Cardiovascular and Metabolic Risk Factors in Inherited Autoinflammation

Gilad Twig, Avi Livneh, Asaf Vivante, Arnon Afek, Estela Derazne, Adi Leiba, Dana Ben-Ami Shor, Chanan Meydan, Ilan Ben-Zvi, Dorit Tzur, Ariel Furer, Massimo Imazio, Yehuda Adler, and Howard Amital

Departments of Medicine B (G.T., D.B.-A.S., H.A.), Department of Medicine F (A.L., I.B.-Z.), and Pediatrics (A.V.), and Heller Institute of Medical Research (A.L., I.B.-Z.), The Pinchas Borenstein Talpiot Medical Leadership Program 2012 (G.T., A.V., I.B.-Z., Y.A.), Chaim Sheba Medical Center, Tel Hashomer 52621, Israel; The Israel Defense Forces Medical Corps (G.T., A.V., E.D., A.L., D.T., A.F.), Israel; The Sackler School of Medicine (A.L., A.A., E.D., C.M., I.B.-Z., Y.A., H.A.), Tel Aviv University, Tel Aviv 69978, Israel; The Israeli Ministry of Health (A.A.), Israel; Department of Medicine I (A.F.), Tel Aviv Medical Center, Tel Aviv 69978, Israel; and Department of Cardiology (M.I.), Maria Vittoria Hospital, 10126 Torino, Italy

Context: The natural progression of metabolic abnormalities among patients with inherited autoinflammation is unclear.

Objective: The objective of the study was to assess the cardiometabolic risk of participants with familial Mediterranean fever (FMF).

Design and Setting: This study included nationwide cross-sectional and longitudinal cohorts.

Participants: The prevalence of components of the metabolic syndrome at age 17 years was assessed from the medical database of the Israeli Defense Force from 1973 through 1997. Included were 745 males with FMF, 902 healthy male siblings, and a control group of 787 714 participants. A prospective follow-up study traced the incidence of components of the metabolic syndrome to age 45 years among 57 FMF and 1568 control army personnel participants.

Interventions: Body mass index (BMI) and blood pressure (BP) were measured at age 17 years (cross-sectional); lifestyle, anthropometric, and biochemical data were periodically recorded from age 25 years.

Main Outcome Measures: Abnormal BMI or BP (age 17y) and Adult Treatment Panel III criteria of the metabolic syndrome were measured.

Results: In multivariable regression analysis adjusted for known confounders of obesity, FMF participants had an odds ratio of 0.65 for the occurrence of overweight [95% confidence interval (CI) 0.44–0.96, P = .03] and 0.66 (95% CI 0.48–0.92, P = .012) for hypertension-range BP; their siblings tended to obesity (odds ratio 1.48; 95% CI 1.04–2.11, P = .008). In the follow-up arm, a multivariable analysis adjusted for age, birth year, BMI, education, socioeconomic status, ethnicity, and physical activity yielded hazard ratios of 0.32 (95% CI 0.10–0.82, P = .002) for incident obesity, 0.49 (95% CI 0.25–0.95, P = .037) for incident triglycerides 150 mg/dL or greater, 0.56 (95% CI 0.31–0.98, P = .048) for low-density lipoprotein cholesterol 130 mg/dL or greater, and 2.14 (1.36–3.35, P = .001) for high-density lipoprotein cholesterol less than 40 mg/dL for FMF participants compared with controls. Incident elevated BP was lower among FMF participants (hazard ratio 0.49; 95% CI 0.23–1.00, P = .05), whereas dysglycemia incidence was comparable.

Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval; FMF, familial Mediterranean fever; IDF, Israeli Defense Forces; HDL, high-density cholesterol; LDL, low-density cholesterol; MELANY, Metabolic, Lifestyle, and Nutrition Assessment in Young Adults; OR, odds ratio; SPEC, Staff Periodic Examination Center.

doi: 10.1210/jc.2014-2096 J Clin Endocrinol Metab, October 2014, 99(10):E2123–E2128 jcem.endojournals.org E2123
Familial Mediterranean fever (FMF) is the most frequent genetic autoinflammatory disease (1) and is characterized by recurrent episodes of fever and serositis (1). Mutations in MEditionereNeFeVer (MEFV) lead to acute episodes of inflammation caused by activation of an inflammasome, which result in spontaneous release of IL-1β, a key inflammatory cytokine in the pathogenesis of FMF (2) that was associated with deleterious cardiometabolic outcomes (3, 4). Current data on cardiometabolic risk in FMF are ambiguous (5–7). We report on the incidence of cardiometabolic risk factors among FMF patients using a large cohort of military personnel of the Israeli Defense Forces (IDF).

Materials and Methods

Study population

The study group consisted of all 17-year-old recruits to military service in the IDF from 1973 through 1997. All eligible Israeli adolescents undergo a thorough medical evaluation as detailed elsewhere (8). Subjects were assigned to the FMF group based on a documented diagnosis by a rheumatologist at the time of medical evaluation, whereas the non-FMF subjects were considered controls (8). A second, separate control group was composed of healthy male siblings of FMF patients. Prospective analysis of the incidence of cardiovascular and metabolic risk factors was based on the medical records of subjects in the above cohort who remained in service as career army personnel. All army personnel older than 25 years of age are referred every 5 years for a routine health examination and screening tests at the Staff Periodic Examination Center (SPEC) as part of the Metabolic, Lifestyle, and Nutrition Assessment in Young Adults (MELANY) cohort (9). At each visit, the participants complete a detailed questionnaire assessing demographic, nutritional, lifestyle, and medical factors and provide blood samples after a 14-hour fast as reported elsewhere (10).

Although a normal creatinine clearance is a prerequisite for recruitment to the army, the diagnosis of FMF does not disqualify a subject from a future army career. Indeed, the overall prevalence of individuals with FMF among career army personnel is even higher than in the general population (0.42% vs 0.11%, respectively).

Inclusion/exclusion criteria

To assess the odds ratio (OR) of FMF patients for abnormal body mass index (BMI) or blood pressure (BP) measurements at adolescence, we included participants aged 16–20 years at the time of enrollment (medical examination at age 17 y) from 1973 through 1997, who were medically eligible for military service. Subjects who were ineligible for military service due to any preexisting medical conditions were excluded from analysis, as reported previously (8) (See Supplemental Figure 1 for details). The current analysis included 788 459 male adolescents (745 with a diagnosis of FMF). No data were available on the rate of colchicine treatment for the FMF group at the time of enrollment. A total of 902 healthy male siblings (related to 593 FMF participants) met the inclusion criteria.

From the above cohort, we prospectively followed up those who became career army personnel and underwent periodic medical screening (the MELANY cohort) with at least one SPEC visit from 1994 through 2011. Because an individual with a diagnosis of FMF is limited to an office-based army service, only office-based army personnel were included in the control group. Excluded from the analysis were subjects who at enrollment had a diagnosis of any dyslipidemia, diabetes, diagnosis of hypertension, and a follow-up period less than 10 years. Included in the final analysis were 1625 men (57 with a diagnosis of FMF and under colchicine treatment). Only four women with FMF at the MELANY cohort met the above inclusion criteria; therefore, the analysis was limited to men only. The Institutional Review Board of the IDF approved the study and waived the requirement for informed consent on the basis of strict maintenance of participants’ anonymity.

Conclusions: FMF is associated with lower rates of most components of the metabolic syndrome compared with normal subjects, unlike other inflammatory conditions. *J Clin Endocrinol Metab* 99: E2123–E2128, 2014

Statistical analysis

Categorical variables were compared between FMF and control group participants with χ² test and Fisher’s exact test in case
Table 1. Characteristics of Cohort Population at Adolescence (Enrollment) and at Early Adulthood

| Variable                        | FMF Group     | Control Group | P Value     |
|--------------------------------|---------------|---------------|-------------|
| **Adolescence**                |               |               |             |
| n                              | 745           | 787 714       |             |
| Age, y                         | 17.6 ± 0.5    | 17.4 ± 0.4    | <.001       |
| Education > 10 y               | 71.4          | 76.4          | .002        |
| Urban residence                | 93.3          | 89.8          | .002        |
| SES                            |               |               | <.001       |
| SES Low                        | 36.8          | 27.6          |             |
| SES Intermediate               | 48.8          | 50.4          |             |
| SES High                       | 14.3          | 22.1          |             |
| Origin                         |               |               | <.001       |
| Israel                         | 1.6           | 4.8           |             |
| Union of Soviet Socialist Republics | 1.2      | 10.9          |             |
| Asia                           | 20.4          | 27.2          |             |
| Africa                         | 71.2          | 26.9          |             |
| West                           | 5.6           | 30.2          |             |
| Birth country                  |               |               | <.001       |
| Israel                         | 89.3          | 84.6          |             |
| Union of Soviet Socialist Republics | 0.5      | 6.0           |             |
| Asia                           | 0.8           | 1.6           |             |
| Africa                         | 8.5           | 3.8           |             |
| West                           | 0.9           | 4.0           |             |
| BMI                            | 20.56 ± 2.80  | 21.37 ± 3.03  | <.001       |
| BMI Underweight (average ± SD) | 15.4% (17.06 ± 0.82) | 8.5% (17.13 ± 0.7) | .235 |
| BMI Normal weight (average ± SD) | 78.8% (20.72 ± 1.79) | 81.9% (21.03 ± 1.81) | <.001 |
| BMI Overweight (average ± SD)  | 4.0% (26.37 ± 1.02) | 6.7% (26.54) | .334 |
| BMI Obese (average ± SD)       | 1.7% (30.82 ± 1.48) | 2.9% (31.1 ± 2.37) | .678 |
| BP sys/m/ BP dia/mm Hg         |               |               | <.001       |
| <120/<80 mm Hg                | 42.3          | 29.3          |             |
| >140, ≥120/90 ≥80 mm Hg        | 50.8          | 59.8          |             |
| ≥140/≥90 mm Hg                | 6.8           | 10.9          |             |
| Height, cm                    | 171.65 ± 6.86 | 173.51 ± 6.80 | <.001       |
| **Early adulthood**            |               |               |             |
| n                              | 57            | 1,568         | <.001       |
| Age, y                         | 29.32 ± 6.81  | 28.52 ± 5.48  | .009        |
| Origin                         | 7.4           | 4             | <.001       |
| Israel                         | 14.3          |               |             |
| Union of Soviet Socialist Republics | 18.5     | 21.6          |             |
| Asia                           | 25.9          |               |             |
| Africa                         | 34.2          |               |             |
| West                           | 11.1          |               |             |
| BMI, kg/m²                     | 24.12 ± 3.64  | 25.93 ± 5.04  | .020        |
| <25                            | 49.4          | 66.6          |             |
| ≥25 to <30                    | 33.4          | 27.8          |             |
| ≥30                            | 17.2          | 5.6           |             |
| BP sys/m/ BP dia/mm Hg         | 113.7 ± 13.1/73.5 ± 9.2 | 119.0 ± 12.5/74.9 ± 9.1 | .0004/293 |
| Fasting glucose level, mg/dL   | 94.8 ± 22.12  | 90.9 ± 17.3   | .113        |
| HDL, mg/dL                    | 43.0 ± 11.3   | 46.4 ± 11.1   | .030        |
| LDL, mg/dL                    | 96.0 ± 40.8   | 109.7 ± 41.9  | .021        |
| Creatinine, mg/dL             | 0.99 ± 0.14   | 0.97 ± 0.12   | .560        |
| WBC, cells/mm³                | 6.72 ± 1.48   | 6.86 ± 1.73   | .494        |
| Triglycerides, mg/dL (25th; 75th) | 117.7 (72;130) | 131.8 (78;157) | .041 |
| Physical activity              |               |               | .187        |
| Inactive                      | 80.9          | 68.2          |             |
| Active < 150 min/wk           | 14.9          | 24.9          |             |
| Active ≥ 150 min/wk           | 4.2           | 6.9           |             |
| Smoking                       |               |               | .681        |
| Never                          | 60.4          | 65.0          |             |
| Former smoker                  | 10.4          | 11.3          |             |
| Current smoker                 | 29.2          | 23.7          |             |

Abbreviation: WBC, white blood cell. Anthropometric, ethnicity, sociodemographic data of 788 459 adolescents according to FMF and control groups. Categorical variables are presented by (percentage). BMI categories are based on the sex- and age-specific definition of the Centers for Disease Control and Prevention. Demographic, lifestyle, physical, and biochemical characteristic data are presented for 1625 early adult participants at the first visit to the SPEC. Note that physical activity, smoking status, WBC count, and plasma creatinine levels were similar between the groups. Categorical variables are presented by percentage.
of 22 tables. A t test was used to test mean differences in continuous variables between FMF and controls. Multinomial logistic regression analysis, with normal weight or BP as the base category for comparison, was used to assess the association between FMF and abnormal BMI and BP, respectively. Cox proportional hazard models were used to estimate the hazard ratio and 95% confidence intervals (CI) for the incidence of the metabolic outcomes at young adulthood using the control participant group as a reference. All tests used were two tailed, and \( P < .05 \) was considered statistically significant. Analyses were performed with IBM SPSS, version 19.

Results

Abnormal weight and BP at adolescence

The baseline characteristics of the study cohort are presented in Table 1. Participants with FMF had lower BMI values (Table 1), with 5.7% of these subjects overweight compared with 9.7% in the control group. In multinomial, multivariable logistic regression analysis, FMF had an OR of 0.65 for occurrence of overweight at adolescence (95% CI 0.44–0.96, \( P = .03 \); Figure 1A), whereas their healthy siblings tended to obesity (OR 1.48; 95% CI 1.04–2.11, \( P = .008 \); Figure 1A). Adolescents with FMF had lower BP compared with controls (Table 1), with an adjusted OR of 0.72 (0.61–0.85, \( P < .001 \)) and 0.66 (0.48–0.92, \( P = .012 \)) for prehypertension- and hypertension-range measurements, respectively (Figure 1A).

Cardiometabolic risk factors during adulthood

Table 1 also presents the characteristics of the 1625 participants at their first SPEC evaluation. Characteristics of each outcome are shown in Supplemental Table 1. Figure 1B shows univariate and multivariable analysis for each outcome. There were 1265 participants with normal BMI at enrollment (55 with FMF). A Cox regression multivariable model adjusted for age, birth year, BMI at adolescence, education, SES, country of origin, and physical activity yielded a hazard ratio of 0.32 (95% CI 0.10–0.82, \( P = .002 \)) for incident obesity and 0.62 (95% CI 0.39–0.98, \( P = .048 \)) for incident overweight at adulthood. Adults with FMF had lower systolic, but not diastolic, BP compared with controls (Table 1); there was a nearly 2-fold increase in incidence rate of elevated BP measurement, which became statistically insignificant in multivariable model (Figure 1B).

The FMF group displayed a distinct plasma lipid profile that was characterized by lower HDL, LDL, and triglyceride levels compared with controls (Table 1). This differences persisted in multivariable analysis (Figure 1B and Supplemental Table 1) and were characterized by an older age of onset among the FMF group compared with controls (\( P < .048 \); Supplemental Table 1).

Fasting plasma glucose levels were similar (Table 1), with similar incidence of dysglycemia (Figure 1B) and diabetes (2.88 vs 3.04 cases per 1000 person-years, respectively).

Discussion

The cardiovascular risk associated with FMF is undetermined (5, 6). Here we found that FMF patients with normal renal status had lower rates of most components of the...
metabolic syndrome yet also a lower HDL with comparable rates of dysglycemia (Figure 1B).

Among the FMF group, a lower prevalence of obesity persisted from adolescence throughout the entire follow-up despite a higher prevalence (>80%) of physical inactivity (Table 1). Previous studies showed that increased BMI at adolescence, already within the high-normal range, is an independent risk factor for cardiometabolic comorbidities and mortality (9, 12, 13). Overweight at adolescence was also associated with an increased risk for end-stage renal disease independent of diabetes status and BP at baseline (14). Indeed, the observation that lower incidence rates of obesity and elevated BP persisted throughout adulthood is concordant with an undetected fraction of nonamyloidosis-related end-stage renal disease during 17,000 person-years of follow-up on men with FMF (8). Although paroxysmal abdominal pain may contribute to the differences in BMI, it is unlikely that chronic illness is the sole explanation for the lower BMI among FMF participants because more than 40% of them became overweight or obese at adulthood (Supplemental Table 1). The latter factor also suggests that men with FMF are only partially protected from the growing obesity epidemic of Western society, including Israel (15).

Ongoing inflammatory state similar to that observed in rheumatoid arthritis was associated with insulin resistance and with decreased total cholesterol and HDL levels (16). Such a mechanism provides a possible explanation for the comparable dysglycemia rates in the presence of BMI differences. However, the FMF group in our study was characterized by lower triglyceride levels (Table 1 and Figure 1B), as opposed to the reported hypertriglyceridemia in a variety of other inflammatory conditions (16). The latter difference persisted after adjustment for BMI and can be another component that is unique to the inflammatory process of FMF (17).

Colchicine is the drug of choice in FMF and can potentially affect some of the studied outcomes. Colchicine was shown recently to benefit patients with stable angina from recurrent cardiovascular events (18), even though it was reported to have no effect on plasma lipids levels (19). It was also suggested to impair insulin release (20), thereby providing another explanation why the lower BMI did not protect from incident dysglycemia. The adverse gastrointestinal effect of chronic colchicine use may lower total caloric intake. However, no obesity-protecting effect of chronic colchicine treatment among adults with gout or relapsing pericarditis was ever reported.

Several limitations of this study warrant consideration. First, the military participants with FMF may be considered healthier than individuals with FMF who are not in military service. To attenuate this potential bias, we included as controls army personnel who were enrolled in the same type of service, with careful consideration of potential confounders. The relatively homogeneous environment with free health care service to which career army personnel are exposed might be advantageous by minimizing the effect of socioeconomic-dependent and unrecognized confounders. Second, the absence of direct measurement of insulin sensitivity limited our ability to evaluate the nature of dysglycemia in the FMF group. Inflammatory markers and underlying genetics were not available, limiting our ability to stratify the findings by the degree of disease activity and genetic variants.

To conclude, the current cardiometabolic profile of young men with FMF demonstrated low rates of incident overweight and obesity, LDL, HDL, abnormal BP, and hypertriglyceridemia but comparable rates of dysglycemia. This profile differentiates FMF patients from those with other inflammatory conditions and supports the contribution of other mechanism(s) than inflammation per se. Future studies are needed to determine whether the different metabolic profile of patients with FMF is protective from cardiovascular events.

Acknowledgments

We thank the Pinchas Borenstein’s family for their continuous support of the Talpiot Medical Leadership Program. We also thank Drs Amir Tirosh and Tali Cukierman-Yaffe for their comments on earlier versions of this manuscript.

Contributors of the authors include the following: GT conceived the study concept and design, acquisition and interpretation of the data, research methods and statistical analyses, and drafting of the manuscript; A.L. and HA developed the study concept and design, interpretation of the data, and critical revision of the manuscript for important intellectual content; A.A., I.B.-Z., A.V., A.L., D.B.-A.S., C.M., A.F., M.I., and Y.A. performed the critical revision of the manuscript for important intellectual content; E.D. developed the study concept and design and research methods and statistical analyses; and D.T. performed the data acquisition.

Address all correspondence and requests for reprints to: Gilad Twig, MD, PhD, Department of Medicine B, Chaim Sheba Medical Center, Tel Hashomer, Ramat Gan 52621, Israel. E-mail: gilad.twig@gmail.com.

Disclosure Summary: The authors have nothing to declare.

References

1. Ben-Zvi I, Livneh A. Chronic inflammation in FMF: markers, risk factors, outcomes and therapy. Nat Rev Rheumatol. 2011;7:105–112.
2. Dinarello CA. Interleukin-1 in the pathogenesis and treatment of inflammatory diseases. Blood. 2011;117:3720–3732.
3. Galea J, Armstrong J, Gadsdon P, Holden H, Francis SE, Holt CM. Interleukin-1β in coronary arteries of patients with ischemic heart disease. *Arterioscler Thromb Vasc Biol*. 1996;16:1000–1006.

4. Maedler K, Sergeev P, Ris F, et al. Glucose-induced beta cell production of IL-1β contributes to glucotoxicity in human pancreatic islets. *J Clin Invest*. 2002;110:851–860.

5. Grimaldi MP, Candore G, Vasto S, et al. Role of the pyrin M694V (A2080G) allele in acute myocardial infarction and longevity: a study in the Sicilian population. *J Leukoc Biol*. 2006;79:611–615.

6. Langevitz P, Livneh A, Neumann I, et al. Prevalence of ischemic heart disease in patients with familial Mediterranean fever. *Isr Med Assoc J*. 2001;3:9–12.

7. Akdogan A, Calguneri M, Yavuz B, et al. Are familial Mediterranean fever (FMF) patients at increased risk for atherosclerosis? Impaired endothelial function and increased intima media thickness are found in FMF. *J Am Coll Cardiol*. 2006;48:2351–2353.

8. Twig G, Livneh A, Vivante A, et al. Mortality risk factors associated with familial Mediterranean fever among a cohort of 1.25 million adolescents. *Ann Rheum Dis*. 2014;73:704–709.

9. Tirosch A, Shai I, Afek A, et al. Adolescent BMI trajectory and risk of diabetes versus coronary disease. *N Engl J Med*. 2011;364:1315–1325.

10. Twig G, Afek A, Shamiss A, et al. White blood cell counts and incidence of type 2 diabetes in young men. *Diabetes Care*. 2013;36(2):276–282.

11. Twig G, Afek A, Shamiss A, et al. White blood cell count and the risk for coronary artery disease in young adults. *PLoS One*. 2012;7:e47183.

12. Twig G, Afek A, Shamiss A, et al. Adolescence BMI and trends in adulthood mortality: a study of 2.16 million adolescents. *J Clin Endocrinol Metab*. 2014;99(6):2095–2103.

13. Tirosch A, Afek A, Rudich A, et al. Progression of normotensive adolescents to hypertensive adults: a study of 26,980 teenagers. *Hypertension*. 2010;56:203–209.

14. Vivante A, Golan E, Tzur D, et al. Body mass index in 1.2 million adolescents and risk for end-stage renal disease. *Arch Intern Med*. 2012;172(21):1644–1650.

15. Meydan C, Afek A, Derazne E, et al. Population-based trends in overweight and obesity: a comparative study of 2,148,342 Israeli male and female adolescents born 1950–1993. *Pediatr Obes*. 2013;8:98–111.

16. Lee YH, Choi SJ, Ji JD, Seo HS, Song GG. Lipoprotein(a) and lipids in relation to inflammation in rheumatoid arthritis. *Clin Rheumatol*. 2000;19:324–325.

17. Korkmaz C, Ozdogan H, Kasapcopur O, Yazici H. Acute phase response in familial Mediterranean fever. *Ann Rheum Dis*. 2002;61:79–81.

18. Nidorf SM, Eikelboom JW, Budgen CA, Thompson PL. Low-dose colchicine for secondary prevention of cardiovascular disease. *J Am Coll Cardiol*. 2013;61:404–410.

19. Lagrué G, Wegrowski J, Khabar K, et al. Effect of colchicine on atherosclerosis. I. Clinical and biological studies. *Clin Physiol Biochem*. 1985;3:221–225.

20. Shah JH, Wongsurawat N. Impairment of glucose-induced insulin secretion and glucose tolerance during colchicine treatment. *Diabetes*. 1978;27:925–930.