Lipid parameters and vitamin A modify cardiovascular risk prediction by plasma neopterin

Indu Dhar, Sumia Siddique, Eva R Pedersen, Gard F T Svingen, Vegard Lysne, Thomas Olsen, Dennis W Nilsen, Jan Erik Nordrehaug, Øivind Midttun, Per M Ueland, Grethe S Tell, Ottar K Nygård

ABSTRACT

Objectives Oxidised cholesterol metabolites are linked to increased production of the active vitamin A (Vit-A) form and monocyte/macrophage activation, which may be reflected by neopterin, a marker of both interferon-γ-mediated immune activation and coronary artery disease risk. We examined the influence of serum lipid parameters and Vit-A on the risk association between neopterin and incident acute myocardial infarction (AMI).

Methods We included 4130 patients with suspected stable angina pectoris (SAP), of whom 80% received lipid-lowering treatment with statins. Risk associations between plasma neopterin and AMI are given as HRs per SD increase in log-transformed neopterin.

Results During a median follow-up of 7.5 years, 530 (12.8%) patients experienced an AMI. In age-adjusted and sex-adjusted analysis, plasma neopterin was positively associated with incident AMI (HR (95% CI) per SD: 1.26 (1.17 to 1.35)). However, the estimates were most pronounced in patients with serum low-density lipoprotein cholesterol (LDL-C) or apolipoprotein (apo) B100 below-median (HR (95% CI) per SD: 1.35 (1.24 to 1.48) and 1.42 (1.27 to 1.58), respectively; both Pinteraction ≤0.03). We also observed a particularly strong risk association in those with above-median Vit-A (HR (95% CI) per SD: 1.32 (1.21 to 1.44); Pinteraction =0.03). The estimates were slightly modified after multivariable adjustment.

Conclusions In patients with suspected SAP, the majority of whom receiving statin therapy, high plasma neopterin was associated with increased risk of AMI particularly among those with low LDL-C and apoB100 or high Vit-A levels. The particularly strong relationship of plasma neopterin with residual cardiovascular risk in patients with low lipid levels should be further investigated.

INTRODUCTION

Atherosclerosis is a multifactorial disease characterised by the accumulation of lipids and chronic inflammation in the arterial wall, and is the major cause of cardiovascular disease (CVD). Elevated serum low-density lipoprotein cholesterol (LDL-C) has been established as a major risk factor for atherosclerotic CVD. LDL-C-lowering therapy with statins significantly reduces the risk of cardiovascular events and is expected to be caused by decreased cholesterol synthesis and increased LDL uptake in the liver suggesting that LDL-C is a cause of atherosclerotic disease. However, residual cardiovascular risk remains prevalent in a substantial proportion of patients on lipid-lowering therapy with statins, reflecting the complex pathophysiology of atherosclerotic disease.

Neopterin is a pteridine derivative secreted from activated macrophages and a marker of interferon-γ (IFN)–mediated immune activity. Elevated circulating neopterin levels have been associated with adverse cardiovascular events in the subsample of the current cohort and in patients undergoing angiography as well as in healthy, elderly adults. Available evidence suggests a mutual interplay between lipid metabolism and cellular immune activation. More specifically, high plasma neopterin has been associated with reduced LDL-C and high-density lipoprotein cholesterol (HDL-C). Further, lipid-lowering therapy with peroxisome proliferator-activated receptor (PPAR) α agonists enhances very-low-density lipoprotein (VLDL) apolipoprotein (apo) B100 catabolism and reduces VLDL apoB100 production, in addition to impairing the transcription of glycine N-methyltransferase (GNMT), a critical regulator of cholesterol homeostasis. Notably, these disturbances are classical components of intracellular hepatic lipid accumulation characterised by the secretion of large buoyant triglyceride (TG)–rich but cholesterol-poor lipoproteins, resulting in the formation of small-dense LDL (sdLDL) particles which are prone to oxidation, and thus considered particularly atherogenic. Oxidised lipids regulate recruitment and activation of monocytes, and lipid oxidation products regulate synthesis of all-trans retinoic acid, an active form of vitamin-A (Vit-A) involved in the monocyte differentiation. Since monocytes/macrophages involved in atherosclerosis development produce neopterin in response to IFN-γ stimulation, cellular cholesterol metabolism and transport in macrophages may be reflected in neopterin production. Of note, neopterin was recently shown to enhance cholesterol efflux and suppress foam-cell formation in human monocyte-derived macrophages, and reduce atherosclerosis development in apolipoprotein E-deficient mice.

Taken together, these observations suggest that altered lipid metabolism may affect IFN-γ-mediated cellular immune activation, and thereby possibly modulate coronary artery disease risk. We investigated the effect of modification by serum lipid measures and Vit-A on the association between...
systemic neopterin and risk of incident acute myocardial infarction (AMI) in a large cohort of patients with suspected stable angina pectoris (SAP). Since the majority of patients in this study population were treated with lipid-modifying statins, we also evaluated the potential interaction by statin treatment.

METHODS

Data sources

The study population has been previously described. In brief, 4164 patients undergoing coronary angiography for suspected SAP during 2000–2004 at Haukeland or Stavanger University Hospitals in Western Norway were studied. Of these, 2573 were enrolled in the Western Norway B-vitamin intervention trial (WENBIT) (ClinicalTrials.gov Identifier: NCT00354081). Subjects with missing data on plasma neopterin (n=34) were excluded, leaving 4130 subjects eligible for the final analyses. All participants provided written informed consent.

Baseline variables

Information about medical history was obtained through self-administered questionnaires and subsequently checked against hospital records, as previously reported. Smoking status was defined according to self-reported smoking habits and also included those who reported having quit smoking within <1 month prior to examination and patients with serum cotinine >85 nmol/L.

Biochemical analyses

Previous reports have described the collection and storage of blood samples and the biochemical analyses of biomarkers. Plasma neopterin was analysed by high-performance liquid chromatography/tandem mass spectrometry at BEVITAL AS, Bergen, Norway (www.bevital.no).

End points and follow-up

Data on study events were collected from the Cardiovascular Disease in Norway project (CVDNOR; https://cvdnor.b.uib.no/). The primary end point was AMI (including fatal and non-fatal) and classification of events have been described previously. Study patients were followed from enrolment until experiencing an AMI or throughout 2009.

Statistical methods

Continuous variables are presented as medians (25th–75th percentiles) and categorical variables as counts (percentages). Patients’ baseline characteristics across plasma neopterin quartiles were tested by linear regression or logistic regression for continuous and categorical variables, respectively.

Cox proportional regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for incident AMI for plasma neopterin. HRs were reported according to per 1 SD increment in log-transformed plasma neopterin. The simple survival model (Model 1) was adjusted for age (continuous) and sex. Additional covariates in the multivariable model (Model 2) included body mass index (continuous), smoking (yes/no), hypertension (yes/no), diabetes mellitus (yes/no), statin treatment (yes/no), apoA1 and apoB100 (both continuous). We additionally included prior AMI in an extended model. Further adjustments for B-vitamin treatment, estimated glomerular filtration rate (eGFR), serum albumin or C-reactive protein (CRP) had minimal influence on the results and were excluded in the final model (data not shown). Proportionality assumptions were evaluated by assessing the Schoenfeld residuals.

Serum lipid parameters and Vit-A were categorised according to their median values and the effect modifications with plasma neopterin were tested by including interaction product terms in the Cox models. Survival according to the median values of neopterin and LDL-C or apoB100 or Vit-A was estimated using the Kaplan-Meier method and compared by the log-rank test. The potential non-linear association between plasma neopterin, serum LDL-C or apoB100 levels and incident AMI was explored visually by plotting generalised additive models, adjusted for age and sex, and surface spline plots from the unadjusted hazards model.

All p values were two-tailed and considered significant when <0.05. Statistical analyses were performed using SPSS V.25 and R (V.3.3.2; R Core Team, Vienna, Austria).

Patient and public involvement

The current study was conducted without patient involvement. Study patients were not involved in research design, the outcome measures, data analysis, result interpretation or the writing of this manuscript. However, we do have plans to disseminate the results of the research to the relevant patient community.

RESULTS

Baseline characteristics

The median (25th–75th percentile) age was 62 (55–70) years, and 72% were men. Median (25th–75th percentile) plasma neopterin, serum LDL-C, apoB100 and Vit-A were 8.2 (6.7–10.4) nmol/L, 2.90 (2.4–3.7) mmol/L, 0.87 (0.73–1.04) g/L and 2.82 (2.3–3.3) μmol/L, respectively. As presented in table 1, a higher proportion of patients in the upper neopterin quartile were older, women, had hypertension, diabetes mellitus or established coronary heart disease. We also observed positive associations of neopterin with CRP, Vit-A and high-sensitivity troponin T, whereas there were inverse associations with eGFR, serum albumin, as well as with current smoking. Plasma neopterin was also negatively associated with serum total cholesterol and LDL-C:apoB100 ratio, whereas no pronounced associations were observed with levels of LDL-C, apoB100, HDL-C or apoA1. Furthermore, patients with higher neopterin levels were less likely to use statins, but were more frequently prescribed β-blockers, ACE inhibitors or angiotensin receptor blockers.

Plasma neopterin and incident AMI

A total of 530 (12.8%) patients experienced an AMI during a median (25th–75th percentile) follow-up time of 7.5 (6.3–8.7) years. Plasma neopterin was associated with increased risk of AMI in age-adjusted and sex-adjusted model (HR (95% CI) per 1 SD: 1.26 (1.17 to 1.35); p<0.001) (table 2 and online supplementary figure 1). Multivariate adjustment table 2 or including prior AMI in model 2 slightly attenuated the risk relationship (table 2).

Neopterin–AMI risk association according to serum lipid parameters and Vit-A

Table 3 depicts risk estimates between plasma neopterin and AMI according to the subgroups of serum lipids and Vit-A. Among patients with below-median LDL-C levels, plasma neopterin showed a linear positive association with incident AMI (HR (95% CI) per SD: 1.35 (1.24 to 1.48)), whereas no significant risk relationship was found among those with above-median LDL-C (pinteraction =0.03) (table 3, figure 1 and online supplementary
serum Vit-A levels above the median (pinteraction=0.03) (table 3).

particularly strong relationship of neopterin in patients with
above-median serum apoB100 (table 3, figure 2 and online
supplementary figure 3) (p interaction=0.002). We also observed a

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BMI, kg/m² 4127 26 (24–28) 26 (24–29) 26 (24–28) 26 (23–28) 26 (23–28) 0.002

eGFR, ml/min per 1.73 m² 4129 91 (78–99) 98 (91–105) 94 (86–101) 88 (77–97) 76 (62–89) <0.001

Serum CRP, mg/L 4128 1.28 (0.87–3.68) 1.45 (0.78–2.69) 1.67 (0.78–3.23) 1.79 (0.90–3.67) 2.44 (1.16–5.41) <0.001

Vit-A, μmol/L 4129 7.5 (6.5–9.0) 8.5 (7.0–9.8) 8.5 (7.0–9.8) 8.5 (7.0–9.8) 8.5 (7.0–9.8) 0.002

TnT, ng/L 4044 4.0 (3.0–10.0) 3.0 (3.0–7.0) 3.0 (3.0–8.0) 5.0 (3.0–10.0) 8.0 (3.0–17.0) <0.001

Serum albumin, g/L 3660 43 (41–45) 43 (42–45) 43 (42–45) 43 (42–45) 42 (41–44) <0.001

Coronary risk factor, n (%) Hypertension 4130 1390 (41.4) 274 (41.4) 274 (41.4) 274 (41.4) 274 (41.4) 0.001

Diabetes mellitus 4130 1589 (38.5) 385 (38.5) 385 (38.5) 385 (38.5) 385 (38.5) 0.002

Current smoking 4130 1311 (33.7) 267 (33.7) 267 (33.7) 267 (33.7) 267 (33.7) <0.001

Prior AMI, n (%) 4130 1665 (40.3) 410 (40.3) 410 (40.3) 410 (40.3) 410 (40.3) <0.001

LVEF (%) 4130 65 (60–70) 65 (60–70) 65 (60–70) 65 (60–70) 65 (60–70) <0.001

Extent of CAD, n (%) No significant stenosis 1040 (25.2) 267 (25.9) 267 (25.9) 267 (25.9) 267 (25.9) 0.001

1-vessel disease 953 (23.1) 260 (25.2) 260 (25.2) 260 (25.2) 260 (25.2) 0.001

2-vessel disease 923 (22.3) 237 (23.0) 237 (23.0) 237 (23.0) 237 (23.0) 0.001

3-vessel disease 1214 (29.4) 268 (26.0) 268 (26.0) 268 (26.0) 268 (26.0) 0.001

Serum lipids and apolipoproteins Total cholesterol, mmol/L 4128 4.9 (4.3–5.7) 4.9 (4.3–5.7) 4.9 (4.3–5.7) 4.9 (4.3–5.7) 4.9 (4.3–5.7) 0.03

LDL-C, mmol/L 4126 2.90 (2.4–3.7) 2.97 (2.4–3.7) 2.91 (2.4–3.7) 2.95 (2.4–3.7) 2.90 (2.3–3.7) 0.19

ApoB100, g/L 4129 0.67 (0.58–0.77) 0.67 (0.58–0.77) 0.67 (0.58–0.77) 0.67 (0.58–0.77) 0.67 (0.58–0.77) <0.001

HDL-C, mmol/L 4129 1.20 (1.0–1.5) 1.20 (1.0–1.5) 1.20 (1.0–1.5) 1.20 (1.0–1.5) 1.20 (1.0–1.5) 0.48

Apo A1, g/L 4128 3.40 (3.0–3.7) 3.40 (3.0–3.7) 3.40 (3.0–3.7) 3.40 (3.0–3.7) 3.40 (3.0–3.7) 0.005

LDL-C apoB100 ratio, mmol/g 4125 3.47 (3.1–3.8) 3.47 (3.1–3.8) 3.47 (3.1–3.8) 3.47 (3.1–3.8) 3.47 (3.1–3.8) 0.005

Medications at discharge, n (%) Statin 4119 3313 (80.4) 837 (80.4) 837 (80.4) 837 (80.4) 837 (80.4) 0.001

β-Blocker 4130 2993 (72.5) 739 (72.5) 739 (72.5) 739 (72.5) 739 (72.5) 0.02

ACEI and/or ARB 4130 1318 (31.9) 279 (27.0) 279 (27.0) 279 (27.0) 279 (27.0) 0.001

Continuous variables are presented as medians (25th–75th percentiles) and categorical variables as numbers (percentages).

*Patients with valid measurements.

ACEI, angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ApoA1, apolipoprotein A1; ApoB100, apolipoprotein B100; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; Tnt, troponin T; Vit-A, vitamin A measured as serum retinol.

figure 2). Similarly, there was a stronger relationship between plasma neopterin and AMI in patients with below compared with above-median serum apoB100 (table 3, figure 2 and online supplementary figure 3) (pinteraction=0.002). We also observed a particularly strong relationship of neopterin in patients with serum Vit-A levels above the median (pinteraction=0.03) (table 3).

Accordingly, reduced survival was observed in patients with a high concentration of neopterin but low concentration of LDL-C or apoB100 (p<0.001) (online supplementary figures 4 and 5). This was also the case in patients with high concentrations of both neopterin and Vit-A (p<0.001) (online supplementary figure 6). The effect modification by LDL-C or apoB100 and Vit-A subgroups were essentially similar after multivariate adjustment (online supplementary table 1). The neopterin–AMI association was not significantly modified by serum HDL-C or apoA1 (table 3 and online supplementary table 1).

Notably, the neopterin–LDL-C or apoB100 risk associations were even stronger among patients receiving statin treatment at discharge (online supplementary table 2 through 4) (both p for three-way interaction ≤0.03).

DISCUSSION

In patients undergoing coronary angiography for suspected SAP, plasma neopterin predicted the risk of incident AMI predominantly in statin-treated patients with low serum LDL-C or apoB100 concentrations, as well in patients with high Vit-A.
Table 3  Associations between plasma neopterin (log transformed per SD) and AMI according to subgroups of prespecified lipid parameters and Vit-A

| Subgroups                  | Events/total | HR (95% CI)* | Pinteraction value |
|----------------------------|--------------|--------------|--------------------|
| LDL-C*                     |              |              |                    |
| ≤Median                    | 263/2075     | 1.35 (1.24 to 1.48) | 0.03               |
| >Median                    | 267/2051     | 1.11 (0.97 to 1.26) |                    |
| ApoB100*                   |              |              |                    |
| ≤Median                    | 253/2127     | 1.42 (1.27 to 1.58) | 0.002              |
| >Median                    | 277/2002     | 1.14 (1.02 to 1.26) |                    |
| HDL-C*                     |              |              |                    |
| ≤Median                    | 312/2123     | 1.19 (1.09 to 1.31) | 0.18               |
| >Median                    | 218/2006     | 1.36 (1.18 to 1.57) |                    |
| ApoA1*                     |              |              |                    |
| ≤Median                    | 303/2107     | 1.21 (1.10 to 1.32) | 0.20               |
| >Median                    | 227/2021     | 1.32 (1.16 to 1.50) |                    |
| LDL-C:ApoB100 ratio*       |              |              |                    |
| ≤Median                    | 292/2066     | 1.27 (1.17 to 1.39) | 0.47               |
| >Median                    | 238/2059     | 1.19 (1.03 to 1.36) |                    |
| Vit-A*                     |              |              |                    |
| ≤Median                    | 267/2043     | 1.11 (0.97 to 1.28) | 0.03               |
| >Median                    | 254/2047     | 1.32 (1.21 to 1.44) |                    |

*Patients with valid measurements=4126 (in LDL-C analyses), 4129 (ApoB100 analyses), 4129 (HDL-C analyses), 4128 (ApoA1 analyses), 4125 (LDL-C:ApoB100 ratio analyses) and 4090 (Vit-A analyses).
†Adjusted for age and sex.
AMI, acute myocardial infarction; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Vit-A, vitamin A measured a serum retinol.

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Possible mechanisms and implications
We observed no significant associations of plasma neopterin with serum LDL-C or apoB100 at baseline; however, the putative associations may be masked by statin therapy, as more subjects in the lower neopterin quartiles were prescribed statins, which is in line with a previous report.7 The activation of monocytes into macrophages accumulating intracellular cholesterol and other lipids in the subendothelial layer of arteries is a hallmark for atherosclerosis and is also fundamental for the concept that inflammation is a promoting factor at all stages of atherosclerosis. Here, we propose that the current findings may be related to the impaired hepatic VLDL production, monocyte/macrophage activation, and the metabolic cross-talk of these interconnected pathways.

Dysfunctional VLDL secretion has been associated with increased hepatic lipid accumulation,11,12 resulting in secretion of large VLDL particles with reduced cholesterol content, which leads to the formation of sdLDL particles with increased susceptibility to oxidative modification.13–15 Oxidised LDL activates monocytes,16 and cholesterol oxidation products (ie, oxysterols) stimulate production of the active Vit-A form, all-trans retinoic acid,16 which again induces monocyte differentiation.17 These findings may indicate the involvement of impaired hepatic apoB-containing lipoprotein secretion in monocyte/macrophage activation, reflected by neopterin production. Accordingly, we observed associations of neopterin with decreased LDL-C:apoB100 ratio and increased Vit-A, which represents the presence of sdLDL particles23 and modified cholesterol product,16 respectively. Activated monocytes take up modified LDL via the scavenger receptor, produces extra cholesterol and export CVD21; however, there remains some uncertainty about the direct role of LDL-C.21 On the other hand, data regarding the association between Vit-A and cardiac events have been contradictory.22 To our knowledge, this is the first large-scale investigation to demonstrate that serum LDL-C, apoB100 and Vit-A concentrations modify the association of neopterin with cardiovascular outcomes.

Neopterin, lipid metabolism and cardiovascular disease
Our findings of an increased cardiovascular risk associated with higher plasma neopterin is concordant with previous research,6–8 including SAP,6 and may underline the importance of immune cell activation in the development of atherogenesis. The LDL-C hypothesis identifies LDL-C as a causal factor of atherosclerotic
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Figure 2 Age-adjusted and sex-adjusted risk association between log-transformed neopterin and acute myocardial infarction according to subgroups of apoB100 levels. Shaded areas around the curves depict 95% CI. Kernel density plots are superimposed along the x-axis to display the distribution of plasma neopterin. apoB100, apolipoprotein B100.

free cholesterol to HDL-C. Notably, this export is regulated by ATP-binding cassette transporter A1, which is stimulated by both neopterin and all-trans retinoic acid. Thus, oxidised LDL, increased Vit-A and neopterin production may primarily be a response and feedback mechanism due to an impaired liver VLDL-C export, aiming to restore this deficiency of cholesterol in VLDL/LDL. Recently, in the same current cohort, we showed that that low apo A1, the primary protein constituent of HDL, was related to incident AMI primarily in those with high Vit-A levels. This may suggest that apoA1 deficiency and low HDL primarily is related to the risk of atherosclerosis when the endothelium produces oxidised LDL as a signal of impaired LDL-C supply. This hypothesis is further supported by our current observation, indicating that that the risk of AMI is particularly high when there are two signals of excess oxidised cholesterol production, that is, the combination of high Vit-A and neopterin. Notably, the neopterin-related risk association was stronger in those with low LDL-C or apoB100, and these findings thus strengthen the hypothesis that an impaired cholesterol supply from the liver to the endothelium may promote atherosclerosis.

The mechanism responsible for reduced hepatic VLDL output is not known but could be related to high endogenous PPARα activity in the liver. Treatment with PPARα agonist has been demonstrated to increase catabolism of apoB100, which is a ligand for LDL-receptor–mediated endocytosis of LDL particles, in addition to being a crucial component of VLDL. In addition, PPARα agonist attenuates GNMT transcription, a critical regulator of lipid export. In line with this, recent animal data suggest that PPARα activation may promote hepatic steatosis. Notably, we observed a strong relationship between neopterin and AMI among patients with low LDL-C or ApoB100, and even more so in those treated with statins, which is suggested to stimulate PPARα mRNA expression and activation. This suggests the involvement of curtailed lipid flux between the liver and peripheral tissues due to excess hepatic PPARα activation in neopterin-related atherogenesis. Lowering of LDL-C levels by statin-treatment has been shown to result in CVD reduction and these findings, at first glance, may, therefore, seem discordant with the current analysis. We do not know the initial lipid levels of these patients as the majority were already treated with statins at the time of angiography; however, residual cardiovascular events are common even in subjects attaining low LDL-C concentrations. Although it is difficult to draw firm conclusions about particular mechanisms based on one study alone, our findings may, however, provide some insight into the residual CVD risk despite treatment with lipid-lowering statins.

Strengths and limitations

The strengths of our study include the large and well-characterised sample and its prospective design with long-term follow-up.

There are limitations to our study. First, the follow-up was ascertained from the patient administrative data; hence, we cannot rule out some underreporting or other misclassification of clinical endpoints. However, we find it unlikely that such misclassification differs according to levels of plasma neopterin or serum lipid parameters. Second, some factors were not assessed, especially malnutrition which can potentially influence the levels of lipids. However, we do not suspect any confounding role of nutrition because adjusting for serum albumin, a marker of undernutrition, and CRP, a measure of systemic inflammation, the interactions remained unchanged.

Third, high neopterin production is associated with increased oxidative stress. Intriguingly, despite the reactive oxygen species generation associated with smoking, we observed an inverse association between plasma neopterin and smoking status. This finding is in line with a previous report and the relationship may be explained by the fact that tobacco smoke has been suggested to attenuate the human immune system via suppressing T-helper-type 1 lymphocytes. Fourth, nearly 46% of the patients received treatments with folic acid plus vitamin B12 or B6, and thus our results may not be generalisable to untreated populations. However, supplementation with B vitamins is reported to have no significant effects on plasma neopterin levels. Moreover, interactions persisted after adjusting for B-vitamin treatment. Finally, the mechanism detailed in our
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study are purely speculative, and additional investigations are thus needed to better explore the role of low lipid measures and statin therapy in neopterin-related atherogenesis.

CONCLUSION

In patients with suspected SAP, the increased risk of AMI associated with elevated neopterin levels was predominantly present in patients with high serum Vit-A, and those with low circulating LDL-C or apoB100 levels, in particular among whom were receiving statin therapy at discharge. It, therefore, seems conceivable that increased levels of neopterin and low serum LDL-C and apoB100 may share some common pathophysiological mechanisms that contribute to the pathogenesis of atherosclerotic CVD, which might include impaired hepatic VLDL-C output. Our findings motivate further investigations on the relationship between lipid metabolism and cellular immune activation, and atherothrombosis.

Key questions

What is already known on this subject?

► Higher plasma neopterin, an interferon-γ-mediated immune activation marker, is associated with increased risk of cardiovascular events.
► Evidence suggests that altered lipid metabolism influences cellular immune activation and is a major contributing factor to the development of atherosclerotic cardiovascular diseases.
► On the other hand, statins, aimed at improving the lipid profile, do not eliminate atherosclerosis, as an incident major cardiovascular event occurs in a substantial proportion of patients who receive statin therapy.

What might this study add?

► Plasma neopterin was associated with increased risk of incident acute myocardial infarction (AMI) predominantly in patients with high serum Vit-A and those with low serum LDL-C and apoB100 levels, in whom a particularly strong relationship was suggested among the majority receiving statin therapy.

How might this impact on clinical practice?

► Future studies should investigate whether the risk relationship between plasma neopterin and incident AMI is primarily due to an impaired cholesterol output from liver.

Author affiliations

1Centre for Nutrition, Department of Clinical Science, University of Bergen, Bergen, Norway
2Faculty of Medicine, University of Bergen, Bergen, Norway
3Department of Heart Disease, Haukeland University Hospital, Bergen, Norway
4Department of Nutrition, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway
5Department of Cardiology, Stavanger University Hospital, Stavanger, Norway
6Department of Clinical Science, University of Bergen, Bergen, Norway
7Bevital AS, Bergen, Norway
8Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway
9Division of Mental and Physical Health, Norwegian Institute of Public Health, Bergen, Norway

Correction notice Since the online publication of this article, the author name ‘Dennis W Nilsen’ has been updated as the middle initial was incorrectly linked to the surname.

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Contributors OKN and ID designed research; ID analysed the data, performed analysis, wrote the manuscript and had primary responsibility for the final content; ID, SS, ERP, GFTS, VL, TO, DWN, JEN, ÖM, PMU, GST and OKN conducted research. All authors critically reviewed and revised the manuscript. OKN and ID are the guarantors.

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Competing interests None declared.

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Patient consent for publication Not required.

Ethics approval The study was performed according to the Declaration of Helsinki, and was approved by the Regional Medical and Health Ethics committee, the Norwegian Medicines Agency and the Norwegian Data Inspectorate.

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ORCID iD

Indu Dhar http://orcid.org/0000-0002-3096-8165

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