10.1148/radiol.211914

Appendix E1

Materials and Methods

Data Preparation

The CTC images were originally in DICOM format but were converted to NIFTI volumes for analysis using the program dcm2niix. All CT images were then rewindowed to the range -160 to 240 HU.

Deep Learning Algorithm for Pancreas Segmentation

Following previous work (17) we generated synthetic non-contrast versions of the CECT CTs to augment our training dataset. We compared CycleGAN (31) and a custom UNIT (32) image translation models for generating synthetic non-contrast CT and found that the CycleGAN led to a higher performance in the validation set than using either the UNIT or a combination of both UNIT and CycleGAN. Therefore, we used the CycleGAN augmented versions.

The model used was a 3D U-Net (33) with dropout and skip connections and 28.5 M parameters. More details have been reported separately (34). We trained the model using Dice loss and the rectified Adam optimizer (35) with a batch size of 4. Data augmentation consisted of random XYZ flipping, 90-degree rotations, rotations between ±10 degrees around one of the XYZ axes, cropping in the z-direction, and elastic deformations using a B-spline.

Extra Pancreatic Analysis

Visceral fat data was taken from a previous study in which automated CT-based body composition measurements were done on the same patient sample (19). The relative percent of visceral fat in these patients was calculated by dividing the visceral fat volume at the L1 vertebra level by the total body volume excluding air. Visceral fat measurements taken at the L1 vertebra is a widely used indication of visceral fat in the total abdominal area (36).

Atherosclerotic plaque data was taken from a previous study that used the same patient sample. Atherosclerotic plaque in the abdominal aorta between the L1 and L4 vertebral levels was measured using a previously validated deep learning method and expressed as an Agatston score (15). Additionally, plaque was measured in a 1 cm dilated region around the pancreas segmentation to measure plaque in pancreas bound arteries. Plaque in this dilated region was labeled peripancreatic plaque. Agatston scores for each case were reported for the intrapancreatic and peripancreatic plaque combined, and for the peripancreatic plaque alone.

Muscle volume and average CT attenuation were taken from a single slice at the L3 vertebra level for analysis as done in a previous study (16). Average liver CT attenuation data were also taken from a previous study (16).

Pancreas Segmentation Analysis for Active Learning and Exclusions

To understand how well the deep learning method performed, an outlier analysis was conducted based on total volume, average CT attenuation, and standard deviation of CT attenuation. The

data were sorted from smallest to largest. Outliers were defined as any measurements above or below 1.5 times the interquartile range. Several random outliers and nonoutliers were examined. Observations were recorded for these randomly selected CT images and then used to select images for active learning.

It was determined that there were several CT images with significantly undersegmented pancreases with the final iteration of the pancreas segmentation model. Thus, any automated segmentations with a pancreas volume less than 25 mL were excluded from the next analytical steps as automated measurements from those cases had low reliability. The volume cut-off was determined through an estimation of the minimum pancreas size in diabetic patients based on previous studies (5).

Final Multivariable Model Based on "Best" Set of CT-derived and Clinical Predictors

The diagnostic group "Non-diabetic" is used as the reference group.

Log (odds of DiabeticNeg1 to Non-diabetic) = ln [prob(DiabeticNeg1)/prob(Non-diabetic)] =

− 12.3057

+ 0.2241·fat_percent_total

+ 0.2018·frac_dim_3d_10

− 0.1969·fat_percent_eroded

− 0.0188·liver_avg_HU

+ 0.1089·BMI

+ 0.6315 (if Agatston_group is 0< <100, compared to Agatston_group=0)

+ 0.8799 (if Agatston_group is 100-300, compared to Agatston_group=0)

+ 1.2799 (if Agatston_group is >300, compared to Agatston_group=0)

Log (odds of DiabeticNeg2 to Non-diabetic) = ln [prob(DiabeticNeg2)/prob(Non-diabetic)] =

+ 10.8358

+ 0.1451·fat_percent_total

− 0.9955·frac_dim_3d_10

− 0.1017·fat_percent_eroded

− 0.00892·liver_avg_HU

+ 0.1242·BMI

− 0.1342(if Agatston_group is 0< <100, compared to Agatston_group=0)

+ 0.1476 (if Agatston_group is 100-300, compared to Agatston_group=0)

+ 0.5501 (if Agatston_group is >300, compared to Agatston_group=0)

Log (odds of DiabeticPos1 to Non-diabetic) = ln [prob(DiabeticPos1)/prob(Non-diabetic)] =

− 3.0310

+ 0.1778·fat_percent_total

− 0.1109·frac_dim_3d_10

− 0.1575·fat_percent_eroded

− 0.0374·liver_avg_HU

+ 0.0794·BMI

+ 0.3237 (if Agatston_group is 0< <100, compared to Agatston_group=0)

+ 0.7920 (if Agatston_group is 100-300, compared to Agatston_group=0)

+ 0.6951 (if Agatston_group is >300, compared to Agatston_group=0)

Log (odds of DiabeticPos2 to Non-diabetic) = ln [prob(DiabeticPos2)/prob(Non-diabetic)] =

− 9.1654

+ 0.1881·fat_percent_total

+ 0.1498·frac_dim_3d_10

− 0.1790·fat_percent_eroded

− 0.0306·liver_avg_HU

+ 0.0929·BMI

− 0.1635 (if Agatston_group is 0< <100, compared to Agatston_group=0)

+ 0.4395 (if Agatston_group is 100-300, compared to Agatston_group=0)

+ 0.7551 (if Agatston_group is >300, compared to Agatston_group=0)

"DiabeticNeg1" refers to diabetic group, CT 0-2499 days post Dx. "DiabeticNeg2" refers to diabetic group, CT ≥ 2500 days post Dx. "DiabeticPos1" refers to diabetic group, CT 0-2499 days pre Dx. "DiabeticPos2" refers to diabetic group, CT ≥ 2500 days pre Dx. Dx = Date pf Diabetes Diagnosis.

References

31. Zhu JY, Park T, Isola P, Efros AA. Unpaired Image-to-Image Translation Using Cycle-Consistent Adversarial Networks. In: 2017 IEEE International Conference on Computer Vision (ICCV), Venice, Italy, October 22–29, 2017. Piscataway, NJ: IEEE, 2017; 2242–2251.

32. Zhu Y, Tang Y, Tang Y, et al. Cross-domain Medical Image Translation by Shared Latent Gaussian Mixture Model. In: Martel AL, Abolmaesumi P, Stoyanov D, et al, eds. Medical Image Computing and Computer Assisted Intervention – MICCAI 2020. MICCAI 2020. Lecture Notes in Computer Science, vol 12262. Cham, Switzerland: Springer, 2020; 379–389.

33. Çiçek Ö, Abdulkadir A, Lienkamp SS, Brox T, Ronneberger O. 3D U-Net Learning Dense Volumetric Segmentation from Sparse Annotation. In: Ourselin S, Joskowicz L, Sabuncu M, Unal G, Wells W, eds. Medical Image Computing and Computer-Assisted Intervention – MICCAI 2016. MICCAI 2016. Lecture Notes in Computer Science, vol 9901. Cham, Switzerland: Springer, 2016; 424–432.

34. Elton D, Sandfort V, Pickhardt PJ, Summers RM. Accurately identifying vertebral levels in large datasets. In: Hahn K, Mazurowski MA, eds. Proceedings of SPIE: medical imaging 2020—computer-aided diagnosis. Vol 11314. Bellingham, Wash: International Society for Optics and Photonics, 2020; 113140O.

35. Liu L, Jiang H, He P, et al. On the Variance of the Adaptive Learning Rate and Beyond. arXiv preprint arXiv:1908.03265. https://arxiv.org/abs/1908.03265. Posted August 8, 2019.

36. Shen W, Punyanitya M, Wang Z, et al. Visceral adipose tissue: relations between single-slice areas and total volume. Am J Clin Nutr 2004;80(2):271–278.

Table E1

Categories of the Response Variable Used in the Multinomial Logistic Regressions, and Number of Patients in Each Category

Category	Sample size (n)*
Nondiabetic	6540
Diabetic, CT ≥ 2500 days pre Dx	183
Diabetic, CT 0–2499 days pre Dx	180
Diabetic, CT 0–2499 days post Dx	174
Diabetic, CT ≥ 2500 days post Dx	35
Dysglycemic, CT ≥ 2500 days pre Dx	491
Dysglycemic, CT 0–2499 days pre Dx	961
Dysglycemic, CT 0–2499 days post Dx	400
Dysglycemic, CT ≥ 2500 days post Dx	28
Total	7112

Note.—Dx = diagnosis.

* The number of observations used in each model will vary depending on the number of explanatory variables included, and the corresponding number of missing values.

Table E2

List of Explanatory Variables and Descriptions for Multinomial Logistic Regressions

Explanatory Variable	Category	Type	Description
avg_HU	CT-derived	Continuous	Pancreas average CT attenuation in Hounsfield Units
std_HU	CT-derived	Continuous	Pancreas standard deviation of CT attenuation in Hounsfield Units
median_HU	CT-derived	Continuous	Pancreas median CT attenuation in Hounsfield Units
Total Volume	CT-derived	Continuous	Pancreatic volume (mL)
fat_percent_total	CT-derived	Continuous	Intrapancreatic fat percentage
frac_dim_3d_10	CT-derived	Continuous	Pancreas fractal dimension in 3D (multiplied by 10)
avg_HU_eroded	CT-derived	Continuous	Average CT attenuation on eroded pancreas volume

std_HU_eroded	CT-derived	Continuous	Standard Deviation on eroded pancreas volume
median_HU_eroded	CT-derived	Continuous	Median CT attenuation on eroded pancreas volume
TotalVolume_eroded (mL)	CT-derived	Continuous	Eroded pancreas volume (mL)
fat_percent_eroded	CT-derived	Continuous	Intrapancreatic fat percentage on eroded volume
VFatVol	CT-derived	Continuous	Visceral Fat volume at L1 vertebra (mL)
VFatPer	CT-derived	Continuous	Relative percent of visceral fat; visceral fat volume (vFatVol)/abdominal volume excluding air
Agatston_100	CT-derived	Continuous	Measure of plaque between L1-L4 vertebra (Agatston score divided by 100)
Agatston_group	CT-derived	Categorical	Agatston score in 4 groups (0, > 0 and < 100, 100–300, > 300)
Agatston_binary	CT-derived	Binary	Presence of plaque between L1-L4 vertebra (Y or N)
Agatston_PandD_100	CT-derived	Continuous	Intrapancreatic and peripancreatic plaque (Agatston score in pancreas and dilation divided by 100)
Agatston_PandD_binary	CT-derived	Binary	Presence of intrapancreatic or peripancreatic plaque (Y or N)
Agatston_Donly_100	CT-derived	Continuous	Peripancreatic plaque; in 1 cm diameter around pancreas (Agatston score divided by 100)
Agatston_Donly_binary	CT-derived	Binary	Presence of peripancreatic plaque (Y or N)
liver_avg_HU	CT-derived	Continuous	Liver average CT attenuation in Hounsfield Units
muscle_avg_HU	CT-derived	Continuous	Muscle average CT attenuation in Hounsfield Units in single slice at L3 vertebra
muscle_vol	CT-derived	Continuous	Muscle volume in single slice at L3 vertebra (mL)
Sex	Clinical	Categorical	Female/Male
Age_at_CT	Clinical	Continuous	Age during CT
BMI	Clinical	Continuous	BMI during CT
BMI30	Clinical	Binary	BMI > 30 (Y or N)
Height_in	Clinical	Continuous	Height in inches

Table E3

Paired Samples T-tests on Measurements from Manual and Automated Pancreas Segmentations (*n* = 25)

Metric	Manual	Automated	Mean difference	95% CI	Two-tailed *P* value
Average CT Attenuation (HU)	28.07 ± 16.78	27.61 ± 17.68	0.47 ± 1.54	−0.17 to 1.10	0.14
Standard Deviation of CT Attenuation (HU)	49.12 ± 10.48	49.48 ± 10.68	−0.35 ± 0.91	−0.73 to 0.02	0.07
Median CT Attenuation (HU)	30.60 ± 16.18	30.32 ± 17.09	0.28 ± 1.37	−0.29 to 0.85	0.32
Volume (mL)	77.44 ± 20.80	78.65 ± 19.31	−1.21 ± 6.32	−3.82 to 1.40	0.35
Fat Fraction	0.1263 ± 0.0992	0.1301 ± 0.1053	−0.0038 ± 0.0107	−0.0082 to 0.0006	0.09
Fractal Dimension	2.1391 ± 0.0799	2.1417 ± 0.0704	−0.0026 ± 0.0162	−0.0093 to 0.0041	0.43

Eroded Average CT Attenuation (HU)	34.47 ± 16.27	34.25 ± 16.35	0.22 ± 1.13	−0.24 to 0.69	0.33
Eroded Standard Deviation of CT Attenuation (HU)	45.37 ± 10.33	45.67 ± 10.43	−0.30 ± 0.85	−0.65 to 0.05	0.09
Eroded Median CT Attenuation (HU)	35.80 ± 15.31	35.72 ± 15.25	0.08 ± 1.08	−0.36 to 0.52	0.71
Eroded Fat Fraction	0.0917 ± 0.0911	0.0937 ± 0.0908	−0.0020 ± 0.0080	−0.0053 to 0.0012	0.21

Note.—All two-tailed *P* values between manual and automated values were NS.

Table E4

Summary of the Univariable Analysis Using Multinomial Logistic Regressions on Type 2 Diabetes (with 5 Nominal Categories), Listed from Highest to Lowest Multilevel AUC

Explanatory variable	Number of observations read	Number of observations used	Overall effect *P* value	Multilevel AUC
VFatVol	7112	7112	<0.0001	0.618
BMI	7112	6987	<0.0001	0.615
avg_HU	7112	7112	<0.0001	0.601
median_HU	7112	7112	<0.0001	0.599
fat_percent_total	7112	7112	<0.0001	0.599
VFatPer	7112	7112	<0.0001	0.593
avg_HU_eroded	7112	7112	<0.0001	0.591
median_HU_eroded	7112	7112	<0.0001	0.591
fat_percent_eroded	7112	7112	<0.0001	0.588
BMI30	7112	6987	<0.0001	0.588
liver_avg_HU	7112	7112	<0.0001	0.587
muscle_vol	7112	7057	<0.0001	0.584
muscle_avg_HU	7112	7057	<0.0001	0.580
std_HU	7112	7112	<0.0001	0.560
Age_at_CT	7112	7112	<0.0001	0.558
Agatston_100	7112	7108	<0.0001	0.556
Agatston_group	7112	7108	<0.0001	0.555
std_HU_eroded	7112	7112	<0.0001	0.554
frac_dim_3d_10	7112	7112	<0.0001	0.554
TotalVolume_eroded (mL)	7112	7112	<0.0001	0.554
TotalVolume (mL)	7112	7112	<0.0001	0.539
Agatston_binary	7112	7108	<0.0001	0.535
Height _in	7112	6993	0.06	0.533
Sex	7112	7112	<0.0001	0.523
Agatston_PandD_binary	7112	7111	0.01	0.520
Agatston_Donly_binary	7112	7111	0.03	0.516
Agatston_PandD_100	7112	7111	0.65	0.510
Agatston_Donly_100	7112	7111	0.74	0.505

Table E5

Results of the Multivariable Analysis (Multinomial Logistic Regression) Showing the Optimal Set of Predictors for Type 2 Diabetes (with 5 Nominal Categories)

Candidate variables considered	Number of observations read	Number of observations used	Multilevel AUC	Selected explanatory variable	Effect *P* value
CT-derived	7112	7054	0.67	frac_dim_3d_10*	<0.0001
				VFatVol	<0.0001
				VFatPer*	0.0004
				Agatston_group*	<0.0001
				liver_avg_HU	<0.0001
				muscle_avg_HU	<0.0001
Clinical	7112	6987	0.63	Sex*	0.0002
				Age_at_CT	<0.0001
				BMI	<0.0001
				BMI30	<0.0001
CT-derived and Clinical (final)	7112	6983	0.68	fat_percent_total*	<0.0001
				frac_dim_3d_10*	<0.0001
				fat_percent_eroded*	<0.0001
				Agatston_group*	<0.0001
				liver_avg_HU	<0.0001
				BMI	<0.0001

Note.—With the addition of the Schwarz information criterion (SC), the CT-derived only, clinical only, and final model had multilevel AUCs of 0.64, 0.63, and 0.64, respectively.

* Explanatory Variables that were not selected with the addition of the Schwarz information criterion (SC). In addition, VFatVol was selected as an explanatory variable in the final model (CT-derived and Clinical).