Supplementary Table 1. Clinical characteristics of type 2 diabetic patients

	Controls		Type 2 Diabetics			
		p	All	Without Complications	p	With Complications
N	45		80	36		44
Sex (%male)	59.3%	0.300	49.4%	39.6%	0.026	65.6%
Ethnicity (%white)	79.6%	0.088	65.9%	62.3%	0.480	71.9%
Age (years)	43 ± 13	0.000	52 ± 9	50 ± 9	0.028	55 ± 7
Blood pressure (mmHg)						
Systolic	124 ± 16	0.020	132 ± 20	128 ± 17	0.046	138 ± 23
Diastolic	79 ± 9	0.260	81 ± 14	80 ± 11	0.330	83 ± 18
Hypertension (%Dx)	7.7%	0.000	40.5%	25.0%	0.000	65.6%
LAE(mL/mmHg x 10)	18.8 ± 5.4	0.048	16.8 ± 5.9	16.5 ± 5.3	0.540	17.3 ± 6.7
SAE(mL/mmHg x 10)	8.3 ± 4.0	0.000	6.0 ± 3.2	6.3 ± 3.1	0.250	5.5 ± 3.4
Duration of DM (years)			7 ± 8	6 ± 8	0.580	8 ± 10
BMI (kg/m2)	28.3 ± 6.0	0.000	37.0 ± 8.4	36.5 ± 7.6	0.470	37.9 ± 9.7
HbA1c (%)	5.2 ± 0.4	0.000	7.7 ± 1.8	7.4 ± 1.6	0.081	8.1 ± 2.0
Fasting Glucose (mg/dL)	88.1 ± 10.6	0.000	141.6 ± 68.5	127.0 ± 53.4	0.026	165.6 ± 83.5
Serum Creatinine (mmol/L)	0.9 ± 0.2	0.350	1.0 ± 0.7	1.0 ± 0.9	0.770	0.9 ± 0.2
ACR (mg/mmol)	9.5 ± 17.6	0.001	34.8 ± 69.4	10.9 ± 7.4	0.001	74.3 ± 101.9
AST (units/L)	26.1 ± 8.0	0.120	28.7 ± 11.1	27.6 ± 9.1	0.270	30.6 ± 13.8
ALT (units/L)	31.3 ± 12.6	0.610	33.2 ± 15.3	32.0 ± 14.4	0.320	39.6 ± 20.2
Total Cholesterol (mmol/L)	180.3 ± 37.1	0.480	185.3 ± 42.1	184.2 ± 39.2	0.760	187.1 ± 47.1
Triglycerides (mmol/L)	94.9 ± 58.3	0.000	176.6 ± 135.2	153.0 ± 105.1	0.039	216.1 ± 169.2
LDL Cholesterol (mmol/L)	113.5 ± 32.1	0.560	110.0 ± 35.4	113.1 ± 34.5	0.310	104.6 ± 36.9
HDL Cholesterol (mmol/L)	47.8 ± 15.6	0.013	41.7 ± 10.7	42.4 ± 11.6	0.480	40.6 ± 8.8
Smoking (%current)	15.1%	0.990	16.5%	15.1%	0.770	18.8%
Alcohol use (%none)	50.9%	0.38	59.5%	55.8%	0.490	65.6%
Vitamin use (%yes)	31.5%	0.079	47.1%	47.2%	0.990	46.9%
Lipid drug use (%yes)	3.8%	0.000	36.5%	22.6%	0.001	59.4%
BP drug use (%yes)	7.4%	0.000	56.0%	42.3%	0.001	78.1%
Aspirin use (%yes)	11.5%	0.000	43.5%	35.8%	0.075	56.3%
Microvascular complications (%)	0%	0.000	32.9%	0%	0.000	87.5%
peripheral neuropathy	0%	0.000	18.1%	0%	0.000	46.9%
retinopathy	0%	0.006	11.8%	0%	0.000	31.2%
nephropathy	0%	0.005	20.0%	0%	0.000	53.1%
autonomic dysfunction	0%	0.290	3.6%	0%	0.054	9.4%
Macro Vasc complications	0%	0.006	11.8%	0%	0.000	31.3%
PVD	0%	0.300	4.7%	0%	0.018	12.5%

BP = blood pressure; LAE = large artery elasticity; SAE = small artery elasticity; BMI = body mass index; ACR = albumin-to-creatinine ratio; AST = aspartate aminotransferase; ALT = alanine aminotransferase; Cx = complications

Supplementary Table 2. Clinical correlations between serum kallistatin levels and HbA1c, albumin-to-creatinine ratio, large artery elasticity, and small artery elasticity.

Supplemental Table 2 (continued), Non-diabetic control subjects, N=45

		KS	HBa1c	ACR	LAE	SAE	logKS	logACR	logLAE	logSAE
KS	Pearson Correlation	1	-.150	.194	.065	-.080	.938	.211	.113	-.053
	Sig. (2-tailed)		.285	.164	.651	.575	.000	.168	.431	.711
HBa1c	Pearson Correlation	-.150	1	.327	-.055	-.112	-.133	.206	-.045	-.202
	Sig. (2-tailed)	.285		.017	.705	.438	.344	.179	.754	.158
ACR	Pearson Correlation	.194	.327	1	.060	-.216	.237	.846	.088	-.321
	Sig. (2-tailed)	.164	.017		.679	.132	.088	.000	.542	.023
LAE	Pearson Correlation	.065	-.055	.060	1	.327	.055	-.007	.970	.337
	Sig. (2-tailed)	.651	.705	.679		.019	.700	.963	.000	.016
SAE	Pearson Correlation	-.080	-.112	-.216	.327	1	-.121	-.269	.393	.946
	Sig. (2-tailed)	.575	.438	.132	.019		.397	.089	.004	.000
logKS	Pearson Correlation	.938	-.133	.237	.055	-.121	1	.286	.103	-.088
	Sig. (2-tailed)	.000	.344	.088	.700	.397		.060	.471	.541
logACR	Pearson Correlation	.211	.206	.846	-.007	-.269	.286	1	.026	-.312
	Sig. (2-tailed)	.168	.179	.000	.963	.089	.060		.874	.047
logLAE	Pearson Correlation	.113	-.045	.088	.970	.393	.103	.026	1	.399
	Sig. (2-tailed)	.431	.754	.542	.000	.004	.471	.874		.004
logSAE	Pearson Correlation	-.053	-.202	-.321	.337	.946	-.088	-.312	.399	1
	Sig. (2-tailed)	.711	.158	.023	.016	.000	.541	.047	.004	

Supplemental Table 2 (continued), Diabetics (all), N=80

		KS	HBa1c	ACR	LAE	SAE	logKS	logACR	logLAE	logSAE
KS	Pearson Correlation	1	.280	.316	.036	-.119	.959	.221	.043	-.139
	Sig. (2-tailed)		.009	.003	.746	.278	.000	.045	.697	.203
HBa1c	Pearson Correlation	.280	1	.210	-.075	-.076	.245	.298	-.145	-.139
	Sig. (2-tailed)	.009		.053	.497	.490	.024	.006	.184	.203
ACR	Pearson Correlation	.316	.210	1	.041	-.156	.267	.834	-.003	-.173
	Sig. (2-tailed)	.003	.053		.710	.153	.013	.000	.982	.113
LAE	Pearson Correlation	.036	-.075	.041	1	.413	.075	.014	.974	.423
	Sig. (2-tailed)	.746	.497	.710		.000	.498	.898	.000	.000
SAE	Pearson Correlation	-.119	-.076	-.156	.413	1	-.138	-.257	.431	.954
	Sig. (2-tailed)	.278	.490	.153	.000		.209	.019	.000	.000
logKS	Pearson Correlation	.959	.245	.267	.075	-.138	1	.179	.092	-.159
	Sig. (2-tailed)	.000	.024	.013	.498	.209		.105	.403	.145
logACR	Pearson Correlation	.221	.298	.834	.014	-.257	.179	1	-.036	-.264
	Sig. (2-tailed)	.045	.006	.000	.898	.019	.105		.747	.016
logLAE	Pearson Correlation	.043	-.145	-.003	.974	.431	.092	-.036	1	.454
	Sig. (2-tailed)	.697	.184	.982	.000	.000	.403	.747		.000
logSAE	Pearson Correlation	-.139	-.139	-.173	.423	.954	-.159	-.264	.454	1
	Sig. (2-tailed)	.203	.203	.113	.000	.000	.145	.016	.000	

Supplemental Table 2 (continued), Diabetic without complications, N=36

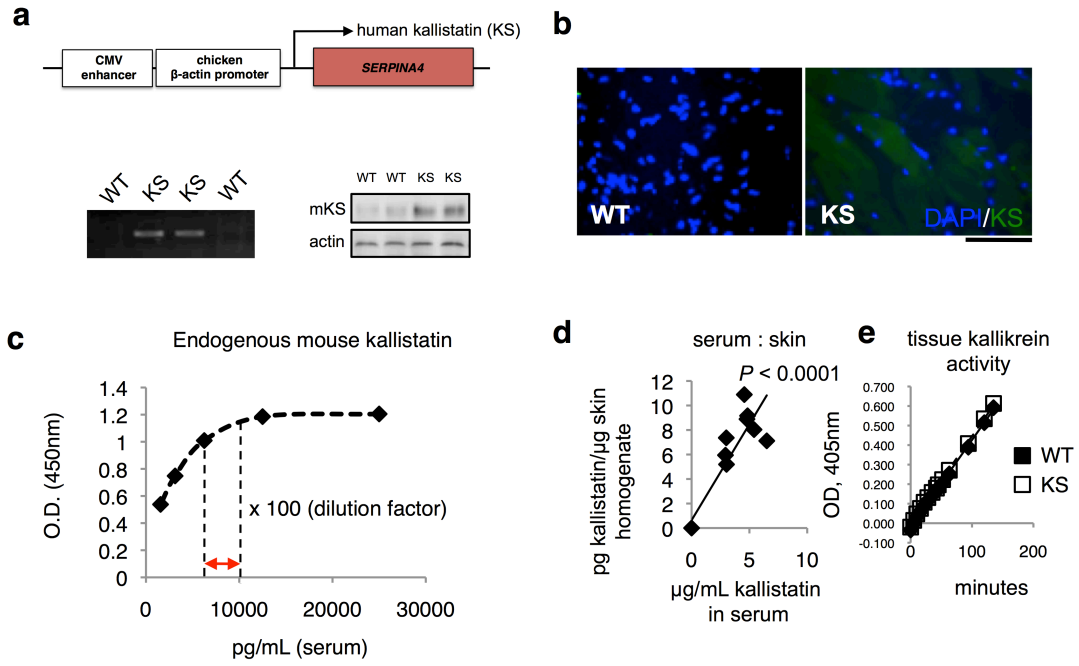
		KS	HBa1c	ACR	LAE	SAE	logKS	logACR	logLAE	logSAE
KS	Pearson Correlation	1	.485	.281	-.306	-.082	.958	.185	-.293	-.101
	Sig. (2-tailed)		.005	.119	.088	.654	.000	.312	.104	.583
HBa1c	Pearson Correlation	.485	1	.184	-.080	.151	.494	.270	-.156	.017
	Sig. (2-tailed)	.005		.312	.662	.409	.004	.135	.395	.927
ACR	Pearson Correlation	.281	.184	1	.025	-.153	.230	.855	-.023	-.167
	Sig. (2-tailed)	.119	.312		.890	.404	.205	.000	.901	.360
LAE	Pearson Correlation	-.306	-.080	.025	1	.560	-.285	.035	.973	.584
	Sig. (2-tailed)	.088	.662	.890		.001	.114	.849	.000	.000
SAE	Pearson Correlation	-.082	.151	-.153	.560	1	-.066	-.224	.545	.937
	Sig. (2-tailed)	.654	.409	.404	.001		.719	.219	.001	.000
logKS	Pearson Correlation	.958	.494	.230	-.285	-.066	1	.121	-.260	-.081
	Sig. (2-tailed)	.000	.004	.205	.114	.719		.509	.150	.660
logACR	Pearson Correlation	.185	.270	.855	.035	-.224	.121	1	-.023	-.253
	Sig. (2-tailed)	.312	.135	.000	.849	.219	.509		.902	.162
logLAE	Pearson Correlation	-.293	-.156	-.023	.973	.545	-.260	-.023	1	.604
	Sig. (2-tailed)	.104	.395	.901	.000	.001	.150	.902		.000
logSAE	Pearson Correlation	-.101	.017	-.167	.584	.937	-.081	-.253	.604	1
	Sig. (2-tailed)	.583	.927	.360	.000	.000	.660	.162	.000	

Diabetics with complications, N=44

		KS	HBa1c	ACR	LAE	SAE	logKS	logACR	logLAE	logSAE
KS	Pearson Correlation	1	-.037	-.140	.376	-.087	.964	-.175	.380	-.094
	Sig. (2-tailed)		.791	.316	.006	.537	.000	.219	.005	.504
HBa1c	Pearson Correlation	-.037	1	.241	-.098	-.216	-.063	.235	-.155	-.215
	Sig. (2-tailed)	.791		.082	.487	.121	.654	.096	.266	.122

ACR	Pearson Correlation	-.140	.241	1	-.079	-.218	-.132	.968	-.088	-.182
	Sig. (2-tailed)	.316	.082		.574	.117	.348	.000	.530	.191
LAE	Pearson Correlation	.376	-.098	-.079	1	.319	.361	-.132	.975	.329
	Sig. (2-tailed)	.006	.487	.574		.020	.008	.355	.000	.016
SAE	Pearson Correlation	-.087	-.216	-.218	.319	1	-.132	-.276	.359	.965
	Sig. (2-tailed)	.537	.121	.117	.020		.345	.050	.008	.000
logKS	Pearson Correlation	.964	-.063	-.132	.361	-.132	1	-.158	.377	-.145
	Sig. (2-tailed)	.000	.654	.348	.008	.345		.269	.005	.300
logACR	Pearson Correlation	-.175	.235	.968	-.132	-.276	-.158	1	-.151	-.221
	Sig. (2-tailed)	.219	.096	.000	.355	.050	.269		.290	.119
logLAE	Pearson Correlation	.380	-.155	-.088	.975	.359	.377	-.151	1	.363
	Sig. (2-tailed)	.005	.266	.530	.000	.008	.005	.290		.007
logSAE	Pearson Correlation	-.094	-.215	-.182	.329	.965	-.145	-.221	.363	1
	Sig. (2-tailed)	.504	.122	.191	.016	.000	.300	.119	.007	

HbA1c= glycosylated hemoglobin; ACR = albumin-to-creatinine ratio; LAE = large artery elasticity; SAE = small artery elasticity. Combined male and female data shown. Pearson Correlations and P-values are indicated.



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SERPINA4   41   ETGEGSPSLKIAPANADFAFRFYYLIASETPGKNIFFSPLSISAAYAMLSLGACSHSRSQ  100
                E G    SL +A  N DFAF  Y  +A + P  NI FSPLSISAA A++SLGA  ++  +
SERPINA3C  37   ENGTQLDSLTLASINTDFAFSLYKKLALKNPDTNIVFSPLSISAALAIVSLGAKGNTLEE  96

           101  ILEGLGFNLTELSESDVHRGFQHLLHTLNLPGHGLETRVGSALFLSHNLKFLAKFLNDTM  160
                ILEGL FNLTE  E+D+H+GF HLL  L+ PG  ++   GSALF+  +L+ LA+F
           97   ILEGLNFNLTETPEADIHQGFGHLLQRLSHPGEQVQISTGSALFVEKHLQILAEFQEKAR  156

           161  AVYEAKLFHTNFYDTVGTIQLINDHVKKETRGKIVDLVSELKKDVLMVLVNYIYFKALWE  220
                A+Y+A+ F  +F   +   +LIND+V  +T+GKI  L+S+L  D LMVLVNYIYFK  W+
           157  ALYQAEAFTADFQQPLEATKLINDYVSNQTQGKIKGLISDLDTDTLMVLVNYIYFKGKWK  216

           221  KPFISSRTTPKDFYVDENTTVRVPMMLQDQEHHWYLHDRYLPCSVLRMDYKGDATVFFIL  280
                 PF    T   +FY+D   +V+VPMM        Y  D  L C+V+ + YKG+A+  FIL
           217  MPFNPRDTFESEFYLDVKRSVKVPMMKIKTLTTPYFRDEELSCTVVELKYKGNASALFIL  276

           281  PNQGKMREIEEVLTPEMLMRWNNLLRKRNFYKKLELHLPKFSISGSYVLDQILPRLGFTD  340
                P+QG+M+++E  L PE L +W N LR R   K  EL+LPKFSIS  Y L  ILP LG  +
           277  PDQGRMQQVEASLQPETLRKWKNSLRPR---KMGELYLPKFSISTDYSLKNILPELGIKE  333

           341  LFSKWADLSGITKQQKLEASKSFHKATLDVDEAGTEAAAATSFAIKFFSAQTNRHILRFN  400
                +FS  ADLSGIT  + L  S+  HK  LDV E GTE  AAT    +  S +T+   L FN
           334  IFSNQADLSGITGTKDLIVSQMVHKVVLDVAETGTEGVAATGVNFRILSRRTS---LWFN  390

           401  RPFLVVIFSTSTQSVLFLGKVVDPTK  426
                RPFL+VI  T  Q+ LF+ K+  P +
           391  RPFLMVISHTDVQTTLFIAKITHPKR  416
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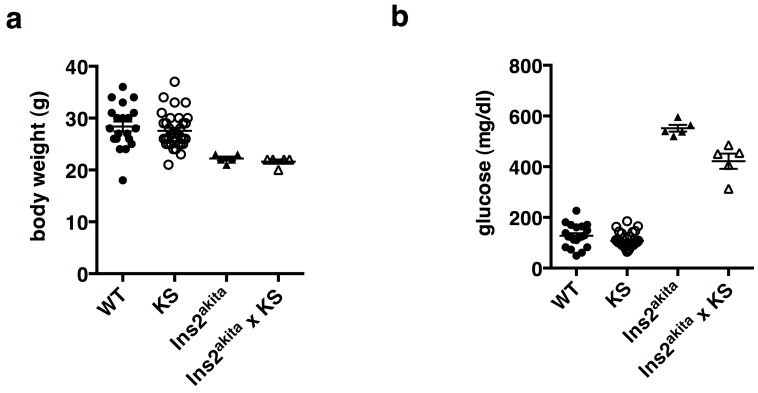
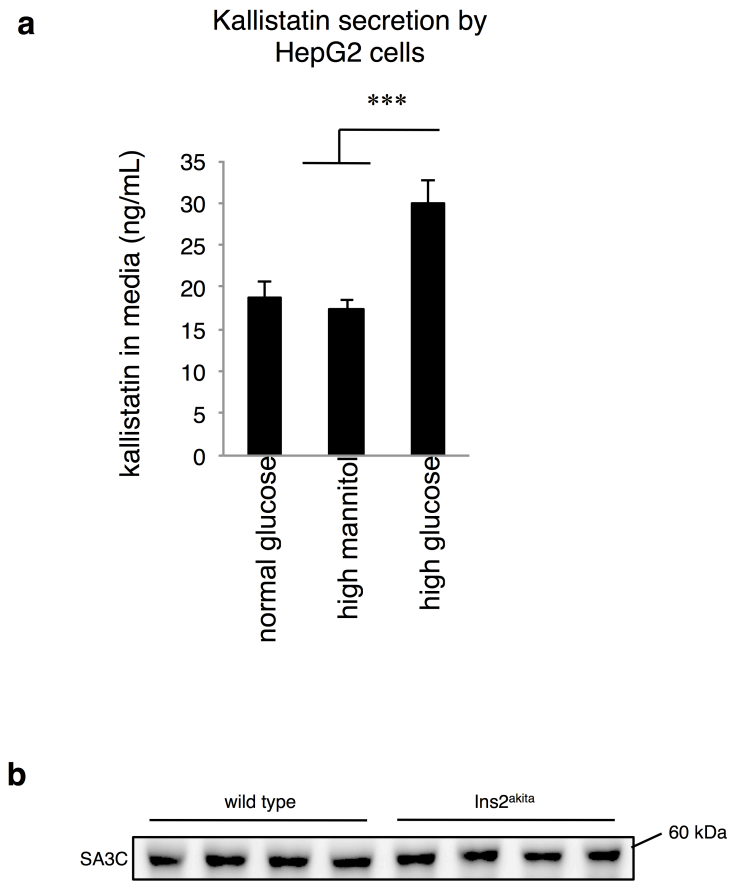
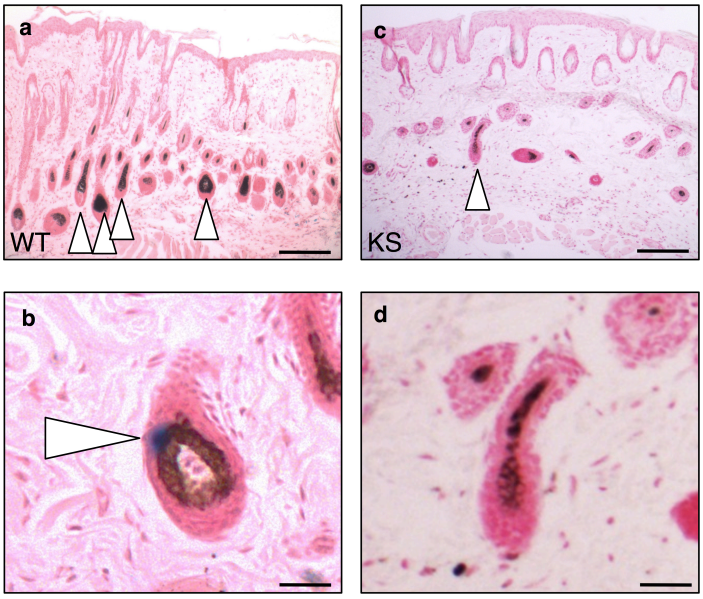
Supplemental Figure 1. Generation of KS-TG mice overexpressing kallistatin. (a) Transgene construct for human kallistatin. Shown below are genotyping and Western blotting in tissue using antibody recognizing both mouse and human kallistatin. **(b)** Images of WT and KS-TG mouse tissue (in this case wound beds at day 7) immunostained with an FITC-conjugated monoclonal antibody specific for human kallistatin in wound beds. Scale bar = 50 µm. **(c)** ELISA detecting endogenous mouse kallistatin (recombinant SERPINA3C). Vertical dotted lines delineate range of kallistatin detectable in serum of 3-month-old WT C57BL/6 mice diluted 1:100, indicating endogenous mouse kallistatin concentrations to be approximately 1 µg/mL in sera. **(d)** Serum levels of human kallistatin correlate with its levels in the skin, as measured in an ELISA that recognizes and measures only human kallistatin (pg/mg total protein). **(e)** Tissue kallikrein activity detectable in serum (n=21 WT; n=36 KS-TG mice). **(f)** Amino acid sequence alignment of human kallistatin (SERPINA4) and mouse kallistatin (SERPINA3C). Red lines indicate residues for interactions with human tissue kallikrein and mouse tissue kallikrein.



Supplemental Figure 2. No significant differences in adult body weight or blood glucose levels between adult WT littermates and KS-TG mice and between Ins2^{akita} and Ins2^{akita} x KS-TG mice. (a) Body weight and **(b)** blood glucose concentrations of 3-month-old male WT (n=20), KS-TG (n=33), Ins2^{akita} (n= 5) and Ins2^{akita} x KS-TG (n=5) mice.



Supplemental Figure 3. High glucose induces immediate secretion of human kallistatin in liver-derived cells, but 3-month-old hyperglycemic Ins2^{akita} mice do not have higher levels of endogenous kallistatin in circulation. (a) Quantification of kallistatin secreted from HepG2 cells treated with normal glucose (5 mM), high mannitol (5 mM glucose + 20 mM mannitol), or high glucose (25 mM glucose) for 24 hr. **(b)** Western blot analysis of endogenous mouse kallistatin (SA3C) using sera from 3-month-old WT and Ins2^{akita} mice. Each lane represents an individual mouse.



Supplemental Figure 4. Attenuated depilation-induced anagen phase hair follicles in kallistatin transgenic mice. Representative images of skin of three-month old littermates 7 days after depilation; **(a)** WT mouse skin, **(b)** detectable Wnt activity in anagen hair follicle (blue), **(c)** KS-TG mouse skin, **(d)** lack of detectable Wnt activity in certain hair follicles following depilation. Scale bars: (a, c) = 200 μm; (b, d) = 50 μm.