation of hepatic glucose output Adipogenesis Inhibition of insulin secretion Acute free-fatty acid release (human) Antithermogenesis Decreased sympathetic outflow	Chronic ↑ GH (lipolysis) Increase lean-body mass (chronic) Decrease oxygen consumption
Adipogenic	Decrease fat-cell lipid export Enhance lipoprotein lipase Reduce insulin sensitivity Stimulate preadipocyte proliferation Promote adipocyte differentiation Augment hepatic glucose output and triacylglyceride content Inhibit fatty acid oxidation Induce leptin and PPAR-gamma Suppress adiponectin Increase appetite	

The aim of the study is to determine whether there is significant difference on ghrelin levels in one of the important malign diseases, AML or not. Other aim is to check out the relation between BMI and ghrelin levels.

Material and Method

The investigation was done on June 16-30, 2009 in Ankara. 17 Patients who were diagnosed and hospitalized as AML to Gulhane Military Medical Faculty, Department of Hematology and as a control group, 30 healthy people, were included in the study. AML diagnosis was made according to its' criterias by the specialists in the Department of Hematology. All patients and control groups were provided written informed consent to take part in the study.

Assessment of patients according to body mass index (BMI) was performed by The American Association of Clinical Endocrinologists / American College of Endocrinology (AACE/ACE) Guideline, published in 1998.

To detect the ghrelin levels; 5ml blood sample had been taken and contained in sterile tubes with no protective agents. In 45 minutes time, after blood sample had been taken, centrifuged at 2500 rpm and serum stored at –80 C. Serum ghrelin levels assayed by Lincon method (RIA).

The investigation's analysis was done at SPSS 10.0 statictical program. For the analysis; Kruskal Wallis and student-t test were used. The level of meaningfulness was taken into consideraton in two ways and p was accepted as $p<0.05$.

Results

Total 47 people (17 patients, 36.17%; 30 control, 63.83%) participated in the study. Average age of the patient group was 38.7±16.7 years and control group was 41.9±12.2 years. Total 46.8% (n:22) of the participants were female and 53.2% (n:25) were male (Table-2).

The mean ghrelin value was detected as 906.4±674.8 ng/L for the patient group and 478.0±254.2 ng/L for the control group. The mean ghrelin value differences between the patient group and the control group was found to be statistically significant (p=0.003) (Table-2).

According to age; no significant difference was found between patient and control groups consistent with the examination of ghrelin

Related with the BMI of the participiants; 41.2% (n:7) of the induviduals at the patient group were considered as lean (BMI<20 kg/m²) and this ratio was calculated as 3.3% (n:1) for the control group. This data was also found to be statistically significant (p=0.001) (Table-3).

When we evaluate the relationship between ghrelin values and the BMI in the patient group no significant difference was determined. In the patient group the mean ghrelin value was documented as 1301.5 ng/L for females and 690.9 ng/L for males. Additionaly no significant difference of ghrelin values due to age groups were obtained.

Discussion

Ghrelin, with GH secretagogue effect, has a role in the energy regulation metabolism; stimulating food intake and so gaining and protecting the energy. This effect is independent from growth hormon. It's a somatotropic and adipogenic hormon associated with systems that regulate the growth and energy balance. Ghrelin's effects ocur by the growth hormone secratagogue receptor (GHS-R) widespread in body. [6]

Table-2: Age, gender and ghrelin level distribution according to groups

Parameters			case	control	p
Age		n/%	17/36.2	30/63.8	-
		Mean± Std. deviation	38.7±16.7	41.9±12.2	
		Minimum-maximum	21-72	21-63	
		Median	42,0	41,0	
Gender	Female	n/%	6/35.3	16/53.3	-
	Male	n/%	11/64.7	14/46.7	
Ghrelin		Mean± Std. deviation	906.4±674.8	478.0±254.3	0.003
		Minimum-maximum	255-2404	56-1153	
		Median	596.0	374.0	

Table-3: Comparison of the groups according to BMI

BMI groups		case	control	p
Lean	n /%	7/41.2	1/3.3	0.127
	Mean±Std. deviation	18.2±1.3	19.4	
	Minimum-maximum	16.1-19.5	19.4-19.4	
	median	18.5	19.4	
	Ghrelin (Mean±SD)	1191.8±731.5	115.0	
Normal	n/%	8/47.1	10/33.3	0.790
	Mean±Std. deviation	22.3±1.7	23.3±1.2	
	Minimum-maximum	20.1-24.5	21.3-24.9	
	median	21.9	23.5	
	Ghrelin (Mean±SD)	541.1±226.8	532.4±279.9	
Overweight	n/%	2/11.8	9/30.0	0.099
	Mean±Std. deviation	26.8±1.9	27.3±1.4	
	Minimum-maximum	25.5-28.1	25.6-30.0	
	median	26.8	26.7	
	Ghrelin (Mean±SD)	1368.5±1284.8	389.3±107.8	
Obese	n/%	-	10/33.3	-
	Mean±Std. deviation	-	32.9±1.9	
	Minimum-maximum	-	30.4-35.6	
	median	-	33.1	
	Ghrelin (Mean±SD)	-	539.8±299.2	

In literature, there is no demonstrated relation between ghrelin and age. There are different studies with estimations over the effects of age on ghrelin as an independent factor.[15,16] Either in human or mice studies, a negative relation between age and ghrelin values is demonstrated.[17] In the first two years of life, it's measured higher than following years.[18] In a study with 121 healty individuals, it's demonstrated that ghrelin levels decrease over years.[19] In the study either patients or control group, no significant difference between age groups could be found. This may be due to the low number of cases in this study. Several studies demonstrate that ghrelin levels are higher in women.[20] However, there is one study demonstrates that there is no difference between the genders when certain parameters are adjusted. [21] In our study groups, women showed higher ghrelin levels than men. But, there was no statistical significant difference. Further studies with more patients may show a significant difference.

Ghrelin level is negative balanced with body mass index and apetite.[5] Ghrelin level is greater in obese. It has been shown, preprandial ghrelin level increase is higher in obese than non-obese patient. As the postprandial ghrelin levels decrease, so much apetite decreases. And also weight gain occurs.[22] In our study, according to BMI, thin patients have higher ghrelin levels than overweight patients. But there is no significant difference between them.

Cachexia is a catabolic period, characterised with break down of the muscle proteins and weight lose, in the last stage of cancer. Cachexia is an independent mortality risk factor and effects half of the cancer patients.[23] Treatment of cachexia increases the survival rate and treatment decreases mortality and morbidity. The cytokines just like TNF-alfa, leukemia inhibiting factor and inteferon gama, produced by tumor cells, mediate the effects of cachexia. In our study, ghrelin levels were found to be increased in patient group. And also thin patients have excess levels, with no statistical significant difference. It has suggested that treatment over ghrelin for weight gain in cancer cachexia, which improves patients survival rate and life standart, will have significant importance in the near future. In one study, that provide evidence for this theory, in cachectic cancer model rats ghrelin administration increase white lipid tissue and leptin.[24]

Conclusion:
All cancer and malign diseases like leukemia cause body energy redistribution. As a result; we think that further studies on the effects of ghrelin, that thought to have significant importance in appetite deficient, need to be done.

References:

1- Cesur G, Özguner MF, Öngel K. Ghrelin and adiponectin hormones and their effects on growth. New World Sciences Academy. 2009; 4(4): 104-117.
2- Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K 1999 Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature 1999; 402: 656–660.
3- Gnanapavan S, Kola B, Bustin SA, et al. The tissue distribution of the mRNA of ghrelin and subtypes of its receptor, GHS-R, in humans. J Clin Endocrinol Metab 2002; 87: 2988.
4- Inui A. Ghrelin: an orexigenic and somatotrophic signal from the stomach. Nat Rev Neurosci. 2001; 2: 551–560.
5- Date Y, Kojima M, Hosoda H, et al. Ghrelin, a novel growth hormone-releasing acylate peptide, is synthesized in a distinct endocrine cell type in the gastrointestinal tracts of rats and humans. Endocrinology. 2000; 141: 4255–4261.
6- Leonetti F, Silecchia G, Iacobellis G, et al. Different plasma ghrelin levels after laparoscopic gastric bypass and adjustable gastric banding in morbid obese subject. J Clin Endocrinol Metab 2003; 88: 4227-4231.
7- Korbonits M, Goldstone AP, Gueorguiev M, Grossman AB. Ghrelin-a hormone with multiple functions. Neuroendocrinology 2004; 25: 27-68.
8- Akamizu T, Takaya K, Irako T, et al. Pharmacokinetics safety, and endocrine and appetite effects of ghrelin administration in young healthy subjects. Eur J Endocrinol 2004; 150: 447-455.
9- Gnanapavan S, Kola B, Bustin SA, et al. The tissue distribution of the mRNA of ghrelin and subtypes of its receptor, GHS-R, in humans. J Clin Endocrinol Metab 2002; 87: 2988-2991.
10- Yiş U, Öztürk Y, Büyükgebiz B. Ghrelin: enerji metabolizmasının düzenlenmesinde yeni bir hormon. Çocuk Sağlığı ve Hastalıkları Dergisi 2005; 48: 196-201.
11- Hosoda H, Kojima M, Kangawa K. Ghrelin and the regulation of food intake and energy balance. Mol İnterv 2002; 2: 493-503.
12- Aydın S, Özercan IH, Dağlı F, Aydın S, Doğru O, Çelebi S. Tükrük bezi mukoepidermoid karsinomu ve gastrik adeno karsinomunun negatif ghrelin immuno histokimyası. Turk J Biochem] 2005; 30 (1): 1-172.
13- Howard AD, Feighner SD, Cully DF, et al. A receptor in pituitary and hypotalamus that functions in growth hormone release. Science 1996; 273: 974-977.
14- Mottershead M, Karteris E, Barclay JY, et al. Immunohistochemical and quantitative mRNA assessment of ghrelin expression in gastric and oesophageal adenocarcinoma. J Clin Pathol 2007; 06(4): 405-409.
15- Chan JL, Bullen J, Lee JH, Yiannakouris N, Mantzoros CS. Ghrelin levels are not regulated by recombinant leptin administration and/or three days of fasting in healthy subjects. J Clin Endocrinol Metab 2004; 89: 335-343.
16- Purnell JQ, Weigle DS, Bren P, Cummings DE. Ghrelin levels correlate with insulin levels, insulin resistance and high-density lipoprotein cholesterol, but not with gender, menopausal status, or cortisol levels in humans. J Clin Endocrinol Metab 2003; 88: 5747-5752.
17- Rigamonti AE, Pincelli AI, Corra B, et al. Plasma ghrelin concentrations in elderly subjects: Comparison with anorexic and ebese patients. J Endocrinol 2002; 175: 1-5.
18- Soriano-Guillen L, Barrios V, Chowen J, et al. Ghrelin levels from fetal life through early adulthood: relationship with endocrine and metabolic and anthropometric measures. J Pediatr 2004; 144: 30-35.
19- Whatmore AJ, Hall CM, Jones J, Westwood M, Clayton PE. Ghrelin concentrations in healthy children and adeloscents. Clin Endocrinol 2003; 59(5): 649-654.
20- Gualillo O, Caminos JE, Kojima M, et al. Gender and gonodal influences on ghrelin mRNA levels in rat stomach. Eur J Endocrinol 2001; 144: 687-690.
21- Corbetta S, Peracchi M, Cappiello V, Lania A, Lauri E, Vago L, Beck-Peccoz P, Spada A. Circulating ghrelin levels in patients with pancreatic and gastrointestinal neuroendocrine tumors: identification of

one pancreatic ghrelinoma. J Clin Endocrinol Metab 2003; 88: 3117-3120.
22- Kojima M, Kangawa K. Ghrelin:Structure and function. Physiol Rev 2005; 85: 495-522.
23- Tisdale MJ. Pathogenesis of cancer cachexia. J Support Oncol. 2003; 1(3): 159-168.
24- Tisdale MJ. Clinical anticachexia treatments. Nutr Clin Pract. 2006; 21(2): 168-174.