SUPPLEMANTAL MATERIALS

Statins are associated with increased insulin resistance and secretion

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Supplementary Methods:

Study Participants

Volunteers were recruited from the San Francisco Bay Area through advertisements in newspapers, posted flyers, the social networking site NextDoor and the Preventive Cardiology Clinics at Stanford Health Care.

Study visits

Participants who responded to our advertisements were screened over the phone. Those that met screening criteria had an initial visit to be consented and determine if they qualified based on anthropomorphic measurements, medical history and laboratory test results.

Inclusion and exclusion criteria

Inclusion criteria were as follows: individuals aged 30-70 years with a BMI 20.0-36.0 kg/m^2, eligible for statin therapy for primary prevention of atherosclerotic cardiovascular disease (ASCVD) based on LDL cholesterol (LDL-C) ≥130 mg/dL, >5% risk of atherosclerotic cardiovascular disease (ASCVD) over 10 years(1), or high-sensitivity C-reactive protein (hs-CRP) ≥2.0 mg/L. Individuals who were receiving statin therapy were included if they were able to undergo a 4-week statin washout with approval of their treating physician.

Exclusion criteria included: diabetes (fasting glucose ≥126 mg/dL or on antidiabetic medications), current use of medications for weight loss or known to affect insulin sensitivity, history of cardiovascular disease (e.g. heart failure, ASCVD), malignant hypertension, anemia (hematocrit <30%), kidney disease (creatinine ≥1.5 mg/dL), liver disease (alanine

aminotransferase >2 times upper limit of normal), active malignancy, history of statin intolerance, pregnant, or lactating.

A pregnancy test was done prior to starting the atorvastatin in women who were of childbearing age and at weeks 4 and 8.

Participants were not given monetary compensation but were offered coaching from a certified dietitian for nutrition and weight loss counseling upon completion of the study.

BMI and Blood Pressure Assessment

Body mass index (BMI) was calculated as weight in kg divided by height in m^2, and waist circumference was measured at the midpoint between upper iliac crest and lower end of the rib cage in mid respiration while subjects were standing. Blood pressure was measured by using an automated blood pressure monitor with appropriately sized arm cuff. Before blood pressure measurement, participants sat quietly in a chair for 5 minutes with arm supported at the heart level. Three blood pressure measurements were obtained at one-minute intervals and the three measurements were averaged.

Oral Glucose Tolerance Test (OGTT)

Blood samples were collected for measurement of glucose and insulin before and at 30, 60, 90, and 120 minutes after the ingestion of a 75-gram oral glucose load. Trapezoidal method was used to calculate area under the curve (AUC) for glucose and insulin.

Graded Glucose Infusion Test (GGIT)

After an overnight fast, continuous intravenous infusions of glucose were given at progressively increasing rates: 1, 2, 3, 4, 5, 6, and 8 kg/min in six infusion periods of 40-minute duration.

Blood samples were collected for measurements of glucose, insulin, and C-peptide concentrations at fasting and at 30 minutes and 40 minutes into each infusion period. The two values during the last 10 minutes of each infusion period were averaged.(2) Insulin secretion rate was calculated by deconvolution of peripheral C-peptide concentrations by using a two-compartment model of C-peptide kinetics and parameters of C-peptide clearance, estimated for each participant by age and body surface area. The GGIT was performed using the same methodology for the duration of the trial by only two study personnel (F.A and C.L).

Insulin Suppression Test (IST)

After an overnight fast, a continuous intravenous infusion of octreotide acetate - an inhibitor of endogenous insulin secretion (0.27 μg/m^2/min), insulin (32 mU/m^2/min), and glucose (267 mg/m^2/min) was given for 180 minutes. Blood samples were collected every 30 minutes until 150 minutes into the infusion and then every 10 minutes to measure the steady-state plasma insulin (SSPI) and steady-state plasma glucose (SSPG) concentration.(3,4) The IST was performed using the same methodology for the duration of the trial by only two study personnel (F.A and C.L).

Laboratory Measurements

Insulin and C-peptide were measured by radioimmunoassay (Millipore, St. Charles, MO). The intra and inter-assay coefficient of variation ranged between 5.1-7.0% and 6.4-8.4% for insulin and 6.4-11% and 6.9-12.8% for C-peptide, respectively. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated by the following formula: (fasting insulin (mU/L) x fasting glucose (mmol/L))/22.5. LDL-cholesterol was calculated based on the Friedewald equation.

Supplementary Table I

Schedule of Study Visits

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12
	Week -3	Week -2	Week -1	Week 0	Week 2	Week 4	Week 6	Week 8	Week 9	Week 10	Week 14	Week 18
Screening	X											
Lipids	X			X						X	X	X
OGTT		X						X				
GGIT			X						X			
IST				X						X		
Follow-up					X	X	X				X	X
Atorvastatin 40 mg				Started						Stopped		

Individuals on a statin at the screening visit underwent a 4-week statin washout before the baseline metabolic tests.

GGIT indicates graded glucose infusion test; IST, insulin suppression test; and OGTT, oral glucose tolerance test.

Supplementary Table II

Baseline Characteristics of Study Subjects (N=71)

		Range
Age, years	61 (53 – 64)	35 – 70
Female, n (%)	26 (36.6)	
Race, n (%)		
African American	2 (2.8)	
East Asian	11 (15.5)	
Hispanic	4 (5.6)	
South Asian	6 (8.5)	
Two or more races	2 (2.8)	
White	46 (64.8)	
BMI, kg/m^2	27.8 (24.8 – 30.7)	20.3 – 36.6
Waist circumference, cm	99.0 (89.5 – 105.7)	77.5 – 127.8
Systolic BP, mm Hg	124 (114 – 132)	95 – 172
Diastolic BP, mm Hg	79 (74 – 84)	60 – 101
Heart rate, bpm	65 (58 – 72)	47 – 86
Prediabetes (abnormal glucose tolerance)	45 (63.4)	
Metabolic syndrome	29 (40.8)	

Data are median (interquartile range) unless otherwise indicated.

BMI indicates body mass index and BP, blood pressure.

Supplementary Table III

Correlations Among Baseline Variables

		Insulin Resistance (by SSPG)	Insulin Secretion (by ISR_{AUC})	Triglycerides	HDL-C
SSPG	Pearson Correlation	1	0.68	0.45	-0.32
	Sig. (2-tailed)		<0.001	<0.001	0.007
	N	71	64	71	71
ISR_{AUC}	Pearson Correlation	0.68	1	0.46	-0.58
	Sig. (2-tailed)	<0.001		<0.001	<0.001
	N	64	64	64	64
FPG	Pearson Correlation	0.37	0.46	0.31	-0.27
	Sig. (2-tailed)	0.002	<0.001	0.01	0.02
	N	71	64	71	71
FPI	Pearson Correlation	0.74	0.80	0.44	-0.48
	Sig. (2-tailed)	<0.001	<0.001	<0.001	<0.001
	N	69	64	69	69
HOMA-IR	Pearson Correlation	0.75	0.81	0.46	-0.49
	Sig. (2-tailed)	<0.001	<0.001	<0.001	<0.001
	N	69	64	69	69
OGTT $Glucose_{AUC}$	Pearson Correlation	0.46	0.31	0.23	-0.22
	Sig. (2-tailed)	<0.001	0.01	0.06	0.06
	N	71	64	71	71
OGTT $Insulin_{AUC}$	Pearson Correlation	0.72	0.77	0.29	-0.38
	Sig. (2-tailed)	<0.001	<0.001	0.02	0.002
	N	64	63	64	64
Triglycerides	Pearson Correlation	0.45	0.46	1	-0.45
	Sig. (2-tailed)	<0.001	<0.001		<0.001
	N	71	64	71	71
HDL-C	Pearson Correlation	-0.32	-0.58	-0.45	1
	Sig. (2-tailed)	0.01	<0.001	<0.001	
	N	71	64	71	71

SSPG, ISR_{AUC}, FPI, HOMA-IR, OGTT $Insulin_{AUC}$, and triglyceride values were log-transformed.

AUC indicates area under the curve; FPG, fasting plasma glucose; FPI, fasting plasma insulin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; ISR, insulin secretion rate; OGTT, oral glucose tolerance test; and SSPG, steady-state plasma glucose.

Supplementary Table IV

Effect of Atorvastatin on Weight, Lipids and hs-CRP (N=71*)

Variable	Baseline	End of Study	Percent Change	*P* value†
Weight, kg	83.1 (70.6 – 95.6)	84.7 (68.4 – 93.3)	0.1 (-0.9 – 1.3)	0.92
Total cholesterol, mg/dL	237 (205 – 256)	149 (125 – 162)	-37 (-42 – -32)	<0.001
LDL cholesterol, mg/dL	156 (129 – 172)	69 (61 – 84)	-53 (-58 – -46)	<0.001
Triglycerides, mg/dL	109 (70 – 150)	78 (59 – 115)	-28 (-39 – -9)	<0.001
HDL cholesterol, mg/dL	51 (43 – 63)	53 (43 – 64)	0 (-8 – 9)	0.73
hs-CRP, mg/L	1.1 (0.6 – 2.3)	0.7 (0.4 – 1.8)	-20 (-52 – 0)	0.002

Data are median (interquartile range).

*LDL cholesterol (N=70) and hs-CRP (N=69).

Triglyceride and hs-CRP values were log-transformed. †Paired sample *t* tests were used to compare baseline and end-of-study means.

HDL indicates high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; and LDL, low-density lipoprotein.

Supplementary Table V

Baseline Characteristics of Study Subjects by Insulin Resistance Status

Variable	Insulin Sensitive (N=36)	Insulin Resistant (N=35)	*P* value*
Age, years	62 (56 – 67)	57 (50 – 63)	0.01
Female, n (%)	14 (38.9)	12 (34.3)	0.69
Race, n (%)			0.69
African American	1 (2.8)	1 (2.9)	
East Asian	3 (8.3)	8 (22.9)	
Hispanic	2 (5.6)	2 (5.7)	
South Asian	3 (8.3)	3 (8.6)	
Two or more races	1 (2.8)	1 (2.9)	
White	26 (72.2)	20 (57.1)	
BMI, kg/m^2	26.0 (24.0 – 28.4)	29.8 (27.1 – 33.2)	<0.001
Waist circumference, cm	94.5 (85.1 – 100.9)	104.0 (98.0 – 110.0)	<0.001
Systolic BP, mm Hg	120 (112 – 129)	129 (120 – 134)	0.10
Diastolic BP, mm Hg	79 (72 – 80)	83 (75 – 86)	0.01
Heart rate, bpm	62 (56 – 68)	70 (64 – 74)	0.001
Statin naïve	23 (63.9)	21 (60.0)	0.74

Data are median (interquartile range) unless otherwise indicated.

The steady-state plasma glucose (SSPG) concentration median (138 mg/dL) was used to define subjects as being insulin sensitive (SSPG ≤138 mg/dL) or insulin resistant (SSPG >138 mg/dL).

*Chi-square test or Fisher's exact test was used to compare proportions and independent samples *t* tests were used to compare means.

BMI indicates body mass index and BP, blood pressure.

Supplementary Table VI

Effect of Atorvastatin on Weight, Lipids and hs-CRP by Insulin Resistance Status

Variable	Insulin Sensitive (N=36)			Insulin Resistant (N=35*)			
	Baseline	End of Study	*P* value†	Baseline	End of Study	*P* value†	*P* value‡
Weight, kg	80.7 (64.4 – 88.2)	80.0 (64.1 – 88.8)	0.59	89.2 (75.6 – 100.8)	87.4 (76.6 – 105.9)	0.71	0.37
Total cholesterol, mg/dL	242 (213 – 259)	154 (136 – 164)	<0.001	231 (190 - 252)	133 (113 – 162)	<0.001	0.21
LDL cholesterol, mg/dL	162 (134 – 179)	75 (64 – 85)	<0.001	149 (119 – 163)	66 (58 – 77)	<0.001	0.67
Triglycerides, mg/dL	90 (66 – 121)	71 (54 – 91)	<0.001	122 (107 – 185)	90 (69 – 148)	<0.001	0.13
HDL cholesterol, mg/dL	61 (49 – 70)	60 (50 – 68)	0.64	46 (38 – 51)	47 (38 – 55)	0.91	0.89
hs-CRP, mg/L	0.7 (0.4 – 1.2)	0.5 (0.2 – 1.0)	0.08	1.7 (1.1 – 3.9)	0.9 (0.5 – 3.1)	0.01	0.97

Data are median (interquartile range).

The steady-state plasma glucose (SSPG) concentration median (138 mg/dL) was used to define subjects as being insulin sensitive (SSPG ≤138 mg/dL) or insulin resistant (SSPG >138 mg/dL).

*LDL cholesterol (N=34) and hs-CRP (N=33).

Triglyceride and hs-CRP values were log-transformed. †Paired sample *t* tests were used to compare baseline and end-of-study means in the insulin sensitive and insulin resistant groups. ‡Independent samples *t* tests were used to compare percent-change means between the insulin sensitive and insulin resistant groups.

HDL indicates high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; and LDL, low-density lipoprotein.

Supplementary Table VII

Effect of Atorvastatin on Insulin Resistance and Insulin Secretion by Insulin Resistance Status

Variable	Insulin Sensitive (N=36*)			Insulin Resistant (N=35†)			
	Baseline	End of Study	*P* value‡	Baseline	End of Study	*P* value‡	*P* value§
Primary Outcome							
Insulin Suppression Test							
Insulin Resistance (by SSPG, mg/dL)	86 (57 – 105)	93 (74 – 129)	<0.001	194 (167 – 247)	208 (154 – 252)	0.68	0.002
SSPI, mU/L	59.1 (50.5 – 66.5)	58.5 (49.0 – 64.1)	0.56	74.8 (61.2 – 88.2)	68.0 (59.7 – 82.1)	0.02	0.11
Graded Glucose Infusion Test							
Insulin Secretion (by ISR_{AUC}, pmol/min x 4 h)	1457 (937 – 1830)	1505 (1068 – 1879)	0.001	2414 (1812 – 3239)	2626 (2095 – 3274)	0.004	0.73
$Glucose_{AUC}$, mmol/L x 4 h	29.3 (26.8 – 32.1)	30.1 (27.4 – 33.8)	0.04	32.7 (29.9 – 34.9)	33.4 (29.3 – 35.6)	0.78	0.16
$Insulin_{AUC}$, pmol/L x 4 h	444 (277 – 562)	472 (336 – 607)	0.004	1104 (703 – 1466)	1221 (791 – 1584)	0.11	0.34
C-$peptide_{AUC}$, nmol/L x 4 h	5.3 (3.7 – 6.2)	5.5 (4.2 – 6.1)	0.002	8.2 (6.6 – 10.4)	8.6 (6.9 – 10.8)	0.01	0.51
Secondary Outcome							
Fasting glucose, mg/dL	97 (91 – 106)	97 (93 – 105)	0.03	103 (96 – 110)	103 (98 – 110)	0.60	0.47
Fasting insulin, mU/L	7.9 (5.1 – 9.5)	8.6 (6.3 – 10.0)	0.03	14.8 (10.6 – 20.9)	15.1 (12.8 – 21.8)	0.12	0.63
HOMA-IR	1.82 (1.25 – 2.39)	1.90 (1.54 – 2.62)	0.02	3.73 (2.70 – 5.49)	3.96 (3.05 – 5.56)	0.14	0.58
OGTT $Glucose_{AUC}$, mg/dL x 2 h	259 (218 – 306)	264 (246 – 301)	0.14	309 (292 – 347)	332 (281 – 364)	0.11	0.67
OGTT $Insulin_{AUC}$, mU/L x 2 h	88 (63 – 131)	90 (70 – 123)	0.63	213 (123 – 351)	217 (137 – 330)	0.31	0.46

Data are median (interquartile range).

The SSPG concentration median (138 mg/dL) was used to define subjects as being insulin sensitive (SSPG ≤138 mg/dL) or insulin resistant (SSPG >138 mg/dL).

*SSPI (N=33); ISR_{AUC}, $Glucose_{AUC}$, $Insulin_{AUC}$, and C-$peptide_{AUC}$ (N=32); fasting insulin and HOMA-IR (N=35); and OGTT $Insulin_{AUC}$ (N=32). †SSPG (N=34); SSPI (N=33), ISR_{AUC}, $Glucose_{AUC}$, $Insulin_{AUC}$, and C-$peptide_{AUC}$ (N=32); fasting insulin and HOMA-IR (N=34); and OGTT $Insulin_{AUC}$ (N=32).

All variables were log-transformed except fasting glucose and $glucose_{AUC}$. ‡Paired sample *t* tests were used to compare baseline and end-of-study means in the insulin sensitive and insulin resistant groups; §Independent samples *t* tests were used to compare percent-change means between the insulin sensitive and insulin resistant groups.

AUC indicates area under the curve; HOMA-IR, homeostasis model assessment of insulin resistance; ISR, insulin secretion rate; OGTT, oral glucose tolerance test; SSPG, steady-state plasma glucose; and SSPI, steady-state plasma insulin.

Supplementary Table VIII

Baseline Characteristics of Study Subjects by Glucose Tolerance Status

Variable	Normal Glucose Tolerance (N=26*)	Abnormal Glucose Tolerance (N=45†)	*P* value‡
Age, years	61 (52 – 63)	61 (53 – 64)	0.93
Female, n (%)	9 (34.6)	17 (37.8)	0.79
Race, n (%)			0.38
African American	0 (0)	2 (4.4)	
East Asian	4 (15.4)	7 (15.6)	
Hispanic	2 (7.7)	2 (4.4)	
South Asian	3 (11.5)	3 (6.7)	
Two or more races	2 (7.7)	0 (0)	
White	15 (57.7)	31 (68.9)	
BMI, kg/m^2	26.3 (23.5 – 29.4)	28.7 (25.9 – 31.0)	0.01
Waist circumference, cm	94.5 (85.4 – 102.1)	100.0 (94.5 – 107.8)	0.03
Total cholesterol, mg/dL	237 (199 – 255)	237 (207 – 259)	0.96
LDL cholesterol, mg/dL	156 (132 – 171)	153 (128 – 175)	0.65
Triglycerides, mg/dL	95 (60 – 145)	114 (81 – 169)	0.09
HDL cholesterol, mg/dL	55 (43 – 65)	51 (44 – 63)	0.55
Fasting glucose, mg/dL	94 (91 – 98)	104 (96 – 111)	<0.001
Fasting insulin, mU/L	8.2 (5.2 – 10.9)	11.0 (8.5 – 16.1)	0.003
Insulin resistance (by SSPG, mg/dL)	100 (58 – 151)	167 (100 – 224)	0.001
Insulin secretion (by ISR_{AUC}, pmol/min x 4 h)	1517 (1225 – 2083)	2030 (1530 – 2822)	0.03

Data are median (interquartile range) unless otherwise indicated.

Normal glucose tolerance was defined as presence of having fasting glucose <100 mg/dL and 2-hour OGTT glucose <140 mg/dL. Abnormal glucose tolerance was defined as presence of having fasting glucose ≥100 mg/dL, 2-hour OGTT glucose ≥140 mg/dL, or both.

*Fasting insulin and ISR_{AUC} (N=25). †LDL cholesterol and fasting insulin (N=44) and ISR_{AUC} (N=39).

Triglyceride, fasting insulin, SSPG, and ISR_{AUC} values were log-transformed. ‡Chi-square test or Fisher's exact test was used to compare proportions and independent samples *t* tests were used to compare means.

BMI indicates body mass index; HDL, high-density lipoprotein; ISR_{AUC}, insulin secretion rate area under the curve; LDL, low-density lipoprotein; and SSPG, steady-state plasma glucose.

Supplementary Table IX

Baseline Characteristics of Study Subjects by Diagnosis of the Metabolic Syndrome

Variable	Metabolic Syndrome		
	No (N=42*)	**Yes (N=29†)**	***P* value‡**
Age, years	61 (55 – 65)	57 (50 – 62)	0.09
Female, n (%)	17 (40.5)	9 (31.0)	0.42
Race, n (%)			0.77
African American	1 (2.4)	1 (3.4)	
East Asian	5 (11.9)	6 (20.7)	
Hispanic	2 (4.8)	2 (6.9)	
South Asian	3 (7.1)	3 (10.3)	
Two or more races	2 (4.8)	0 (0)	
White	29 (69.0)	17 (58.6)	
BMI, kg/m^2	26.1 (24.0 – 28.8)	29.8 (28.2 – 33.2)	<0.001
Waist circumference, cm	95.0 (85.0 – 101.1)	104.0 (98.3 – 114.0)	<0.001
Total cholesterol, mg/dL	226 (195 – 257)	243 (215 – 258)	0.43
LDL cholesterol, mg/dL	142 (126 – 173)	159 (144 – 172)	0.50
Triglycerides, mg/dL	91 (62 – 115)	150 (114 – 188)	<0.001
HDL cholesterol, mg/dL	59 (48 – 69)	45 (40 – 53)	<0.001
Fasting glucose, mg/dL	95 (91 – 99)	105 (101 – 112)	<0.001
Fasting insulin, mU/L	8.2 (6.7 – 10.9)	13.7 (9.7 – 19.5)	<0.001
Insulin resistance (by SSPG, mg/dL)	99 (64 – 169)	173 (130 – 242)	<0.001
Insulin secretion (by ISR_{AUC}, pmol/min x 4 h)	1497 (1146 – 2042)	2161 (1939 – 3020)	<0.001

Data are median (interquartile range) unless otherwise indicated.

*Fasting insulin (N=41) and ISR_{AUC} (N=39). †Fasting insulin (N=28) and ISR_{AUC} (N=25).

Triglyceride, fasting insulin, SSPG, and ISR_{AUC} values were log-transformed. ‡Chi-square test or Fisher's exact test was used to compare proportions and independent samples *t* tests were used to compare means.

BMI indicates body mass index; HDL, high-density lipoprotein; ISR_{AUC}, insulin secretion rate area under the curve; LDL, low-density lipoprotein; and SSPG, steady-state plasma glucose.

Supplementary Table X

Baseline Insulin Resistance and Insulin Secretion and Changes after Atorvastatin Treatment as a Function of Number of Metabolic Syndrome Elements

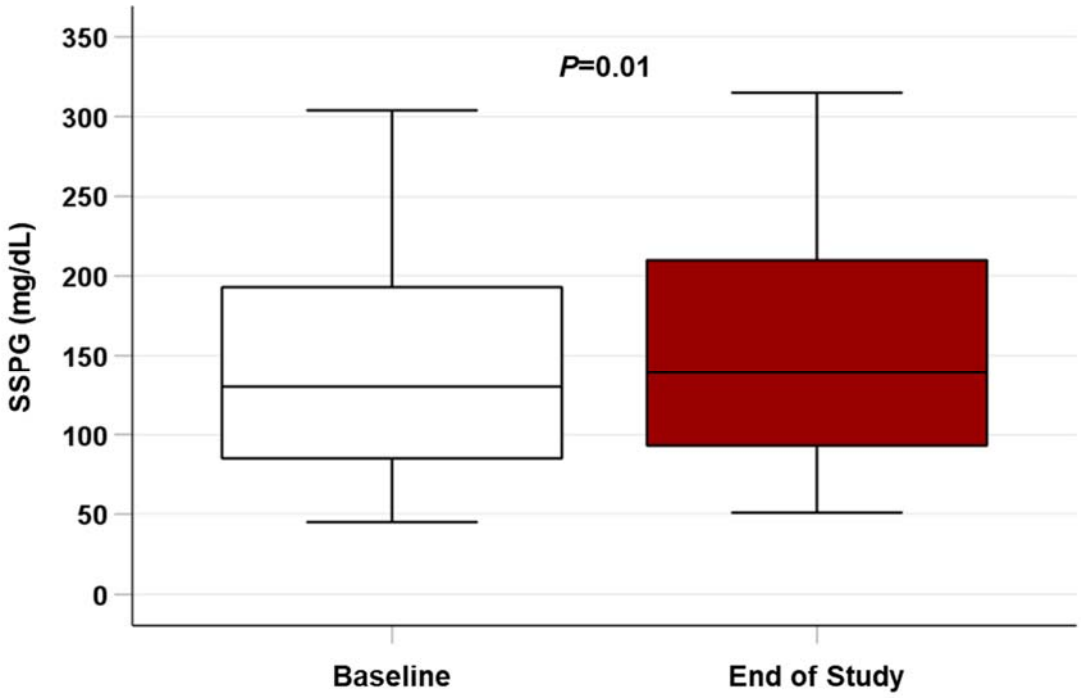
Elements of the MetSyn	Insulin Resistance (by SSPG) N=70			Insulin Secretion (by ISR_{AUC}) N=64		
	N	Baseline	Percent Change	N	Baseline	Percent Change
Zero	3	86 ± 28	-11 (-86 – 65)	3	834 ± 389	25 (-5 – 55)
One	14	82 ± 36	17 (-2 – 36)	13	1236 ± 536	15 (2 – 28)
Two	25	139 ± 65	26 (6 – 45)	23	2111 ± 1031	10 (2 – 19)
Three	18	171 ± 73	8 (-4 – 21)	15	2290 ± 845	7 (-1 – 16)
Four	7	191 ± 46	3 (-23 – 29)	7	2463 ± 445	8 (-6 – 22)
Five	3	244 ± 63	0.4 (-48 – 48)	3	3140 ± 913	26 (-22 – 74)

Baseline data are mean ± SD and percent change data are mean (95% confidence interval) on participants with both baseline and end-of-study tests. One subject with *three* MetSyn elements did not complete the end-of-study insulin suppression test.

ISR_{AUC} indicates insulin secretion rate area under the curve; MetSyn, the metabolic syndrome; and SSPG, steady-state plasma glucose.

Supplementary Figure I

Effect of Atorvastatin Treatment on Insulin Resistance (by SSPG) (N=70)

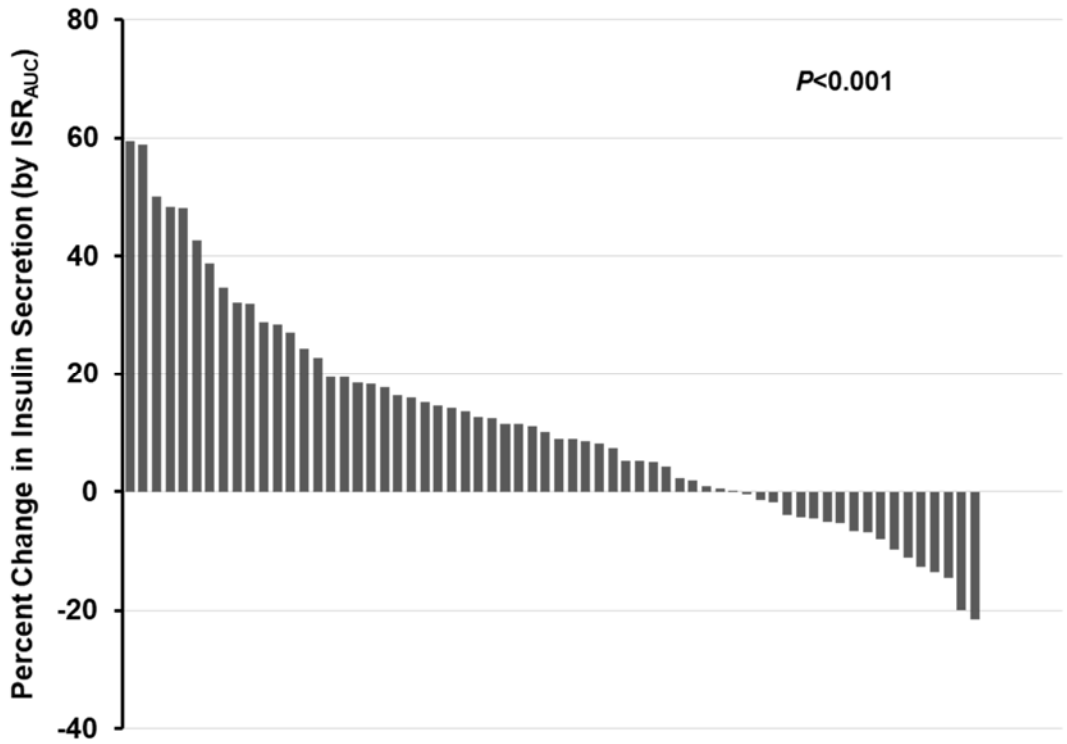


For statistical analysis, SSPG values were log-transformed. Paired sample *t* test was used to compare baseline and end-of-study SSPG concentration means.

SSPG (steady-state plasma glucose) is a direct measure of insulin resistance obtained during the insulin suppression test. A higher SSPG concentration denotes greater insulin resistance than a lower SSPG concentration.

Supplementary Figure II

Waterfall Plot of Percent Change in Insulin Secretion (by ISR_{AUC}) after Atorvastatin Treatment (N=64)



One sample *t* test was used to compare mean percent change in ISR_{AUC} to zero (no change).

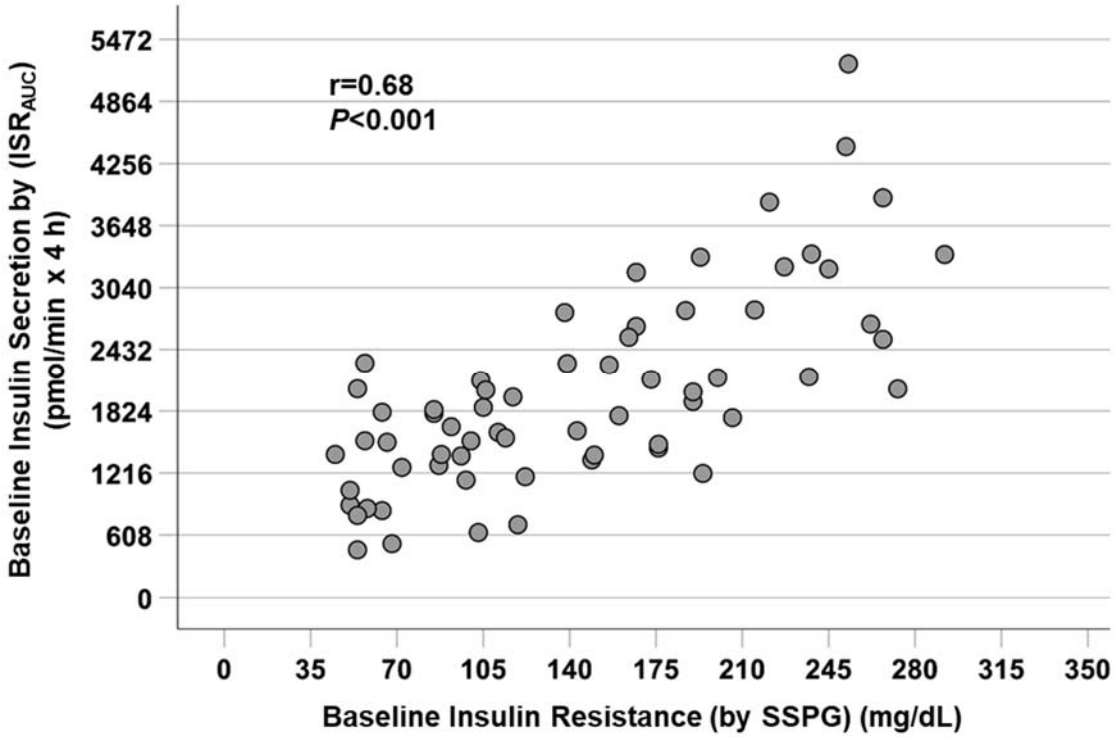
The mean (95% CI) percent change in ISR_{AUC} was 12 (7 – 16) pmol/min x 4 h and the median (interquartile range) percent change in ISR_{AUC} was 9 (-2 – 19) pmol/min x 4 h.

ISR_{AUC} is a direct measure of insulin secretion obtained during the graded glucose infusion test. A higher ISR_{AUC} denotes greater insulin secretion than a lower ISR_{AUC}.

ISR_{AUC} indicates insulin secretion rate area under the curve.

Supplementary Figure III

Relationship Between Baseline Insulin Resistance (by SSPG) and Insulin Secretion (by ISR_{AUC}) (N=64)



For statistical analysis, ISR_{AUC} and SSPG values were log-transformed. The r value is the Pearson correlation coefficient between baseline SSPG and ISR_{AUC}.

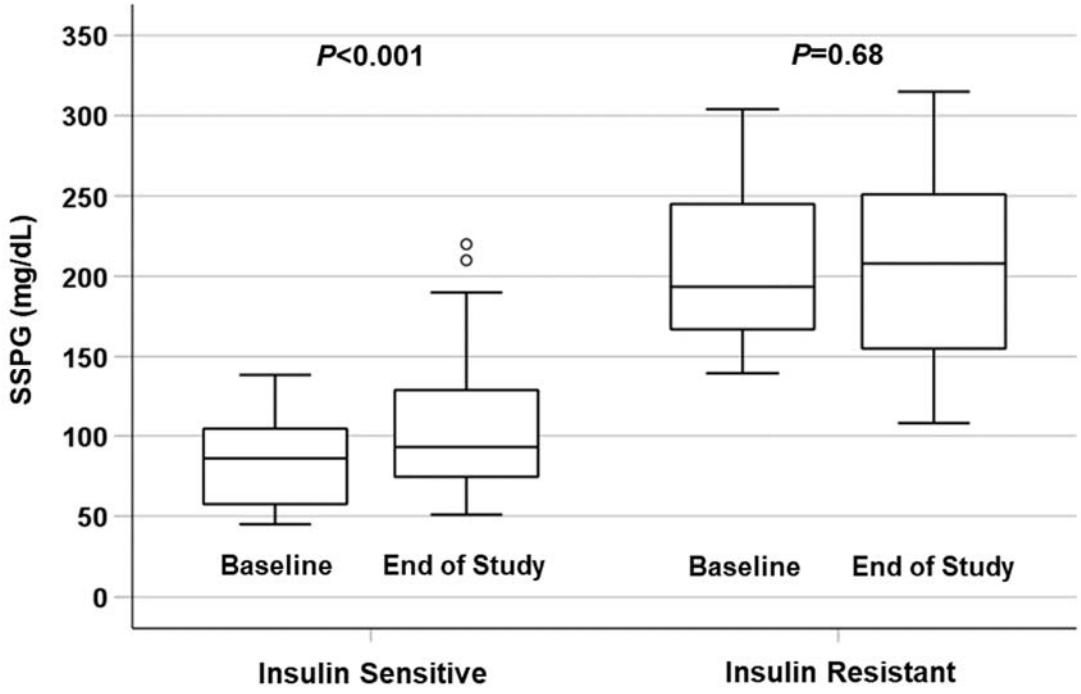
SSPG is a direct measure of insulin resistance obtained during the insulin suppression test. A higher SSPG concentration denotes greater insulin resistance than a lower SSPG concentration.

ISR_{AUC} is a direct measure of insulin secretion obtained during the graded glucose infusion test. A higher ISR_{AUC} denotes greater insulin secretion than a lower ISR_{AUC}.

ISR_{AUC} indicates insulin secretion rate area under the curve and SSPG, steady-state plasma glucose.

Supplementary Figure IV

Effect of Atorvastatin Treatment on Insulin Resistance (by SSPG) in Insulin Sensitive (N=36) and Insulin Resistant Groups (N=34)



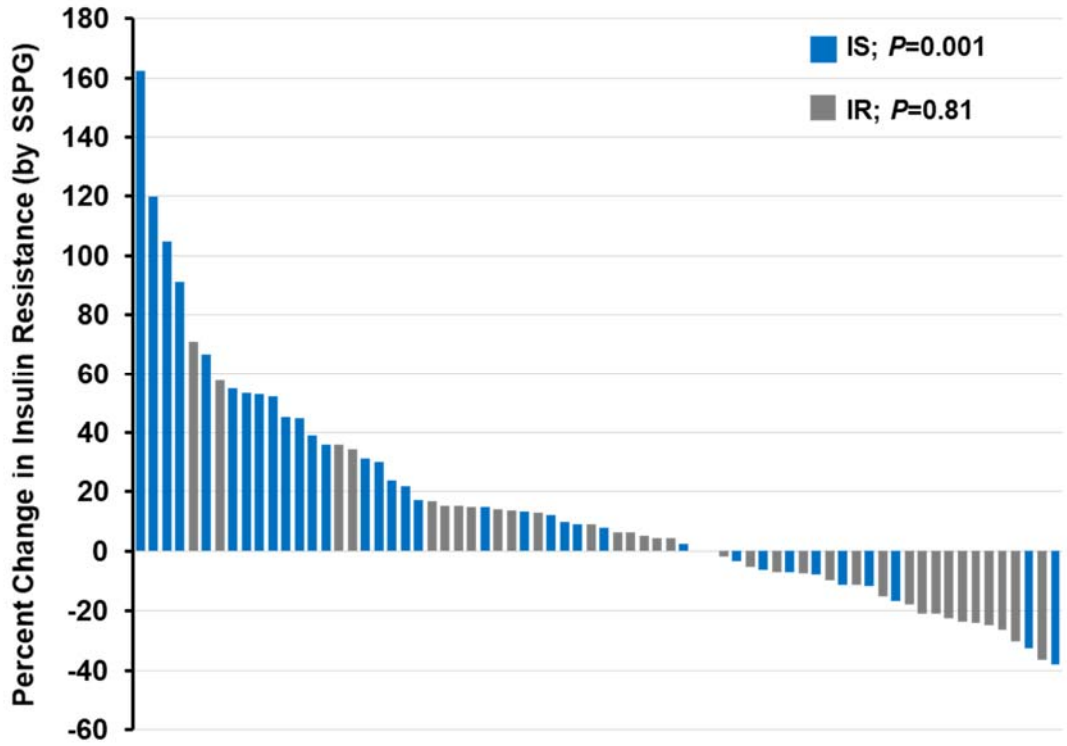
For statistical analysis, SSPG values were log-transformed. Paired sample *t* tests were used to compare baseline and end-of-study SSPG concentration values in the insulin sensitive and the insulin resistant groups.

The SSPG concentration median (138 mg/dL) was used to define subjects as being insulin sensitive (SSPG ≤138 mg/dL) or insulin resistant (SSPG >138 mg/dL).

SSPG (steady-state plasma glucose) is a direct measure of insulin resistance obtained during the insulin suppression test. A higher SSPG concentration denotes greater insulin resistance than a lower SSPG concentration.

Supplementary Figure V

Waterfall Plot of Percent Change in Insulin Resistance (by SSPG) in Insulin Sensitive (N=36*) and Insulin Resistant (N=34) Groups after Atorvastatin Treatment



Blue bars represent percent changes in insulin resistance in the insulin sensitive subjects and gray bars represent percent changes in insulin resistance in the insulin resistant subjects.

*Percent change was zero in two participants in the insulin sensitive group.

In the insulin sensitive and insulin resistant groups, one sample *t* tests were used to compare means of percent changes in SSPG to zero (no change).

The SSPG concentration median (138 mg/dL) was used to define subjects as being insulin sensitive (SSPG ≤138 mg/dL) or insulin resistant (SSPG >138 mg/dL).

SSPG (steady-state plasma glucose) is a direct measure of insulin resistance obtained during the insulin suppression test. A higher SSPG concentration denotes greater insulin resistance than a lower SSPG concentration.

IR indicates insulin resistant and IS, insulin sensitive.

References

1. Stone NJ, Robinson J, Lichtenstein AH et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology 2013.
2. Jones CN, Pei D, Staris P, Polonsky KS, Chen YD, Reaven GM. Alterations in the glucose-stimulated insulin secretory dose-response curve and in insulin clearance in nondiabetic insulin-resistant individuals. J Clin Endocrinol Metab 1997;82:1834-8.
3. Shen SW, Reaven GM, Farquhar JW. Comparison of impedance to insulin-mediated glucose uptake in normal subjects and in subjects with latent diabetes. J Clin Invest 1970;49:2151-60.
4. Pei D, Jones CN, Bhargava R, Chen YD, Reaven GM. Evaluation of octreotide to assess insulin-mediated glucose disposal by the insulin suppression test. Diabetologia 1994;37:843-5.

Major Resources Table

In order to allow validation and replication of experiments, all essential research materials listed in the Methods should be included in the Major Resources Table below. Authors are encouraged to use public repositories for protocols, data, code, and other materials and provide persistent identifiers and/or links to repositories when available. Authors may add or delete rows as needed.

Animals (in vivo studies)

Species	Vendor or Source	Background Strain	Sex	Persistent ID / URL
NA	NA	NA	NA	NA

Genetically Modified Animals

	Species	Vendor or Source	Background Strain	Other Information	Persistent ID / URL
Parent - Male	NA	NA	NA	NA	NA
Parent - Female	NA	NA	NA	NA	NA

Antibodies

Target antigen	Vendor or Source	Catalog #	Working concentration	Lot # (preferred but not required)	Persistent ID / URL
NA	NA	NA	NA	NA	NA

DNA/cDNA Clones

Clone Name	Sequence	Source / Repository	Persistent ID / URL
NA	NA	NA	NA

Cultured Cells

Name	Vendor or Source	Sex (F, M, or unknown)	Persistent ID / URL
NA	NA	NA	NA

Data & Code Availability

Description	Source / Repository	Persistent ID / URL
NA	NA	NA

Other

Description	Source / Repository	Persistent ID / URL
NA	NA	NA

DOI [to be added]