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EDITORIAL

Pentraxin 3

– A Link Between Obesity, Inflammation and Vascular Disease? –

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Obesity is reaching epidemic proportions in Western countries, and is associated with an increased risk of cardiovascular disease (CVD) and mortality.[1] Inflammation, oxidative stress and CV alterations, including endothelial dysfunction[2] and cardiac remodeling, are responsible for this CVD risk.

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Obesity-induced inflammation involves many cellular types, including immune and inflammatory cells. Pentraxin (PTX) 3 is released by leukocytes and myeloid dendritic cells in response to pro-inflammatory cytokines, or following stimulation with microbial components. PTX3 recognizes and binds many pathogens, facilitating their phagocytosis and clearance. Endothelial cells, smooth muscle cells, fibroblasts, adipocytes, chondrocytes, epithelial cells, and adipose tissue also produce PTX3.

PTX3 may represent a link between obesity, inflammation and CV. However, data on this topic are unclear. PTX3 levels

Table. Observational Clinical Studies of the Relationship Between PTX3 and Cardiovascular Disease

Study/Author	Population	Main outcome	Results
Cardiovascular Health Study (CHS)[3]	1,583 subjects free from CVEs	Angina, MI, stroke, CVD death and all-cause death	A standard deviation increase in PTX3 (189 ng/ml) predicted CVD death and all-cause death but not angina, MI, or stroke
Multi-Ethnic Study of Atherosclerosis (MESA)[4]	2,838 subjects free from CVEs	85-year CVEs and mortality	A standard deviation higher level of PTX3 predicted MI, CVEs but not stroke, CVD mortality, or all-cause death
Haibo et al[10]	596 patients with stable CAD	CVEs at 3 years from PCI	High post-PCI PTX3 levels predicted CVEs
Tomandlova et al[11]	262 patients with STEMI	30-day and 1-year mortality	PTX3 at 24 h after STEMI was a predictor of 30-day and 1-year mortality
Liu et al[12]	377 patients with CHF	CVEs: cardiac death or re-hospitalization for worsening HF at 3 years	PTX3 ≥364 ng/ml predicted CVEs
Heart and Soul Study[13]	986 patients with stable CAD	All-cause mortality, CVEs (MI, stroke or CAD death), incident HF at 37 months	High PTX-3 predicted all-cause mortality, CVEs and incident HF
CARE Trial[14]	749 patients with recurrent MI	Recurrent MI or coronary death during at 5 years	No significant difference in plasma PTX3 levels between the cases and controls PTX3 did not predict CAD risk (non-fatal MI and fatal CAD)
Akgul et al[15]	499 STEMI patients	In-hospital CV mortality and 2-year all-cause mortality	PTX3 ≥32 ng/ml predicted 2-year all-cause mortality
Guo et al[16]	525 NSTEMI patients	30-day CVEs and mortality	PTX3 ≥30 ng/ml predicted 30-day CVEs and mortality
Mjelva et al[17]	871 patients with chest pain and suspected ACS	MI and mortality at 7 years	PTX3 >588 ng/ml predicted mortality
Matsui et al[18]	204 patients with unstable angina/NSTEMI	6-month cardiac death, re-hospitalization for ACS, or for worsening HF	PTX3 levels predicted CVEs
Latini et al[19]	1,457 patients from the CORONA and 1,233 patients from the GISSI-HF trials	Baseline and 3-month changes in PTX3 levels correlated with all-cause and CV mortality Median follow-up was 33 in CORONA and 47 months in GISSI-HF	Baseline elevated PTX3 was associated with all-cause mortality, CV mortality or hospitalization for worsening HF; 3-month changes in PTX3 predicted mortality
Eggers et al[20]	401 NSTE-ACS patients from the GUSTO IV study	1-year mortality	PTX3 did not predict 1-year mortality

ACS, acute coronary syndrome; CAD, coronary artery disease; CHF, chronic heart failure; CV(E), cardiovascular (event); MI, myocardial infarction; NSTEMI, non-ST-segment elevation MI; PCI, percutaneous coronary intervention; PTX, pentraxin; STEMI, ST-segment elevation MI.

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have been equivocally associated with obesity,[3,4] and PTX3 is elevated in patients with metabolic syndrome, which is prevalently characterized by visceral adiposity. Another piece of information is provided by Santilli et al[5] in this issue of the Journal, who analyze the interplay of obesity, PTX3 and platelet activation. Platelets play a key role in the atherothrombosis, as evidenced by interventional trials with aspirin, which inhibits COX1 preventing formation of the pro-aggregating thromboxane (Tx)A_2.[6]

Obesity is associated with platelet activation; a 10% weight loss reduces oxidative stress and platelet TxA_2 formation, suggesting that oxidative stress could promote platelet activation.[7] Moreover, NOX2-derived oxidative stress is implicated in platelet activation via formation of isoprostanes.[8] PTX3 may represent an alternative mechanism for obesity-related platelet activation. Santilli et al[5] explore this hypothesis in a study that included 12 obese patients evaluated at baseline and at 3, 6 and 12 months after laparoscopic gastric banding (LAGB). At 6 and 12 months, PTX3 increased by 178.8% and 214.9% ($P<0.0001$), respectively, while C-reactive protein decreased by 24% and 29.7% ($P<0.0001$).

Coincidentally, markers of platelet activation, as assessed by plasma levels of sCD40L (decreased by 64.3% and 58.6%, $P=0.002$) and urinary 11-dehydro-TXB_2 excretion (from 1,443 pre-surgery to 715 and 564 pg/mg creatinine, respectively, $P<0.0001$) significantly improved.

PTX3 was inversely related to 11-dehydro-TXB_2 and sCD40L levels, suggesting that PTX3 could possess antiplatelet efficacy. This finding may provide further insight into the putative anti-atherosclerotic effect of PTX3, as experimental studies have suggested a role for PTX3 as a modulator of vascular disease.[9] Thus, PTX3 inhibits fibroblast growth factor 2, and knockout animals for PTX3 show more severe inflammation and atherosclerotic lesion. Unfortunately, there is no evidence yet that PTX3 specifically interacts with platelets and promotes inhibition. As correctly underscored by the authors, the association between PTX3 and platelet activation lowering achieved by weight loss could merely reflect a reduction in the inflammatory process. Moreover, weight loss could ameliorate endothelial dysfunction and, in turn, secretion of PTX3 by endothelial cells, which are the main source of circulating PTX3.

Specific inhibition of PTX3 with ensuing analysis of its clinical effect would be relevant to explore if this protein has an important role in platelet activation and eventually in atherothrombosis.

A crucial point, however, is how to transfer experimental data to human CVD. Most observational clinical studies evaluating the predictive role of PTX3 against CVD in long-term follow-up have reported a direct association between PXT3 and CVD (**Table**).[3,4,10–20]

Together these data suggest that increased PTX3 serum levels depict patients with severe inflammatory disease and likely at higher risk of death, but the role in clinically overt atherosclerotic disease progression is difficult to explain, also in the light of experimental data suggesting an inverse relationship between PTX3 and atherosclerotic disease.

In conclusion, there is still uncertainty on how to interpret experimental and clinical data about the role of PTX3 in vascular disease and to explain, more particularly, if PTX3 actually has atheroprotective activity. The increase in PTX3 levels observed in clinical studies may represent a reactive protective mechanism, but there is no study that has explored if modulation of PTX3 levels affects CV events. Further studies are needed to establish if a cause-effect relationship between PTX3 and CV events does exist.

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