ASSOCIATION BETWEEN SERUM LEPTIN LEVEL AND MORTALITY IN KIDNEY TRANSPLANT RECIPIENTS

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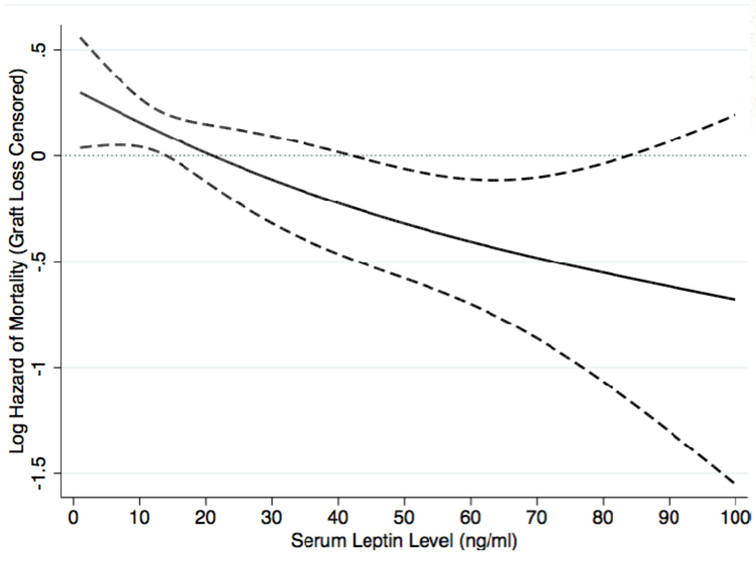
Background

- Leptin is a hormone made by adipocytes and associated with hypertension, inflammation, and coronary artery disease in patients without kidney disease.
- Low serum leptin level was associated with higher risk of death in patients with advanced chronic kidney disease.
- Little is known about the association of serum leptin with outcomes in kidney transplant recipients.
- Our aim was to analyze the association between **serum leptin levels and outcomes in prevalent kidney transplant recipients**.
- We hypothesized that lower serum leptin levels are associated with higher risk of death and graft loss and this effect is modified by body composition.

Methods

- We recruited all prevalent kidney transplant recipients (n=1,214), who were followed at a single transplant outpatient clinic at the Department of Transplantation and Surgery at Semmelweis University, Faculty of Medicine in Budapest, Hungary between 2006 and 2007.
- Patients have been excluded if experienced acute rejection within the last 4 weeks before study entry; were hospitalized at the study entry; received kidney transplantation in the previous 3 months; or had acute infection or bleeding.
- We collected and measured baseline the parameters of 979 prevalent kidney transplant recipients enrolled in the Malnutrition-Inflammation in Transplant-Hungary Study(MINIT-HU study).
- Associations between serum leptin level and death with a functioning graft, all-cause death and death-censored graft loss over a 6-year (76 (46-79) months) follow-up period were examined using Cox proportional regression analysis and Kaplan-Meier plots with the log rank test.



Results

	All patients (n=979)	First tertile of serum leptin (n=327)	Second tertile of serum leptin (n=326)	Third tertile of serum leptin (n=326)
Leptin (ng/ml)	**15.1 (6.8-32.1)**	**4.7 (2.6-6.9)**	**15.1 (12.4-19.8)**	**45.5 (32.1-65.9)**
Age (year)	51±13	51±14	51±13	52±12
Sex - Male (%)	58	76	67	29
Charlson Comorbidity Index	2 (2-4)	2 (2-3)	2 (2-4)	2 (2-4)
Presence of HT (%)	94	92	94	94
Presence of DM (%)	21	19	20	24
Presence of coronary heart disease (%)	9	7	9	10
Smoking (%)	19	27	19	10
Blood Hgb (g/L)	134.8±17.0	135.2±17.4	139.1±17.5	130.1±14.8
eGFR (CKD-EPI) (ml/min/1.73 m²)	52.6±21.7	53.9±22.8	57.1±20.3	46.9±20.8
Serum PTH (pg/ml)	67 (47-103)	65 (43-98)	66 (46-95)	75 (50-121)
Serum albumin (g/L)	40.3±4.1	40.1±4.4	40.6±4.0	40.1±4.0
WBC (10^9/L)	7.9±2.3	7.7±2.	7.8±2.2	8.2±2.5
CRP (mg/L)	3.1 (1.5-6.9)	2.6 (1.2-5.4)	2.8 (1.4-6.1)	4.2 (1.9-8.7)
IL6 (pg/ml)	2.1 (1.2-3.6)	1.9 (1.2-3.5)	2 (1.2-3.4)	2.4 (1.4-3.9)
TNF-Alpha (pg/ml)	2.1 (1.5-2.8)	2.1 (1.6-2.9)	1.9 (1.4-2.7)	2.1 (1.6-2.9)
BMI (kg/m²)	27.0±4.9	24.0±4.0	27.2±4.0	29.9±4.6
Abdominal circumference (cm)	99.0±14.4	92.0±12.2	100.8±13.5	104.1±14.6
Cholesterol (mmol/l)	5.5±1.3	5.3±1.3	5.6±1.2	5.7±1.3
Triglyceride (mmol/l)	1.7 (1.2-2.5)	1.4 (1.1-2.0)	1.9 (1.3-2.6)	1.9 (1.4-2.9)
Time since Tx (month)	72 (39-113)	72 (41-115)	72 (39-113)	71 (37-113)
Previous time on dialysis (month)	20 (9-38)	24 (10-48)	19 (9-36)	18 (8-36)
Total ESRD time (month)	107 (68-154)	115 (74-156)	103 (66-148)	104 (64-153)
Cold ischemic time (minute)	1251 ± 345	1239 ± 345	1234 ± 380	1279 ± 306
PRA mean (min, max)	3.80 (0-85)	4.0 (0-85)	2.6 (0-85)	4.6 (0-85)

- The mean age±SD of the population was 51±13 years, 58% were male, 21% had diabetes mellitus, 9% had coronary heart disease, and the median time since last kidney transplantation was 72 months.
- Serum leptin levels showed moderate negative correlation with eGFR(R=-0.21, p<0.001) and positive correlations with BMI(R=0.48, p<0.001) and C-reactive protein(R=0.20, p<0.001).
- There were 180 deaths over a median follow-up period of 76 months; the rate of death with a functioning graft was 36/1000 patient-years (95%CI: 31-41).
- Patients` survival curves in the lowest serum leptin tertile separated from their counterparts with higher serum leptin levels indicating better survival for patients with lower leptin levels (**Figure 1**).
- Each 10 ng/ml higher serum leptin level was associated with 7% lower risk of death with functioning graft(Hazard Ratio (HR) (95%CI): 0.93 (0.87-0.99)), and this association persisted after adjustment for confounders: HR (95%CI): 0.90 (0.84-0.98) (**Figure 2**).

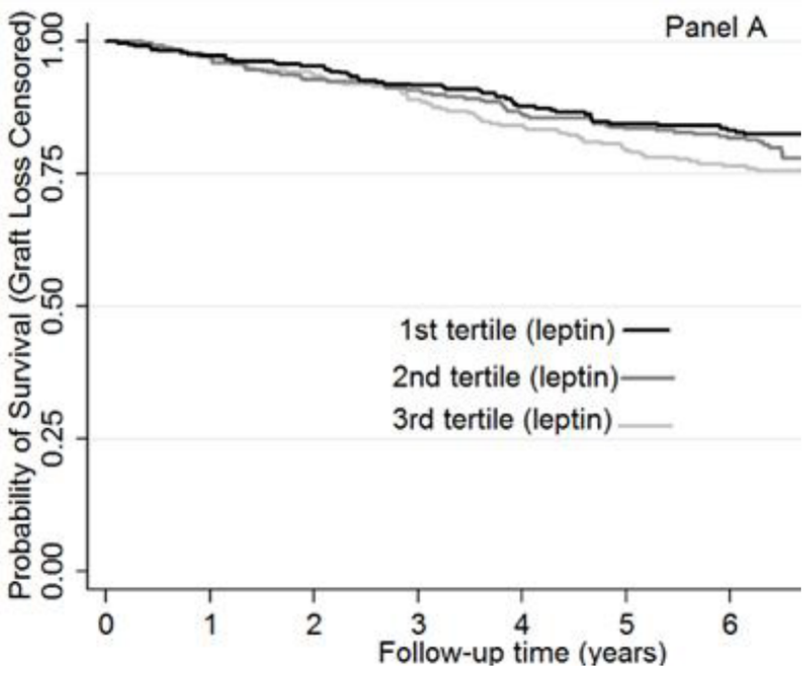


Figure 1: Kaplan Meier curves showing the association between serum leptin tertiles and death with a functioning graft for 979 kidney transplant recipients.

Figure 2: Association of serum leptin levels with death with functioning graft in adjusted Cox proportional regression models in 979 kidney transplant recipients.

- Similar associations were found with all-cause death as outcome.
- The association between serum leptin level and risk of graft loss was non-linear, and only low serum leptin level was associated with higher risk of graft loss.
- In subgroup analyses tests of interactions were statistically significant in some subgroups indicating effect modification by residual renal function and BMI (**Figure 3**).

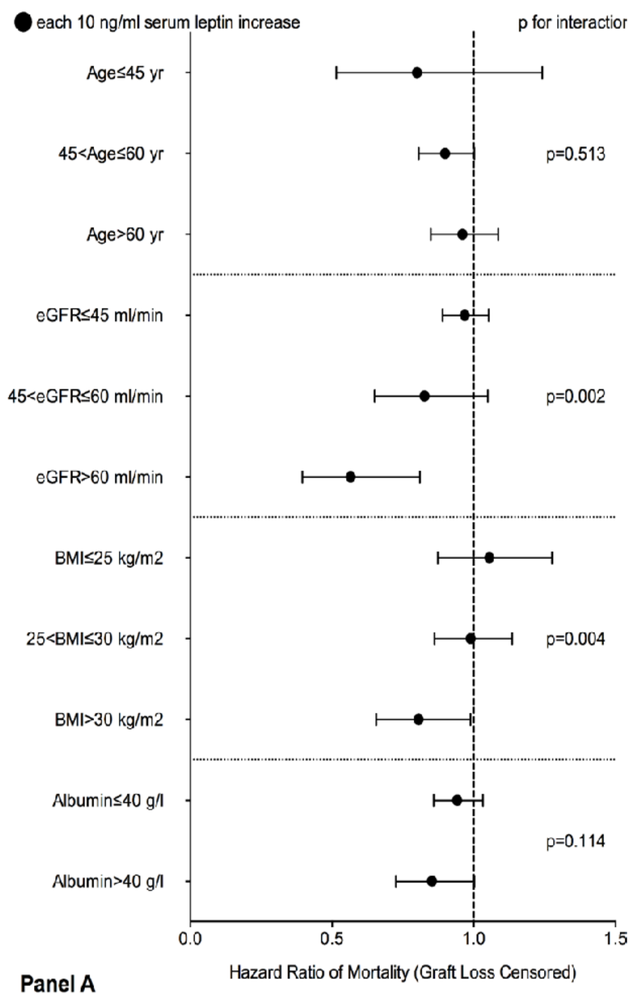


Figure 3. : Association of serum leptin levels with death with functioning graft in adjusted Cox proportional regression models in different subgroups.

Conclusions

- Serum leptin showed significant associations with residual graft function, BMI and C-reactive protein.
- In addition, we reported strong, inverse linear associations between serum leptin level and mortality, however only low serum leptin level showed association with graft loss.
- BMI and graft function were strong effect modifiers for the association between serum leptin and risk of death.

Acknowledgements

The authors thank the patients and the staff in the Department of Transplantation and Surgery, Semmelweis University, Budapest, Hungary.
This study was supported by grants from the National Research Fund (OTKA) **(F-68841; KTIA-OTKA-EU 7KP-HUMAN-MB08-A-81231)**, ETT (206/09).

Reference: Molnar MZ et al.; Association between serum leptin level and mortality in kidney transplant recipients; Under review

DOI: 10.3252/pso.eu.53era.2016
ePosters supported by F. Hoffmann- La Roche Ltd.