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Plasma Total Ghrelin Levels in Patients with Chronic Renal Failure: Comparison with Healthy Subjects and Relationship with Hemodynamic Parameters

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Introduction

Ghrelin is a 28-amino-acid peptide, originally identified in the rat stomach as the endogenous ligand for the growth hormone secretagogue-receptor (GHS-R1a). It is involved in the regulation of growth hormone release from the pituitary, but it has also recently been found that it may have numerous other actions, including effects on appetite, carbohydrate metabolism, heart, kidney, pancreas, gonads and cell proliferation [1]. It is an orexigenic peptide, acting via stimulation of the hypothalamic neuropeptide Y (NPY) and agouti-related protein (AGRP), thus antagonizing the anorectic actions of leptin. Its secretion occurs in a pulse way during the day and shows a surge just before meals and a marked decline nearly one hour after the meal, coinciding with satiety feelings [2].

Metabolism of ghrelin has been poorly studied, and kidney clearance is believed to be the major pathway of its elimination. Although the stomach is the main site of its production, other sites in the body have been found to produce it as well, among which the kidney has been shown to be one [3]. There is a paucity of studies in the literature examining the association between kidney function and ghrelin levels [4]. In addition, patients with CRF have often left ventricular (LV) dysfunction [5]. However, no data exist on the relationship between plasma ghrelin concentrations and cardiac function in patients with CRF. In this cross-sectional study, we examined the association between plasma ghrelin levels and kidney function in patients with chronic renal failure (CRF) and healthy subjects. In addition, the potential association between plasma ghrelin levels with indices of cardiac function was also evaluated.

Methods

A total of 122 patients with CRF (stages 4 and 5 according to the Kidney Disease Outcomes Quality Initiative guidelines of the National Kidney Foundation) [6] of varying etiology (57 on hemodialysis and 65 not on hemodialysis) were studied, and compared to 57 healthy controls. The underlying renal diseases were: diabetes mellitus (36.9%), nephrangiosclerosis (13.9%), chronic glomerular nephritis (13.1%), tubolointerstitial nephropathy (9.1%), polycystic liver and kidney disease (5.7%), and 21.3% were of unknown cause. The 57 hemodialysis patients studied received a minimum of 12 h per week maintenance hemodialysis therapy.

The mean value of two blood pressure measurements was used in the statistical analysis. Blood was collected after an overnight fast of at least 12 hours. Dialysis patients had their blood drawn before the dialysis session, in the morning, while fasted.

Using pulsed-Doppler from the mitral inflow velocity curve the following parameters were calculated: peak early velocity (E-wave), peak velocity at the time of atrial contraction (A-wave), E/A ratio, deceleration time (DT) of the peak early velocity, and the isovolumic relaxation time (IVRT). Myocardial performance index of the LV (MPI), a noninvasive Doppler measurement of the left ventricular systolic and diastolic function, has been measured and calculated [7]. Higher values of this index indicate worse LV function.

Glomerular filtration rate (GFR) was calculated according to the equation of Cockroft and Gault. Fasting total plasma ghrelin concentrations were measured using a commercial RIA kit with a sensitivity of 10 pg/ml.

Results

Control patients were younger than patients with CRF [mean age (95% confidence interval of mean) 50.7 (46.4-55.1) vs 58.5 (55.8-61.2) years, p=0.002], having also lower blood pressure (systolic and diastolic). BMI, WHR and serum albumin were not significantly different between the two groups. In the control group fasting plasma ghrelin levels were lower than the CRF patients with all comparisons adjusted for age [1,998.6 (1,674.5-2,322.6) vs 4,620.4 (4,305.2-4,935.8) pg/ml, p<0.001]. In addition, the values of the indices of LV systolic (ejection fraction), and diastolic function (E/A, IVRT, DT) were all lower in CRF patients (p<0.001). The values of the left ventricular mass and myocardial performance index were lower in the control group (both p<0.001).

Comparisons among the patients with CRF (divided based on their need for hemodialysis or not) showed that the hemodialysis-dependent patients had lower GFR [10.2 (9.2-11.3) vs 12.0 (10.5-13.2) ml/min, p=0.02], lower systolic and diastolic blood pressure, lower total- and LDL-cholesterol and lower PTH levels, but no difference in the fasting plasma ghrelin levels [4,520.1 (4,055.3-4,984.3) vs 4,742.6 (4,305.8-5,170.5) pg/ml, p=0.85] compared with the ones not on hemodialysis. In addition, pre-dialysis patients had higher ejection fraction [51.9 (50.7-53.3) vs 49.5 (47.3-51.7) %, p=0.01] and lower values of MPI than

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found in LV mass and in the indices of LV diastolic function between the two groups.

Patients with diabetic nephropathy were older than those with other causes of CRF [mean age (95% confidence intervals) 63.2 (59.6-66.9) vs 55.4 (51.9-59.1) years, p=0.003) and had higher WHR The two groups did not differ significantly in terms of sex, BMI, systolic and diastolic blood pressure. In addition, patients with diabetic nephropathy had higher and GFR. Age-adjusted plasma ghrelin concentrations were not different between patients with diabetic nephropathy compared to their non-diabetic counterparts [4,148.8 (3,768.2-4,592.3 vs 4,912.4 (4,468.3-5,365.5) pg/ml, respectively, p=0.12).

In a multivariate linear regression analysis, in the control group, only sex, albumin level, DBP and PTH levels predicted the variance of ghrelin in a statistically significant way (adjusted R^2=0.73). In the CRF patients group, only HDL-C had a significant association with ghrelin levels (adjusted R^2=0.06). In the whole sample of participants, sex, BMI and presence or not of renal disease, explained 46% of the variance of ghrelin values (adjusted R^2=0.46) in this model, while presence of renal disease only accounted for 41% of the variance of the ghrelin levels.

In the CRF patients, no significant association was found between plasma ghrelin concentrations and ejection fraction of the LV. In addition, plasma ghrelin levels were not associated significantly with indices of diastolic function of the LV. A significant, however, relationship was found with the E/A ratio. In a multivariate linear regression analysis model, the relationship between plasma ghrelin levels and E/A ratio remained significant (p=0.03) after adjustment for age, heart rate, and GFR. Furthermore, no significant relationship was found between plasma ghrelin levels and LV mass, neither with MPI.

Discussion

In the present study we observed that fasting plasma total ghrelin levels were significantly affected by kidney dysfunction, being nearly 2.3-fold higher in CRF patients, compared to controls. The presence of renal dysfunction accounted for 41% of the variability of plasma ghrelin values, with sex and BMI accounting for another 5% in the whole group of participants.

Among patients with CRF, plasma ghrelin levels did not differ significantly depending on their need for haemodialysis or not. Ghrelin levels were marginally associated with HDL-C levels in this group of patients in the multivariate model, after adjusting for other co-variates. When we stratified our CRF patient group into those with diabetic nephropathy and those with CRF due to other causes, the etiology of renal failure did not seem to have any effect on the fasting plasma total ghrelin concentrations.

Our results are generally in accordance with the only study so far, which has evaluated the effect of kidney function on plasma ghrelin levels [4]. This study used a relatively small number of participants (41 in total, only 30 with kidney dysfunction), while in the present study we have examined a total of 179 subjects, 122 with kidney failure. Thus, our results are more robust and corroborate those of the previous study, showing increased concentrations of total plasma ghrelin levels in renal failure patients compared to controls. In addition, the finding that plasma ghrelin levels were not different between CRF patients on and not on hemodialysis implies that ghrelin is not filtered during hemodialysis sessions.

Concerning the hemodynamic parameters, this study has shown that patients with diabetic nephropathy, in comparison with those with CRF of other causes, have more detrimental LV performance, confirming the findings of previous studies [5].

In conclusion, this study has demonstrated that fasting plasma total ghrelin concentrations are higher in patients with renal failure (regardless of their need for hemodialysis or not) compared to control subjects. The etiology of renal failure, that is diabetic nephropathy or nephropathy from other causes does not have any effect on ghrelin levels. In addition, it was shown for first time that plasma ghrelin levels are not associated with the hemodynamic parameters in patients with CRF. This study contributes to a better understanding of the physiology of this new hormone in cases of kidney dysfunction.

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