



Supplementary Figure S1. Inclusion flowchart for study participants.

Abbreviations: DKD, diabetic kidney disease; OC, osteocalcin; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio.

Supplementary Table S1. Correlations between osteocalcin and other characteristics at baseline.

	Non-diabetes subcohort				Diabetes subcohort			
	Crude	P value	Age- and sex adjusted	P value	Crude coefficient	P value	Age- and sex adjusted	P value
Current smoker, n (%)	-0.28	<0.001	0.03	0.048	-0.22	<0.001	0.02	0.47
Current drinker, n (%)	-0.29	<0.001	-0.07	<0.001	-0.24	<0.001	-0.06	0.040
Physical activity, n (%)	-0.03	0.013	-0.04	0.001	-0.09	0.002	-0.08	0.004
BMI, kg/m ²	-0.15	<0.001	-0.19	<0.001	-0.15	<0.001	-0.16	<0.001
SBP, mmHg	-0.01	0.65	-0.02	0.17	-0.05	0.075	-0.06	0.030
DBP, mmHg	-0.06	<0.001	-0.03	0.020	-0.07	0.024	0.00	0.10
TC, mmol/L	0.08	<0.001	-0.02	0.076	0.10	<0.001	0.03	0.36
TG, mmol/L	-0.02	0.21	-0.08	<0.001	-0.02	0.58	-0.04	0.17
HDL-C, mmol/L	0.13	<0.001	0.05	<0.001	0.16	<0.001	0.09	0.003
LDL-C, mmol/L	0.07	<0.001	-0.01	0.32	0.10	0.001	0.04	0.17
FINS, µU/mL	0.03	0.039	-0.12	<0.001	-0.04	0.21	-0.11	<0.001
HOMA-IR	0.01	0.52	-0.13	<0.001	-0.10	0.001	-0.16	<0.001
FPG, mmol/L	-0.12	<0.001	-0.12	<0.001	-0.21	<0.001	-0.21	<0.001
HbA1c, %	0.01	0.30	-0.05	<0.001	-0.15	<0.001	-0.19	<0.001
eGFR, ml/min/1.73 m ²	0.02	0.068	-0.06	<0.001	0.01	0.71	-0.05	0.11
UACR, mg/mg	0.16	<0.001	-0.01	0.71	0.07	0.016	-0.04	0.18
Adiponectin, µg/mL	0.27	<0.001	0.16	<0.001	0.26	<0.001	0.16	<0.001

Abbreviations: DKD, diabetic kidney disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; FINS, fasting insulin; HOMA-IR, homeostasis model assessment of insulin resistance; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio.

Supplementary Table S2. Regression-based estimators of the causal indirect, direct, and total effects of mediators on incident diabetes.

Mediators	Total Effect	Controlled Direct Effect	Natural Direct Effect	Natural Indirect Effect	Percentage Mediated
	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	% (95%CI)
BMI	0.51 (0.34-0.77)	0.68 (0.44-1.03)	0.68 (0.44-1.03)	0.75 (0.70-0.81)	34.29 (15.09-112.19)
SBP	0.50 (0.33-0.76)	0.51 (0.34-0.77)	0.51 (0.34-0.77)	0.98 (0.95-1.01)	2.06 (-1.10-8.28)
DBP	0.50 (0.33-0.75)	0.51 (0.33-0.77)	0.51 (0.33-0.77)	0.98 (0.95-1.00)	2.27 (0.13-8.46)
TG	0.51 (0.34-0.76)	0.53 (0.35-0.81)	0.53 (0.35-0.81)	0.95 (0.92-0.97)	5.44 (2.09-17.93)
HDL-C	0.50 (0.33-0.75)	0.54 (0.36-0.81)	0.54 (0.36-0.81)	0.93 (0.88-0.97)	7.67 (2.58-25.63)
LDL-C	0.50 (0.33-0.75)	0.51 (0.33-0.76)	0.51 (0.33-0.76)	0.99 (0.97-1.01)	0.89 (-0.89-4.18)
TC	0.50 (0.33-0.75)	0.51 (0.33-0.76)	0.51 (0.33-0.76)	0.99 (0.97-1.00)	1.03 (-0.24-4.22)
FINS	0.53 (0.35-0.81)	0.62 (0.40-0.95)	0.62 (0.40-0.95)	0.86 (0.81-0.90)	18.61 (7.56-70.76)
HOMA-IR	0.55 (0.36-0.83)	0.66 (0.43-1.01)	0.66 (0.43-1.01)	0.82 (0.77-0.87)	25.54 (10.60-101.95)
FPG	0.46 (0.29-0.70)	0.65 (0.42-0.99)	0.65 (0.42-0.99)	0.70 (0.63-0.77)	36.33 (17.08-96.20)
HbA1c	0.50 (0.31-0.80)	0.65 (0.41-0.99)	0.65 (0.41-0.99)	0.77 (0.67-0.88)	29.65 (11.27-92.76)
eGFR	0.50 (0.33-0.75)	0.51 (0.34-0.76)	0.51 (0.34-0.76)	0.98 (0.94-1.01)	2.22 (-0.62-9.69)
UACR	0.50 (0.34-0.77)	0.50 (0.33-0.75)	0.50 (0.33-0.75)	1.01 (0.99-1.08)	-0.94 (-11.23-0.96)
Adiponectin	0.41 (0.26-0.64)	0.54 (0.35-0.83)	0.54 (0.35-0.83)	0.76 (0.68-0.83)	22.11 (10.55-52.57)

Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; FINS, fasting insulin; HOMA-IR, homeostasis model assessment of insulin resistance; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio.

Two multivariable-adjusted regression models (linear regression model for the mediator and logistic regression model for the outcome) were established to evaluate these effects. Effects were derived when the mediators were fixed at the mean values and when loge-transformed osteocalcin was fixed at mean value minus 0.5 and mean value plus 0.5. All covariates are fixed at mean values of age, women, family history of diabetes (yes), having physical activity ≥ 30 minutes/day (yes), current smoker (yes), and current drinker (yes). Confidence intervals were calculated using percentile bootstrap (replications =1000).

Supplementary Table S3. Regression-based estimators of the causal indirect, direct, and total effects of mediators on incident DKD.

Mediators	Total Effect	Controlled Direct Effect	Natural Direct Effect	Natural Indirect Effect	Percentage Mediated
	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	% (95%CI)
BMI	0.36 (0.20-0.62)	0.38 (0.20-0.64)	0.38 (0.20-0.64)	0.95 (0.88-1.02)	2.75 (-1.15-11.09)
SBP	0.35 (0.19-0.61)	0.37 (0.20-0.63)	0.37 (0.20-0.63)	0.96 (0.90-1.01)	2.40 (-0.40-8.53)
DBP	0.36 (0.19-0.62)	0.36 (0.19-0.62)	0.36 (0.19-0.62)	0.99 (0.96-1.02)	0.29 (-1.24-2.73)
TG	0.37 (0.20-0.63)	0.39 (0.21-0.68)	0.39 (0.21-0.68)	0.94 (0.89-0.98)	3.56 (0.78-12.19)
HDL-C	0.35 (0.18-0.62)	0.37 (0.20-0.64)	0.37 (0.20-0.64)	0.95 (0.88-1.00)	3.07 (0.27-11.61)
LDL-C	0.36 (0.20-0.62)	0.36 (0.20-0.62)	0.36 (0.20-0.62)	1.00 (0.97-1.01)	0.22 (-0.86-2.50)
TC	0.36 (0.20-0.62)	0.36 (0.20-0.62)	0.36 (0.20-0.62)	1.00 (0.98-1.02)	-0.02 (-1.35-1.19)
FINS	0.36 (0.20-0.62)	0.36 (0.20-0.62)	0.36 (0.20-0.62)	1.00 (0.98-1.01)	0.09 (-1.02-1.70)
HOMA-IR	0.36 (0.20-0.62)	0.36 (0.20-0.62)	0.36 (0.20-0.62)	0.99 (0.97-1.01)	0.30 (-1.07-2.36)
FPG	0.37 (0.20-0.63)	0.39 (0.21-0.67)	0.39 (0.21-0.67)	0.93 (0.85-1.01)	4.15 (-0.35-15.53)
HbA1c	0.37 (0.20-0.63)	0.40 (0.21-0.66)	0.40 (0.21-0.66)	0.93 (0.85-1.00)	4.47 (0.13-16.69)
eGFR	0.35 (0.19-0.60)	0.34 (0.18-0.58)	0.34 (0.18-0.58)	1.02 (0.93-1.13)	-1.14 (-10.08-4.08)
UACR	0.34 (0.18-0.59)	0.36 (0.19-0.61)	0.36 (0.19-0.61)	0.96 (0.86-1.05)	2.31 (-3.15-10.68)
Adiponectin	0.38 (0.20-0.68)	0.39 (0.21-0.72)	0.39 (0.21-0.72)	0.97 (0.87-1.06)	1.63 (-4.66-13.46)

Abbreviations: DKD, diabetic kidney disease; OR, odds ratio; CI, confidence interval; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; FINS, fasting insulin; HOMA-IR, homeostasis model assessment of insulin resistance; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio.

Two multivariable-adjusted regression models (linear regression model for the mediator and Logistic regression model for the outcome) were established to evaluate these effects. Effects were derived when the mediators were fixed at the mean values and when loge-transformed osteocalcin was fixed at mean value minus 0.5 and mean value plus 0.5. All covariates are fixed at mean values of age and diabetes duration, women, current smoker (yes), current drinker (yes), glucose-lowering treatment (yes), antihypertensive treatment (yes), and prevalent CVD (yes) at baseline. Confidence intervals were calculated using percentile bootstrap (replications =1000).

Supplementary Table S4. Additional predictive value of OC compared to the traditional risk model.

	AUC		NRI*		IDI*		LR test P value
	Estimate	P value	Estimate	P value	Estimate	P value	
Diabetes model [†]	0.82		Reference		Reference		
+ OC	0.82	0.63	0.02	0.71	0.00	0.40	0.34
DKD model [‡]	0.73		Reference		Reference		
+ OC	0.74	0.24	0.12	0.14	0.01	0.027 [§]	0.008 [§]

Abbreviations: AUC, area under the curve; NRI, continuous net reclassification index; IDI, integrated discriminant index; LR, likelihood ratio; DKD, diabetic kidney disease; BMI, body mass index; HbA1c, hemoglobin A1c; DR, diabetic retinopathy; SBP, systolic blood pressure; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; UACR, urine albumin-to-creatinine ratio.

*NRI and IDI were estimated by using the package PredictABEL in R software (version 4.0.2). [†]Diabetes model included age, sex, current smoker, family history of diabetes, BMI, and HbA1c. [‡]DKD model included age, current smoker, prevalent DR, SBP, BMI, HDL-C, TG, HbA1c, and UACR. [§]P value <0.05 indicated a significant improvement compared with the initial model.