Mediation of the association between abdominal adiposity and subclinical inflammation in type 2 diabetes

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Background and aims: The association between adiposity and risk of type 2 diabetes and cardiovascular disease may be mediated by systemic subclinical inflammation. However, it is unknown whether adiposity itself or other causal and/or mediating traits are the main drivers of subclinical inflammation in type 2 diabetes. We aimed to determine the extent to which adiposity is associated with subclinical inflammation in persons with newly diagnosed type 2 diabetes, and if so, to understand the extent to which this may be mediated by physical activity, fasting hyperinsulinemia, glycemic control, plasma lipids, blood pressure, and/or other comorbidities.
Materials and methods: Using Meso Scale Discovery (MSD) assays, we measured plasma levels of the inflammatory biomarkers IL-6 (n=9,105), TNF-α (n=9,112) and hsCRP (n=9,680) in participants from the Danish Center for Strategic Research in Type 2 Diabetes (DD2) cohort. Applying a cross-sectional setup, we conducted multiple mediation analysis using structural equation modelling with post hoc estimations of total, direct and indirect effects.
Results: Waist circumference as a proxy for abdominal adiposity was positively associated with all markers of subclinical inflammation. Hence, one standard deviation (SD) increase in waist circumference (equal to 15 cm) was associated with 0.20 (95% CI 0.18; 0.22), 0.30 (95% CI 0.28; 0.32) and 0.38 (95% CI 0.36; 0.40) SD increase in TNF-α (equal to 1.5 pg/mL), IL-6 (equal to 4.4 pg/mL) and hsCRP (equal to 6.9 mg/L), respectively. Using multiple mediation analysis, we found that high fasting C-peptide, low physical activity, high triglycerides, Charlson Comorbidity Index, and high HbA_1c were significant traits involved in mediating the association between waist circumference and levels of IL-6, TNF-α and hsCRP (Table 1). Notably, fasting C-peptide was the quantitatively most important mediator, accounting for 9-25% of the association between abdominal adiposity and subclinical inflammation, followed by physical activity (5-7%) and triglyceride levels (2-6%). Although mediation by comorbidities and HbA_1c reached statistical significance, their impact was minor (1-2%).
Conclusion: In persons with new onset type 2 diabetes, abdominal adiposity is associated with subclinical inflammation, and fasting C-peptide is the quantitatively most important mediating factor suggesting a role for hyperinsulinemia in adiposity-driven inflammation.

Table 1 Estimation of mediation (indirect effect) of the associations between waist circumference and subclinical inflammation

	IL-6		TNF-α		hsCRP	
	Beta (95% CI)	%	Beta (95% CI)	%	Beta (95% CI)	%
Total effect	0.296	100	0.231	100	0.390	100
Direct effect	0.221 (0.190; 0.253)	74.7	0.139 (0.107; 0.170)	60.2	0.313 (0.282; 0.344)	80.3
Indirect effect	0.075	25.3	0.092	39.8	0.077	19.7
C-Peptide	0.038 (0.025; 0.052)	12.8	0.058 (0.045; 0.072)	25.1	0.036 (0.023; 0.048)	9.2
Physical activity	0.021 (0.014; 0.029)	7.1	0.012 (0.005; 0.019)	5.2	0.022 (0.015; 0.029)	5.6
Triglyceride	0.005 (0.001; 0.010)	1.7	0.014 (0.009; 0.019)	6.1	0.008 (0.003; 0.012)	2.1
Comorbidities	0.007 (0.004; 0.011)	2.4	0.004 (0.002; 0.007)	1.7	0.006 (0.003; 0.009)	1.5
HbA_1c	0.004 (0.002; 0.007)	1.4	0.004 (0.002; 0.007)	1.7	0.005 (0.002; 0.008)	1.3

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