SERUM LEPTIN, INTIMAL THICKNESS, MEDIAL FIRBOSIS, AND ARTERIOVENOUS FISTULA MATURATION FAILURE

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Objectives

- Adequate maturation of arteriovenous fistula (AVF) is crucial for maintaining long-term hemodialysis.
- Pre-existing vascular diseases such as intimal hyperplasia or medial fibrosis in the native veins of uremic patients may predispose AVF maturation failure.
- However, the pathogenetic mechanisms of pre-existing venous neointimal hyperplasia at the time of arteriovenous (AV) access creation on final clinical success is currently unknown.
- Recently, a growing proportion of incident dialysis patients are obese, and leptin is regarded as a pivotal mediator between obesity and cardiovascular disease.
- This study is designed to explore the association between serum leptin and pre-existing vascular disease and AVF maturation failure in patients with end-stage renal disease (ESRD).

Methods

- Vein samples from 62 patients were collected at the time of AV access creation near the site of AV anastomosis.
- Early and late primary maturation failure was defined as the failure to use AVF successfully by 3 months and 6 months after its creation, respectively.
- Histological (Hematoxylin and eosin stain [H&E] and trichrome staining), immunohistochemistry (α-smooth muscle actin [SMA], vimentin and desmin staining to identify intrinsic cells of the vascular wall) were performed on these vein samples.
- Furthermore, we analyzed expression of the leptin receptor in vascular specimen using immunohistochemistry and western blot analysis.

Results

- Mean age was 62.8 ± 13.5 years, 38 (61.3%) were male, and the prevalence of diabetes 61.3% (n=38).
- Mean BMI was 25.4 ± 5.0 and the prevalence of obesity (BMI ≥25 kg/m2) was 46.8% (n=29).
- Mean serum leptin levels were 2.02 ± 1.37 pg/mL (log transformed), and patients in the highest leptin tertile had significantly increased BMI, higher triglyceride, hs-CRP, and TGF-β level but decreased HDL levels than those in the two lower tertiles (P<001), suggesting metabolic loads.

Table 1. Baseline characteristics according to leptin tertiles

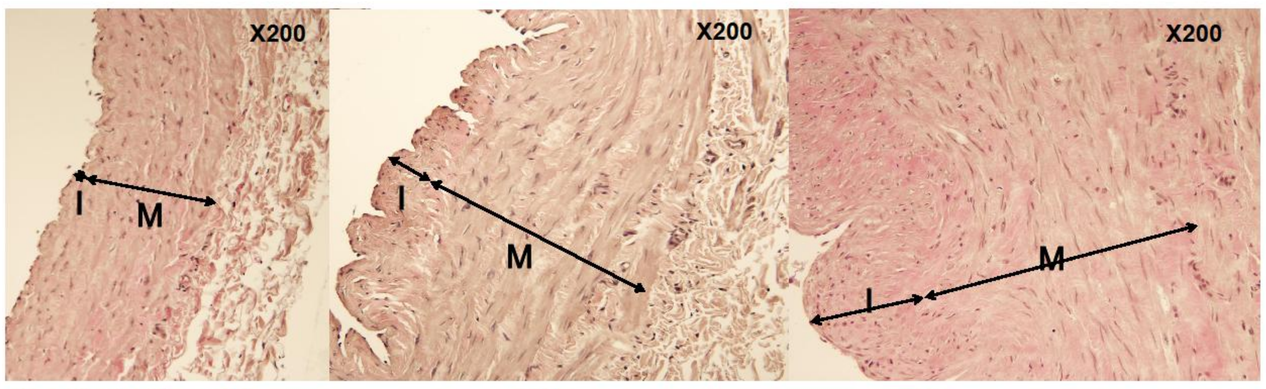
Characteristics	Total (n=62)	ln_leptin, tertiles T1 (n=20)	T2 (n=21)	T3 (n=21)	P
Leptin*	2.02 ± 1.43	0.33 ± 0.50	2.01 ± 0.47	3.70 ± 0.45	<0.001
Age (year)	62.8 ± 13.5	62.6 ± 12.0	66.6 ± 13.6	59.0 ± 14.0	0.405
Gender, male (%)	38 (61.3)	18 (85.7)	13 (61.9)	7 (35.0)	0.001
Diabetes mellitus, n (%)	38 (61.3)	9 (45.0)	14 (66.7)	15 (71.4)	0.035
Systolic BP (mmHg)	137.6 ± 17.3	137.1 ± 11.2	136.0 ± 21.3	139.4 ± 18.4	0.641
Diastolic BP (mmHg)	79.0 ± 9.5	80.0 ± 8.6	78.5 ± 9.8	78.5 ± 10.3	0.625
Body mass index (kg/m²)	25.6 ± 5.0	22.9 ± 3.6	24.2 ± 3.3	29.5 ± 5.3	<0.001
Laboratory parameters					
Hemoglobin (g/dL)	9.19 ± 1.62	9.19 ± 1.63	9.13 ± 1.49	9.27 ± 1.82	0.883
Albumin (g/dL)	3.48 ± 0.58	3.50 ± 0.62	3.48 ± 0.54	3.46 ± 0.54	0.125
Total cholesterol (mg/dL)	161.3 ± 47.1	165.5 ± 61.4	160.7 ± 40.7	157.8 ± 39.0	0.114
LDL cholesterol (mg/dL)	94.7 ± 37.9	97.4 ± 45.8	97.4 ± 43.8	89.6 ± 20.5	0.567
HDL cholesterol (mg/dL)	44.5 ± 15.5	52.5 ± 19.4	42.0 ± 12.0	38.3 ± 9.1	0.004
Triglyceride (mg/dL)	131.0 ± 78.3	102.4 ± 64.7	128.4 ± 60.9	152.7 ± 85.3	0.006
hs-CRP (mg/L)	0.49 ± 1.03	0.01 ± 0.61	0.32 ± 1.05	1.14 ± 1.05	0.001
TGF-β (pg/mL)	8.75 ± 0.47	8.59 ± 0.58	8.68 ± 0.46	9.00 ± 0.18	0.033
Intra-op findings					
Diameter of vein, mm	2.88 ± 0.62	3.01 ± 0.72	2.94 ± 0.59	2.69 ± 0.51	0.088
Diameter of artery, mm	3.37 ± 0.98	3.19 ± 1.01	3.63 ± 0.98	2.96 ± 0.65	0.535
Intraoperative blood flow (mL/min)	255.4 ± 106.3	282.1 ± 93.4	269.3 ± 110.5	213.4 ± 106.3	0.043

- Early and late maturation failure was occurred in 28 and 10 patients, respectively. As the higher leptin tertiles, the higher risk of maturation failure.

Table 2. Fistula outcomes according to leptin tertiles

Primary maturation failure	Total	ln_leptin, tertiles T1 (n=20)	T2 (n=21)	T3 (n=21)	P
Early, n (%)	28 (45.2)	5 (25.0)	8 (38.1)	15 (71.4)	0.007
Late, n (%)	10 (16.1)	2 (10.0)	3(14.3)	5 (23.8)	0.047

Figure 1. H&E staining of vessels according to leptin tertiles

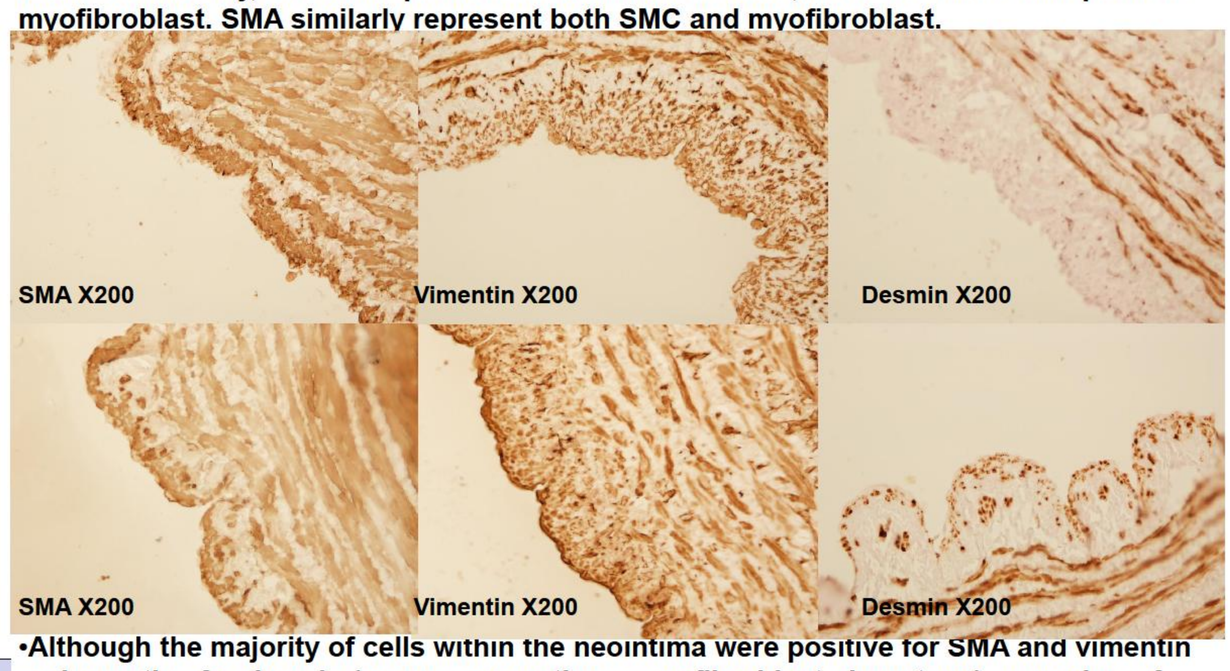


Leptin tertiles: T1 T2 T3

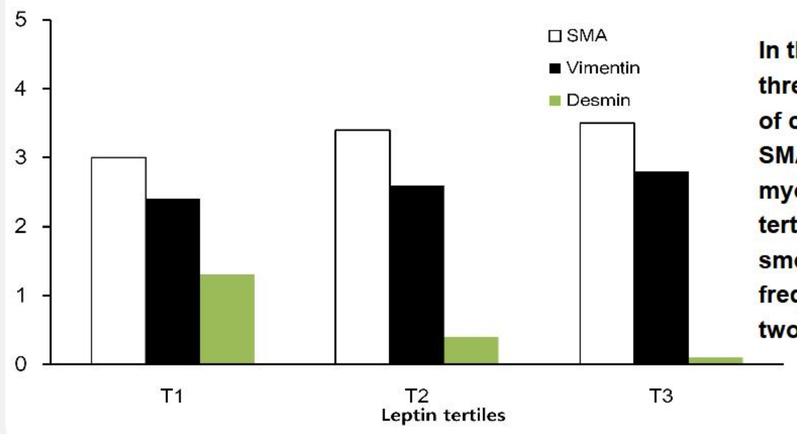
Table 3. Histopathologic findings of cephalic vein according to leptin tertiles

Primary maturation failure	Total	ln_leptin, tertiles T1 (n=20)	T2 (n=21)	T3 (n=21)	P
Average thickness					
Intima	19.4 ± 10.5	13.5 ± 6.9	18.9 ± 7.25	25.9 ± 12.9	<0.001
Media	97.2 ± 34.5	76.8 ± 23.7	103.9 ± 33.6	109.3 ± 36.5	0.002
Medial fibrosis	1.87 ± 0.85	1.61 ± 0.77	1.85 ± 0.98	2.16 ± 0.71	0.042

- In patients with higher leptin tertiles, significant degree of intimal hyperplasia and medial fibrosis were present in cephalic vein at the time of AV access creation.
- Furthermore, we evaluated cellular phenotype scores of the neointima by staining for SMA, Vimentin and Desmin , and made grade using a semiquantatitve scoring scale from 0 to 4+. Generally, Desmin represent smooth muscle cells, whereas Vimentin represent myofibroblast. SMA similarly represent both SMC and myofibroblast.

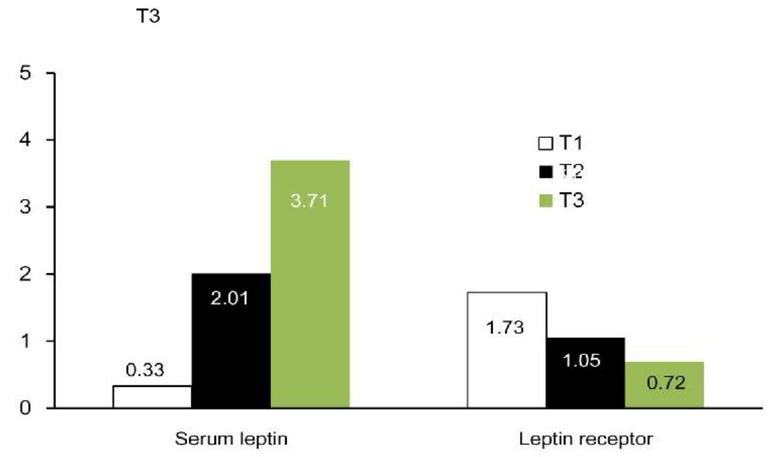


- Although the majority of cells within the neointima were positive for SMA and vimentin and negative for desmin (upper, suggesting a myofibroblast phenotype), a number of vascular sections in lowest leptin tertile also had desmin-positive cells suggesting contractile smooth muscle cells (lower).



In the most specimens across the three tertiles of leptin, the majority of cells in the intima appears to be SMA-positive, vimentin-positive myofibroblast. Particularly, in lowest tertile of leptin, desmin-positive smooth muscle cells more frequently observed than those in two upper tertiles of leptin.

Furthermore, immunohistochemical staining of leptin receptor showed significant inverse relationship with serum leptin level, suggesting leptin resistance in obese population.



Conclusions

Higher serum leptin levels are closely related to significant degree of preexisting vascular disease, and these changes may increase the risk of AVF maturation failure. Obesity related fistula complications may be mediated by high leptin level - associated preexisting vascular diseases in ESRD patients.

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