

Online-Only Supplemental Material

Glucose-dependent insulinotropic peptide in the high normal range is associated with increased carotid intima-media thickness

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Supplemental Table S1. Associations of fasting and post-challenge GIP and IMT_{mean}CCA/IMT_{max}Bulb

	IMT _{mean} CCA				IMT _{max} Bulb			
	GIP ^f		GIP ^{2h}		GIP ^f		GIP ^{2h}	
	n=3342	p	n=2948	p	n=3229	p	n=2856	p
Unadjusted								
GIP	0.016	3.0x10⁻⁵	0.010	0.012	0.031	7.0x10⁻⁵	0.011	0.140
	Model 1							
GIP	0.012	0.002	0.005	0.171	0.024	2.8x10⁻⁴	0.010	0.162
Sex	-0.039	3.8x10⁻⁷	-0.037	3.2x10⁻⁶	-0.105	4.0x10⁻¹⁵	-0.119	4.6x10⁻¹⁶
Age	0.009	3.9x10⁻³⁹	0.008	5.5x10⁻³⁴	0.013	3.9x10⁻²⁶	0.013	7.5x10⁻²³
	Model 2a		Model 2b		Model 2a		Model 2b	
GIP	0.010	0.010	0.005	0.188	0.014	0.040	0.003	0.668
Sex	-0.022	0.008	-0.013	0.140	-0.077	7.8x10⁻⁸	-0.086	4.3x10⁻⁸
Age	0.008	8.3x10⁻³⁰	0.007	9.7x10⁻²⁶	0.010	6.2x10⁻¹⁸	0.010	5.1x10⁻¹⁵
BMI	0.001	0.203	0.002	0.013	-0.001	0.583	0.000	0.812
AHT	-0.026	0.004	-0.018	0.044	0.022	0.160	0.032	0.048
Lipid-lowering treatment	0.016	0.073	0.013	0.140	0.056	3.4x10⁻⁴	0.053	0.002
Triglycerides	-0.004	0.682	-0.009	0.366	0.013	0.471	0.001	0.955
Current smoking	0.043	0.003	0.035	0.016	0.111	1.2x10⁻⁵	0.114	1.9x10⁻⁵
Systolic blood pressure	0.002	7.3x10⁻²⁰	0.002	1.9x10⁻¹⁶	0.003	3.6x10⁻¹⁴	0.003	9.8x10⁻¹⁴
Diabetes status	-0.013	0.401	-0.018	0.826	-0.014	0.597	0.170	0.253
HDL	-0.055	3.6x10⁻⁴	-0.072	4.4x10⁻⁶	-0.057	0.035	-0.064	0.026
Glucose	-0.026	0.323	0.014	0.316	0.046	0.327	0.008	0.749
Insulin	-0.010	0.236	-0.015	0.026	-0.007	0.642	-0.008	0.520

^fFasting

^{2h} Post-challenge (at 120 minutes)

Values are unstandardized β coefficients (1 SD increase of incretins per mm IMT_{mean}CCA or IMT_{max}Bulb).

Model 2a: adjusted for age, sex, BMI, systolic blood pressure (SBP), smoking status, diabetes status, FPG, fasting insulin, HDL, triglycerides, AHT and lipid-lowering treatment.

Model 2b: adjusted for age, sex, BMI, SBP, smoking status, diabetes status, post-challenge plasma glucose, post-challenge insulin, HDL, triglycerides, AHT and lipid-lowering treatment.

AHT=antihypertensive treatment; BMI=body mass index; GIP= glucose-dependent insulinotropic peptide; HDL=high density lipoprotein cholesterol; HOMA-IR= Homeostatic Model Assessment of Insulin Resistance, IMT_{mean}CCA=intima-media thickness in the common carotid artery; IMT_{max}Bulb=intima-media thickness in the carotid bifurcation; SBP=systolic blood pressure

Supplemental Table S2. Associations of fasting and post-challenge GLP-1 and IMT_{mean}CCA/IMT_{max}Bulb

	IMT _{mean} CCA				IMT _{max} Bulb			
	GLP-1 ^f		GLP-1 ^{2h}		GLP-1 ^f		GLP-1 ^{2h}	
	n=3299	n=2893	n=3187	n=2828	β	p	β	p
Unadjusted								
GLP-1	-0.005	0.244	-0.007	0.097	-0.015	0.033	-0.019	0.009
Model 1								
GLP-1	-0.005	0.174	-0.010	0.008	-0.016	0.016	-0.017	0.018
Sex	-0.042	7.2x10⁻⁸	-0.032	6.1x10⁻⁵	-0.109	9.0x10⁻¹⁶	-0.108	4.4x10⁻¹³
Age	0.009	2.4x10⁻⁴⁰	0.009	8.4x10⁻³⁷	0.013	9.7x10⁻²⁷	0.013	3.1x10⁻²⁴
Model 2a								
GLP-1	-0.003	0.426	-0.006	0.142	-0.016	0.014	-0.013	0.069
Sex	-0.025	0.003	-0.011	0.200	-0.081	2.2x10⁻⁸	-0.080	3.6x10⁻⁷
Age	0.008	1.2x10⁻³⁰	0.008	4.2x10⁻²⁷	0.010	5.3x10⁻¹⁸	0.010	4.1x10⁻¹⁵
BMI	0.001	0.196	0.002	0.020	-0.001	0.419	-0.001	0.581
AHT	-0.023	0.009	-0.015	0.094	0.020	0.207	0.033	0.044
Lipid-lowering treatment	0.017	0.063	0.013	0.140	0.062	7.6x10⁻⁵	0.055	0.001
Triglycerides	-0.002	0.803	-0.008	0.441	0.015	0.401	0.001	0.940
Current smoking	0.046	0.002	0.038	0.010	0.113	10.0x10⁻⁶	0.111	3.3x10⁻⁵
Systolic blood pressure	0.002	6.7x10⁻¹⁹	0.002	9.6x10⁻¹⁶	0.003	2.6x10⁻¹³	0.003	1.6x10⁻¹³
Diabetes status	-0.008	0.612	-0.017	0.834	-0.003	0.920	0.173	0.247
HDL	-0.048	0.002	-0.068	1.6x10⁻⁵	-0.046	0.090	-0.059	0.040
Glucose	-0.024	0.375	0.012	0.375	0.053	0.257	0.002	0.924
Insulin	-0.007	0.451	-0.016	0.024	0.003	0.836	-0.008	0.548

^fFasting

^{2h}Post-challenge (at 120 minutes)

Values are unstandardized β coefficients (1 SD increase of incretins per mm IMT_{mean}CCA or IMT_{max}Bulb).

Model 2a: adjusted for age, sex, BMI, systolic blood pressure (SBP), smoking status, diabetes status, FPG, fasting insulin, HDL, triglycerides, AHT and lipid-lowering treatment.

Model 2b: adjusted for age, sex, BMI, SBP, smoking status, diabetes status, post-challenge plasma glucose, post-challenge insulin, HDL, triglycerides, AHT and lipid-lowering treatment.

AHT=antihypertensive treatment; BMI=body mass index; GLP-1=glucagon-like peptide 1; HDL=high density lipoprotein cholesterol; HOMA-IR=Homeostatic Model Assessment of Insulin Resistance, IMT_{mean}CCA=intima-media thickness in the common carotid artery; IMT_{max}Bulb=intima-media thickness in the carotid bifurcation; SBP=systolic blood pressure

Supplemental Table S3. Associations between GIP and IMT_{meanCCA}/IMT_{maxBulb} in subjects free from diabetes

	IMT _{meanCCA}				IMT _{maxBulb}			
	GIP ^f		GIP ^{2h}		GIP ^f		GIP ^{2h}	
	n=2986	n=2806	n=2897	n=2708	β	p	β	p
Unadjusted								
GIP	0.014	3.7x10⁻⁴	0.010	0.013	0.026	4.5x10⁻⁴	0.011	0.150
Model 1								
GIP	0.010	0.012	0.005	0.184	0.019	0.007	0.010	0.195
Sex	-0.034	1.1x10⁻⁵	-0.038	2.2x10⁻⁶	-0.113	1.7x10⁻¹⁵	-0.118	2.8x10⁻¹⁵
Age	0.009	4.4x10⁻³⁷	0.009	1.6x10⁻³³	0.013	2.3x10⁻²⁵	0.013	7.6x10⁻²³
Model 3a								
GIP	0.008	0.033	0.003	0.401	0.012	0.096	0.001	0.872
Sex	-0.016	0.053	-0.018	0.041	-0.087	8.4x10⁻⁹	-0.087	3.1x10⁻⁸
Age	0.008	1.5x10⁻²⁸	0.008	8.7x10⁻²⁶	0.011	3.2x10⁻¹⁷	0.010	2.4x10⁻¹⁵
BMI	0.002	0.018	0.002	0.029	-0.001	0.567	-0.003	0.128
AHT	-0.020	0.024	-0.018	0.049	0.029	0.070	0.035	0.032
Lipid-lowering treatment	0.009	0.309	0.009	0.327	0.051	0.002	0.045	0.009
Triglycerides	-0.010	0.319	-0.011	0.289	0.008	0.662	0.002	0.935
Current smoking	0.044	0.003	0.042	0.006	0.115	1.2x10⁻⁵	0.124	6.1x10⁻⁶
Systolic blood pressure	0.002	1.1x10⁻¹⁷	0.002	5.0x10⁻¹⁷	0.003	1.3x10⁻¹²	0.003	6.7x10⁻¹³
HDL	-0.060	1.3x10⁻⁴	-0.066	3.3x10⁻⁵	-0.057	0.045	-0.054	0.067
HOMA-IR	-0.015	0.082	-0.012	0.172	0.000	0.978	0.018	0.256

^fFasting

^{2h} Post-challenge (at 120 minutes)

Values are unstandardized β coefficients.

Model 3a: adjusted for age, sex, BMI, SBP, smoking status, HOMA-IR, fasting plasma glucose, fasting insulin, HDL, triglycerides, AHT and lipid-lowering treatment.

Model 3b: adjusted for age, sex, BMI, SBP, smoking status, HOMA-IR, post-challenge plasma glucose, post-challenge insulin, HDL, triglycerides, AHT and lipid-lowering treatment.

AHT=antihypertensive treatment; BMI=body mass index; GIP=glucose-dependent insulinotropic peptide; HDL=high density lipoprotein cholesterol; HOMA-IR= Homeostatic Model Assessment of Insulin Resistance, IMT_{meanCCA}=intima-media thickness in the common carotid artery; IMT_{maxBulb}=intima-media thickness in the carotid bifurcation; SBP=systolic blood pressure

Supplemental Table S4. Associations between GLP-1 and IMT_{meanCCA}/IMT_{maxBulb} in subjects free from diabetes

	IMT _{meanCCA}				IMT _{maxBulb}			
	GLP-1 ^f n=2949		GLP-1 ^{2h} n=2908		GLP-1 ^f n=2859		GLP-1 ^{2h} n=2808	
	β	p	β	p	β	p	β	p
Unadjusted								
GLP-1	-0.007	0.071	-0.008	0.031	-0.019	0.008	-0.016	0.026
Model 1								
GLP-1	-0.007	0.062	-0.013	0.002	-0.020	0.006	-0.014	0.055
Sex	-0.036	2.8x10⁻⁶	-0.030	2.2x10⁻⁴	-0.115	6.5x10⁻¹⁶	-0.106	9.6x10⁻¹³
Age	0.009	4.2x10⁻³⁸	0.009	2.2x10⁻³⁹	0.013	1.2x10⁻²⁵	0.013	7.8x10⁻²⁶
Model 3a								
GLP-1	-0.004	0.265	-0.009	0.020	-0.017	0.016	-0.010	0.176
Sex	-0.019	0.018	-0.015	0.082	-0.090	2.5x10⁻⁹	-0.082	1.4x10⁻⁷
Age	0.008	3.0x10⁻²⁹	0.008	1.0x10⁻²⁹	0.011	3.8x10⁻¹⁷	0.011	5.0x10⁻¹⁷
BMI	0.002	0.019	0.002	0.024	-0.002	0.438	-0.002	0.280
AHT	-0.017	0.053	-0.015	0.098	0.028	0.081	0.031	0.059
Lipid-lowering treatment	0.010	0.288	0.008	0.360	0.056	0.001	0.052	0.002
Triglycerides	-0.008	0.423	-0.008	0.399	0.009	0.609	0.007	0.716
Current smoking	0.048	0.001	0.049	0.001	0.115	1.3x10⁻⁵	0.116	1.5x10⁻⁵
Systolic blood pressure	0.002	6.3x10⁻¹⁷	0.002	4.14x10⁻¹⁷	0.003	6.94x10⁻¹²	0.003	3.4x10⁻¹²
HDL	-0.052	0.001	-0.053	0.001	-0.048	0.097	-0.058	0.046
HOMA-IR	-0.011	0.168	-0.013	0.116	0.007	0.637	0.006	0.677

^fFasting

^{2h} Post-challenge (at 120 minutes)

Values are unstandardized β coefficients (1 SD increase of incretins per mm IMT_{meanCCA} or IMT_{maxBulb}).

Model 3a: adjusted for age, sex, BMI, SBP, smoking status, HOMA-IR, fasting plasma glucose, fasting insulin, HDL, triglycerides, AHT and lipid-lowering treatment.

Model 3b: adjusted for age, sex, BMI, SBP, smoking status, HOMA-IR, post-challenge plasma glucose, post-challenge insulin, HDL, triglycerides, AHT and lipid-lowering treatment.

AHT=antihypertensive treatment; BMI=body mass index; GLP-1=glucagon-like peptide 1; HDL=high density lipoprotein cholesterol; HOMA-IR= Homeostatic Model Assessment of Insulin Resistance, IMT_{meanCCA}=intima-media thickness in the common carotid artery; IMT_{maxBulb}=intima-media thickness in the carotid bifurcation; SBP=systolic blood pressure

Supplemental Table S5. Associations of fasting GIP and GLP-1 with IMT_{mean}CCA/IMT_{max}Bulb in subjects with diabetes

	Fasting GIP				Fasting GLP-1			
	IMT _{mean} CCA n=356		IMT _{max} bulb n=332		IMT _{mean} CCA n=350		IMT _{max} bulb n=328	
	β	p	β	p	β	p	β	p
Unadjusted	0.028	0.071	0.036	0.083	0.010	0.521	-0.005	0.819
Model 1	0.026	0.078	0.033	0.110	0.006	0.682	-0.007	0.750
Model 2	0.026	0.101	0.027	0.207	-0.003	0.863	-0.015	0.493

Model 1 is adjusted for age and sex. Model 2 is adjusted for adjusted for age, sex, BMI, systolic blood pressure (SBP), smoking status, diabetes status, fasting plasma glucose, fasting insulin, HDL, triglycerides, AHT and lipid-lowering treatment.

Supplemental Table S6. Standardized associations of fasting and post-challenge GIP/GLP-1 and IMT_{mean}CCA/IMT_{max}Bulb

	IMT _{mean} CCA				
	β	p		β	p
Fasting GIP	0.044	0.010	Post-challenge GIP	0.024	0.211
Sex	-0.048	0.008	Sex	-0.035	0.078
Age	0.197	8.3x10 ⁻³⁰	Age	0.198	1.8x10 ⁻²⁵
BMI	0.025	0.203	BMI	0.052	0.009
AHT	-0.057	0.004	AHT	-0.038	0.072
Lipid-lowering treatment	0.033	0.073	Lipid-lowering treatment	0.029	0.134
Triglycerides	-0.008	0.682	Triglycerides	-0.016	0.444
Smoking	0.049	0.003	Smoking	0.046	0.011
Systolic blood pressure	0.175	7.3x10 ⁻²⁰	Systolic blood pressure	0.164	1.2x10 ⁻¹⁵
Diabetes status	-0.018	0.401	Diabetes status	-0.004	0.815
HDL	-0.073	3.6x10 ⁻⁴	HDL	-0.098	6.9x10 ⁻⁶
Fasting glucose	-0.021	0.323	Post-challenge glucose	0.024	0.259
Fasting insulin	-0.025	0.236	Post-challenge insulin	-0.060	0.012
	β	p		β	p
Fasting GLP-1	-0.014	0.426	Post-challenge GLP-1	-0.028	0.142
Sex	-0.055	0.003	Sex	-0.025	0.200
Age	0.201	1.2x10 ⁻³⁰	Age	0.206	4.2x10 ⁻²⁷
BMI	0.026	0.196	BMI	0.046	0.020
AHT	-0.052	0.009	AHT	-0.035	0.094
Lipid-lowering treatment	0.034	0.063	Lipid-lowering treatment	0.028	0.140
Triglycerides	-0.005	0.803	Triglycerides	-0.016	0.441
Smoking	0.053	0.002	Smoking	0.047	0.010
Systolic blood pressure	0.172	6.7x10 ⁻¹⁹	Systolic blood pressure	0.165	9.6x10 ⁻¹⁶
Diabetes status	-0.011	0.612	Diabetes status	-0.004	0.834
HDL	-0.065	0.002	HDL	-0.095	1.6x10 ⁻⁵
Fasting glucose	-0.019	0.375	Post-challenge glucose	0.019	0.375
Fasting insulin	-0.016	0.451	Post-challenge insulin	-0.053	0.024
	IMT _{max} Bulb				
	β	p		β	p
Fasting GIP	0.036	0.040	Post-challenge GIP	0.008	0.663
Sex	-0.098	7.8x10 ⁻⁸	Sex	-0.111	3.7x10 ⁻⁸
Age	0.152	6.2x10 ⁻¹⁸	Age	0.144	5.8x10 ⁻¹⁴
BMI	-0.011	0.583	BMI	-0.008	0.679
AHT	0.028	0.160	AHT	0.042	0.048
Lipid-lowering treatment	0.066	3.4x10 ⁻⁴	Lipid-lowering treatment	0.061	0.002
Triglycerides	0.015	0.471	Triglycerides	0.002	0.912
Smoking	0.075	1.2x10 ⁻⁵	Smoking	0.078	2.5x10 ⁻⁵
Systolic blood pressure	0.147	3.6x10 ⁻¹⁴	Systolic blood pressure	0.154	1.5x10 ⁻¹³
Diabetes status	-0.011	0.597	Diabetes status	0.021	0.257
HDL	-0.044	0.035	HDL	-0.048	0.033
Fasting glucose	0.021	0.327	Post-challenge glucose	0.009	0.693

Fasting insulin	-0.010	0.642	Post-challenge insulin	-0.017	0.485
	β	p		β	p
Fasting GLP-1	-0,042	0,014	Post-challenge GLP-1	-0,035	0,071
Sex	-0,103	2,2x10 ⁻⁸	Sex	-0,103	3,4x10 ⁻⁷
Age	0,153	5,3x10 ⁻¹⁸	Age	0,151	4,4x10 ⁻¹⁵
BMI	-0,016	0,419	BMI	-0,013	0,517
AHT	0,026	0,207	AHT	0,044	0,037
Lipid-lowering treatment	0,074	7,6x10 ⁻⁵	Lipid-lowering treatment	0,060	0,002
Triglycerides	0,017	0,401	Triglycerides	0,003	0,900
Smoking	0,076	9,9x10 ⁻⁶	Smoking	0,077	2,7x10 ⁻⁵
Systolic blood pressure	0,143	2,6x10 ⁻¹³	Systolic blood pressure	0,154	1,5x10 ⁻¹³
Diabetes status	-0,002	0,920	Diabetes status	0,021	0,248
HDL	-0,036	0,090	HDL	-0,043	0,053
Fasting glucose	0,025	0,257	Post-challenge glucose	0,003	0,891
Fasting insulin	0,004	0,836	Post-challenge insulin	-0,013	0,582

Values are standardized β coefficients.