Selective pressures for the high prevalence of MEFV variants induced by smallpox infection in the "Old World": A hypothesis

Sirs,

High frequency of the heterozygous carriers of MEFV mutations, which are associated with familial Mediterranean fever, in certain ethnic groups poses an important question of selective advantage against yet unknown fatal infections by a tendency to develop stronger inflammatory response (Fig. 1). Cattan recently discussed the possibility of a lower rate of mortality from tuberculosis conferred by MEFV variants based on mortality records of Tunis in the first half of the 20th century (1). I herein propose that smallpox may be a more likely selective pressure for the MEFV variations. Smallpox had been one of the most dreadful infections in human life, with a case fatality rate of 20% (2). Historical sources indicate that smallpox was already endemic in Egypt and Mesopotamia by the second century AD. It spread to Northern Europe in the 11th and 12th centuries, and to America much later (2). These records may suggest that smallpox may have acted as a selective pressure longer and increased the MEFV allele frequencies in geographic regions where FMF is prevalent.

Recently, Galvani and Slatkin evaluated the bubonic plague and smallpox as the selective pressures for the chemokine receptor CCR5-Δ32 allele using an age-structured model (3). They suggested that smallpox can explain better than plague the selective rise of CCR5-Δ32 allele to current frequencies with a relatively high case fatality rate, the persistence of the infection more continuously since the origin of the allele, the affection of mainly younger people with reproductive potential, and a higher cumulative death toll (3). Their argument about the timing of the appearance of the resistance allele and the number of generations that the disease can drive the allele to its current frequencies can be applied to the MEFV variants. Age of MEFV mutations reaching up to 2500 years can be explained by considering an incomplete dominance model, in which a heterozygous allele confers less protection against disease mortality compared to the carriers of two copies of the resistance alleles and also the presence of more than one variant with varying degrees of protection (3, 4).

The MEFV variants can cause a reduced expression of pyrin, which results in increased activation caspase 1 (also known as interleukin-1β (IL-1β) converting enzyme (ICE)) and IL-1β. Poxviruses developed many defence strategies to suppress host immunity, which included serin protease inhibitors (serpins) interfering with proteolytic activity of ICE, thus inhibiting the IL-1β activation (5). Inactivation of the serpin genes in the vaccinia virus resulted in an increased vaccine safety with attenuated activity without compromising the strength of the immune responses (5). Thus, inherent increased ICE activity resulting from MEFV mutations can be advantageous by conferring decreased smallpox mortality, if not inhibiting the contraction of infection itself.

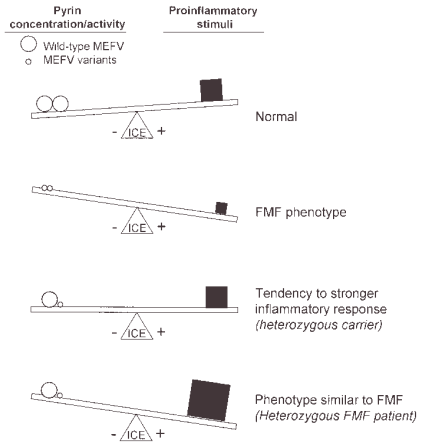

Fig. 1. Proposed model of pyrin activity in fine-tuning of inflammation through contolling the interleukin-1β converting enzyme (ICE) activity in normal individuals and in carriers of 1 or 2 copies of MEFV variants.

On the other hand, selective increase of heterozygous carriers of the MEFV mutations due to smallpox or other infections may also constitute a population health problem. FMF has been known as an autosomal recessively inherited disorder. However, depending on the type or location of the mutations (i.e. ΔM694, complex E148Q/-M694V or H478Y), occasional cases with true autosomal dominant inheritance can be seen (6, 7). Other genetic polymorphisms or accompanying inflammatory disorders can also affect the expression of FMF in heterozygous carriers (8, 9). It can be assumed that depending on the site, intensity, duration or other characteristics of accompanying inflammation, FMF phenotype can be developed in individuals carrying a single MEFV mutation, at least temporarily (Fig. 1). MEFV mutations can also affect the severity of the accompanying inflammatory condition, as observed in patients with multiple sclerosis and rheumatoid arthritis (10, 11).

Pyrin seems to act as negative regulator in the fine-tuning of inflammation through affecting the ICE activity, and MEFV-variants-related disadvantages, especially for populations with a high heterozygous carrier rate, need to be studied further.

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What effect do dietary antioxidants have on the symptoms and structural progression of knee osteoarthritis over two years?

Sirs,

There has been evidence that antioxidant intake may be associated with reduced progression of radiographic knee osteoarthritis (OA). We performed a prospective cohort study to examine the effect of dietary antioxidants on symptoms, cartilage volume and their change over 2 years in subjects with knee OA.

One hundred and thirty-six subjects who fulfilled American College of Rheumatology clinical and radiographic criteria for knee OA (1) entered the study. General health, pain, stiffness, and function were assessed using 36-Item Short-Form Health Survey (SF-36) (2) and Western Ontario

Table I. The relationship between symptoms and antioxidant vitamin intake.

	Univariate analysis Regression Coefficient (95% CI)	P -value	Multivariate analysis Regression Coefficient** (95% CI)	P -value
WOMAC				
Pain score				
Total daily vitamin C intake	0.079 (-0.027, 0.184)	0.14	0.069 (-0.036, 0.175)	0.20
Total daily beta-carotene intake	0.001 (-0.002, 0.003)	0.62	0.001 (-0.001, 0.004)	0.40
Total daily retinol equivalents intake	-0.000 (-0.004, 0.004)	1.00	0.000 (-0.004, 0.003)	0.86
Stiffness score				
Total daily vitamin C intake	0.045 (-0.001, 0.091)	0.06	0.041 (-0.005, 0.087)	0.08
Total daily beta-carotene intake	0.000 (-0.001, 0.001)	0.55	0.001 (-0.001, 0.002)	0.31
Total daily retinol equivalents intake	-0.001 (-0.002, 0.001)	0.36	-0.001 (-0.002, 0.001)	0.27
Function score				
Total daily vitamin C intake	0.440 (0.068, 0.811)	0.02	0.406 (0.037, 0.774)	0.03
Total daily beta-carotene intake	0.004 (-0.004, 0.013)	0.32	0.006 (-0.002, 0.015)	0.15
Total daily retinol equivalents intake	0.000 (-0.013, 0.013)	0.97	-0.001 (-0.014, 0.011)	0.82
Total score				
Total daily vitamin C intake	0.564 (0.057, 1.070)	0.03	0.516 (0.014, 1.018)	0.04
Total daily beta-carotene intake	0.005 (-0.006, 0.017)	0.37	0.008 (-0.004, 0.020)	0.18
Total daily retinol equivalents intake	-0.001 (-0.019, 0.017)	0.91	-0.003 (-0.020, 0.015)	0.76
SF-36 score				
Total daily vitamin C intake	-0.003 (-0.025, 0.019)	0.80	-0.003 (-0.025, 0.019)	0.79
Total daily beta-carotene intake	0.000 (0.000, 0.001)	0.77	0.000 (0.000, 0.001)	0.76
Total daily retinol equivalents intake	0.000 (0.000, 0.001)	0.51	0.000 (-0.001, 0.001)	0.60

* Change in symptomatic score per unit increase in total daily vitamin intake.
** Change in symptomatic score per unit increase in total daily vitamin intake after adjusting for age, gender, BMI, and supplementary vitamin E/placebo.

and McMaster University Osteoarthritis Index (WOMAC) (3). One hundred and twenty six subjects had tibial and patellar cartilage volume measured using magnetic resonance imaging (MRI), at baseline and 2 year follow-up (4). Dietary intake of antioxidant vitamin C, beta-carotene, and retinol activity equivalents was estimated using food frequency questionnaire (5). Height and weight were measured and body mass index (BMI) was calculated. Multiple linear regression techniques were used to explore the effect of dietary antioxidant vitamins on symptoms, cartilage volume and their change over 2 years.

One hundred and twenty subjects (88%) completed the longitudinal component of this study, with 117 of 126 (92%) completing the MRI component. Subjects with higher dietary vitamin C intake had significantly higher WOMAC function score (P = 0.02) and total WOMAC score (P = 0.03), even after adjusting for age, gender, BMI and supplementary vitamin E/placebo (Table I). There was no significant effect of dietary vitamin C, beta-carotene, and retinol activity equivalents intake on tibial and patellar cartilage volume and rate of cartilage loss and change in symptoms in knee OA over 2 years.

Evidence of effect of dietary antioxidant intake on symptoms of OA is limited. The Framingham OA Cohort Study showed subjects with high vitamin C intake had a reduced risk of developing knee pain (6). We showed an adverse effect of high vitamin C intake on function in established knee OA. However, these studies examined different populations: our subjects had symptomatic knee OA at baseline and the severity of symptoms was measured; the Framingham study examined a community-based population, not all of whom had radiographic or symptomatic knee OA, with an assessment for the presence of pain.

Few studies have examined the effect of dietary antioxidants on structural progression of knee OA. The Framingham study showed that higher intake of vitamin C and beta-carotene reduced the risk of progression of knee OA, higher intake of vitamin E reduced the risk of OA progression in men only (6). In contrast, we did not show any effect of dietary antioxidants on structural progression of knee OA. The Framingham study used a radiographic endpoint to determine structural progression. We used cartilage volume as an endpoint, which has shown test-retest reliability (7), correlation with radiography (8), symptoms (9) and is also predictive of clinical outcome (joint replacement) (10). Subjects in the two studies were similar with respect to dietary antioxidant intake, although our subjects all had symptomatic knee OA, were younger and more obese. The Framingham study used a single measure of dietary antioxidant intake at the midpoint of 10-year period as the exposure measure. Intervening illness during the period may have affected antioxidant intake. In our study dietary antioxidant intake was measured at baseline, 12 months and 24 months, which was shown to be stable and the average intake was used as the exposure variable.

Although we were unable to detect a significant effect of the main dietary antioxidant vitamins in usual dietary intake amounts, on structural or symptomatic progression in subjects with OA of the knee over 2 years, we showed an adverse effect of high dietary vitamin C intake on function of the knee. These findings need to be confirmed by larger studies.

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