Coronary artery disease risk among obese metabolically healthy young men

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Abstract

Objective: The aim of this study was to assess coronary artery disease (CAD) risk among obese young men without metabolic risk factors.

Design: A longitudinal study in a historical cohort.

Methods: Incident CAD during a median follow-up of 6.1 years was assessed among 31 684 young men (mean age 31.2 ± 5.7 years) of the Metabolic, Lifestyle and Nutrition Assessment in Young Adults (MELANY) cohort. Participants were categorized by BMI and the number of metabolic abnormalities (based on the Adult Treatment Panel-III). Metabolically healthy (MH) obesity was defined as BMI ≥ 30 kg/m² in the presence of normal blood pressure (BP) and normal levels of fasting glucose, triglyceride, and HDL-cholesterol (HDL-c) levels (n = 599; 1.9%). Cox proportional hazard models were applied.

Results: There were 198 new cases of CAD that were diagnosed during 209 971 person-years of follow-up, of which six cases occurred among MH obese. The incidence of CAD among MH lean, overweight, and obese participants was 0.23, 0.45, and 1.0/1000 person-years respectively. In a multivariable model adjusted for clinical and biochemical CAD risk factors, a higher CAD risk was observed among MH-obese (hazard ratio = 3.08; 95% CI = 1.10–8.68, P = 0.033), compared to MH-normal weight (NW) subjects. This risk persisted when BMI was treated as a time-dependent variable, or when fasting glucose, HDL-c, triglycerides, or BP were added to the model. Similar results were also obtained when a more permissive definition of MH was used.

Conclusions: Obesity may continue to contribute to increased risk for incident CAD in young men even in the presence of a healthy metabolic profile.

Introduction

Obesity is considered to be an independent risk factor for coronary artery disease (CAD) (1, 2). However, some reports have suggested that not all obese individuals are at an increased risk. Specifically, they have hypothesized that a subgroup of metabolically healthy (MH) obese individuals are protected from CAD (3, 4, 5). Nevertheless, there is conflicting evidence regarding future CAD risk for this subpopulation even when a variety of definitions for MH is used (5). For example, with the prevailing definition in the clinical setting that is based on the number of Adult Treatment Panel-III (ATP-III) criteria of the metabolic syndrome (3, 4, 5), the adjusted CAD risk among MH obese individuals was reported to be unchanged (6, 7, 8) or increased (9, 10, 11) compared to MH–normal weight (NW) participants.

There is a clinical need to assess the effect of obesity on cardiovascular risk among MH-obese young adults as most studies included middle-aged individuals, usually at their
sixth decade of life or older, and individuals with one or even two metabolic abnormalities labeled as MH (3, 4). In addition, the trend in cardiovascular mortality has declined in the middle-age group but remained stable or even increased among young adults in the last decades (12, 13). Within that time interval, obesity rates among young men have more than tripled, and young obese men have recently been shown not to benefit from the gradual progression in life expectancy in recent decades as compared to their lean counterparts (14).

The objective of the current study was to evaluate whether obese young men with no metabolic abnormalities are at increased cardiovascular risk. To address this question, we studied the incidence of CAD among participants of the Metabolic, Lifestyle and Nutrition Assessment in Young Adults (MELANY) cohort. All of the men in the Israel Defense Forces (IDF) aged 25 and older have been metabolically characterized and followed in this large ongoing study. Data from this cohort were analyzed to compare the incidence of CAD among overweight and obese individuals with or without the various components of the metabolic syndrome.

**Subjects and methods**

**Study population**

All career service personnel aged 25 or older in the IDF undergo a routine health examination that includes screening tests every 3–5 years. Data from these examinations are collected within the MELANY Cohort Study (15). A detailed questionnaire reviewing demographic, lifestyle, and medical factors was completed by participants at each visit. Blood samples were drawn and analyzed immediately following a 14-h fast. BMI was measured as part of a complete physical examination. For each subject, all of the medical information was recorded in the same central database, thereby allowing ongoing, uniform follow-up as described previously. All participants in MELANY had similar access to medical services, which were provided free of charge.

Figure 1 shows a diagram of the study design. This study included men with a measured BMI in at least one visit to the screening center between 1st January 1995 and 8th March 2011. Participants with a CAD or diabetes mellitus diagnosis prior to their first visit and those with a follow-up shorter than 1 year from enrollment to the diagnosis of CAD were excluded from this study. The current analysis was limited to men due to a small number of CAD cases among women in our cohort. A total of 31,684 participants were included in this study. The Institutional Review Board of the IDF Medical Corps approved this study with assurance of strict maintenance of participants’ anonymity during data analyses.

**Definitions of study groups**

BMI (the weight in kilograms divided by the square of the height in meters) was used to define obesity (≥30 kg/m²), overweight (30 > BMI ≥ 25 kg/m²), and NW (<25 kg/m²). The number of metabolic syndrome components that were present at enrollment was used to further divide each weight group. These were defined according to the criteria of the ATP-III (16) as follows: triglyceride level ≥ 150 mg/dl (1.7 mmol/l) or use of lipid lowering drugs, fasting plasma glucose (FPG) ≥ 100 mg/dl (FPG ≥ 5.6 mmol/l), systolic blood pressure (BP) ≥ 130 mmHg or diastolic BP ≥ 85 mmHg or use of antihypertensive drugs, and HDL < 40 mg/dl. MH participants were defined as individuals with none of the metabolic abnormalities of the ATP-III criteria, while metabolically abnormal (MA) included at least one abnormality from the above criteria (waist circumference was not routinely measured during study period). For comparison purposes with other studies, we conducted an additional subanalysis with a permissive definition of MH (less than or equal to one metabolic abnormality of the ATP-III criteria), whereas those with greater than or equal to two metabolic abnormalities are considered MA.

**Outcomes and follow-up**

The outcome definition for CAD in the MELANY study is angiography-proven stenosis of 50% in at least one coronary artery (1, 17, 18). Follow-up began at participants’ first visit to the screening center and ended at the time of CAD diagnosis, death, retirement from military service, or 8th March 2011, whichever came first.

**CAD screening in the MELANY**

Screening for CAD was conducted as reported previously (1, 17). Referral for a diagnostic procedure was based on clinical suspicion for participants ≤35 years of age, while participants above 35 years of age were referred for a treadmill exercise test (Bruce protocol) in the presence of a board-certified cardiologist. An abnormal exercise test was defined as ST-segment depression > 2 mm in two contiguous leads, measured 80 ms after the J-point, symptoms of angina, exhaustion, or achievement of the target heart
Subjects with a pathologic stress test were referred to coronary angiography. When the stress test was borderline or when participants reported angina symptoms without diagnostic ECG changes, stress perfusion thallium-201 imaging was performed, followed by coronary angiography for participants with a pathological scan. Participants presenting with symptoms of angina and/or myocardial infarction between scheduled visits were referred to coronary angiography following consultation with a board-certified cardiologist.

Assessment of clinical variables

Physical activity was assessed by questions relating to the frequency and duration of trainings and treated as a categorical variable (not active, <150 and ≥150 min/week). Smoking status (never, ex-smoker, and current) and family history of CAD (yes and no) data were obtained at each visit to the screening center. The most recent status of family history of CAD was used in the models.

Statistical analysis

Continuous variables were summarized using means and s.d. or medians with intra-quartile ranges. Counts with percentages were used for categorical variables. We first assessed the hazard ratio (HR) and 95% CIs of BMI at enrollment on CAD risk using Cox proportional hazard analysis adjusted for CAD risk factors at baseline. Variables that were significant at $P<0.05$ in the age adjusted analysis were included in the final multivariable analysis that included age, family history of CAD, smoking status, physical activity, LDL- and HDL-cholesterol (LDL-c and HDL-c respectively), systolic and diastolic BP, triglyceride level, and white blood cells (WBC) count. Next, the cohort was divided into six groups based on BMI status (NW, overweight, or obese) and MH status (MH and MA). Overall, CAD incidence was calculated by dividing the total number in each group by the cumulative follow-up. Cox proportional hazard multivariable models were used to estimate the HR and 95% CI for developing CAD across
BMI groups and MH status. To better differentiate between the effect of obesity and its associated metabolic abnormalities, the multivariable analysis was also adjusted for FPG, triglyceride level, HDL-c, and systolic BP. Additional analysis was conducted using repeated assessments of BMI, smoking status, and physical activity during the follow-up period as a time-dependent variable in the Cox regression model, while the additional metabolic parameters were used only at baseline. To minimize the contribution of referral bias due to high clinical suspicion attributed to obesity, we conducted a subgroup analysis that included only those who were 35 years of age at enrollment.

To assess an interaction between BMI status and metabolic risk factors, we conducted an additional Cox model adjusted for age, MH status, BMI status, and the interaction of the latter with MH status. We added in turn the absence of additional risk factors to the above noted definition of MH status. These risk factors included absence or existence of family history of CAD (yes and no), LDL-c (lower tertile (<101 mg/dl or above)), WBC count (lower tertile (<6000 cells/mm³) or above) (17), smoking status (never, current, or ex-smokers), and physical activity (inactivity, any degree of activity). All variables used in the model were tested for colinearity using the Pearson correlation. The maximal R recorded was 0.35 (triglyceride and BMI at enrollment). For Cox models, log minus log plots for each variable were inspected to verify the assumption of proportionality of the hazards. Subjects with missing data (~18.9%) were excluded from multivariable analysis and their detailed characteristics are detailed in the supplements (Supplementary Table S1, see section on supplementary data given at the end of this article). Analyses were performed with IBM SPSS Statistical Software, version 21.0.

### Results

Table 1 presents the baseline characteristics of the cohort across BMI and MH status. MH-obese constituted 14.9% of the obese group (1.9% of the entire cohort) and, with respect to obese subjects with metabolic abnormalities, were characterized by younger age, lower current and past rates of smoking, and higher degree of physical activity.

**Table 1** Characteristics of the cohort at baseline. Categorical variables are presented by (%). For continuous variables, the mean (S.D.) is given. For the triglyceride level the median (25th, 75th) is shown.

<table>
<thead>
<tr>
<th></th>
<th>Normal weight</th>
<th>Overweight</th>
<th>Obese</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>8536</td>
<td>6792</td>
<td>3946</td>
<td>8209</td>
</tr>
<tr>
<td>Age (years)</td>
<td>29.5 ± 4.8</td>
<td>30.9 ± 5.6</td>
<td>30.9 ± 5.4</td>
<td>32.7 ± 6.0</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.3 ± 1.7</td>
<td>22.8 ± 1.6</td>
<td>26.8 ± 1.3</td>
<td>27.2 ± 1.4</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dl)</td>
<td>86.4 ± 6.7</td>
<td>90.5 ± 9.7</td>
<td>87.7 ± 6.6</td>
<td>91.9 ± 9.5</td>
</tr>
<tr>
<td>Impaired fasting glucose</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>BP systolic</td>
<td>111.8 ± 8.7</td>
<td>120.1 ± 12.9</td>
<td>113.1 ± 8.1</td>
<td>121.0 ± 12.8</td>
</tr>
<tr>
<td>BP diastolic</td>
<td>70.3 ± 7.7</td>
<td>74.7 ± 9.7</td>
<td>72.0 ± 7.3</td>
<td>78.2 ± 9.8</td>
</tr>
<tr>
<td>Abnormal BP</td>
<td>–</td>
<td>39</td>
<td>–</td>
<td>43</td>
</tr>
<tr>
<td>HDL-c (mg/dl)</td>
<td>52.6 ± 9.2</td>
<td>43.6 ± 10.7</td>
<td>50.3 ± 8.0</td>
<td>41.7 ± 9.6</td>
</tr>
<tr>
<td>Abnormal HDL-c</td>
<td>–</td>
<td>51</td>
<td>–</td>
<td>53</td>
</tr>
<tr>
<td>Triglyceride level (mg/dl) (25th, 75th)</td>
<td>74 (57; 96)</td>
<td>107 (75; 155)</td>
<td>89 (68; 113)</td>
<td>146 (95; 198)</td>
</tr>
<tr>
<td>Abnormal triglyceride level</td>
<td>–</td>
<td>28</td>
<td>–</td>
<td>48</td>
</tr>
<tr>
<td>LDL-c (mg/dl)</td>
<td>107.4 ± 29.3</td>
<td>114.9 ± 32.4</td>
<td>120.0 ± 31.8</td>
<td>126.0 ± 34.8</td>
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<tr>
<td>Physical activity</td>
<td>none</td>
<td>60</td>
<td>63</td>
<td>59</td>
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<tr>
<td></td>
<td>&lt;150 min/week</td>
<td>31</td>
<td>29</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>≥150 min/week</td>
<td>9</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>5.4</td>
<td>6.1</td>
<td>5.7</td>
<td>7.1</td>
</tr>
<tr>
<td>Smoking status</td>
<td>never</td>
<td>65</td>
<td>59</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Ex-smoker</td>
<td>11</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Current</td>
<td>24</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>WBC (10³ cells/mm³)</td>
<td>6.2 ± 1.4</td>
<td>6.6 ± 1.5</td>
<td>6.6 ± 1.4</td>
<td>6.9 ± 1.5</td>
</tr>
</tbody>
</table>

BP, blood pressure.
For comparison purposes, a more discrete categorization of the cohort based on the exact number of metabolic abnormalities and BMI status is available in Supplementary Table S2a, b and c, see section on supplementary data given at the end of this article.

There were 198 new cases of CAD during 209,971 person-years of follow-up. In a multivariable analysis adjusted for age, family history of CAD, smoking status, physical activity, LDL-c, HDL-c, systolic and diastolic BP, triglyceride level, and WBC count, each one-unit increase in BMI was associated with a 5.7% increase in CAD risk (95% CI = 1.019–1.096, P = 0.003). The incident rate of CAD among MH participants was lower in those of NW compared to obese participants (0.23 vs 1.00 cases/1000 person-years, P < 0.001; Fig. 2A). BMI had no interaction with MH status at enrollment in an age-adjusted model (P of interaction = 0.376), nor when the definition of MH was extended to the absence of other risk factors including smoking status, physical inactivity, positive family history of CAD, LDL-c level, or WBC count (P > 0.3 for all tests). In a multivariable model adjusted for age, MH status, family history of CAD, smoking status, physical activity, and LDL and WBC count, MH obese participants had an HR of 5.08 (95% CI = 1.69–11.24, P = 0.004) as compared with MH NW participants (Table 2). These results persisted only when participants at age 35 years or older were included (123 cases out of 8148 participants; HR = 5.87, 95% CI = 1.78–19.29, P = 0.004) or when BMI and lifestyle covariates (physical activity and smoking status) were added to the model as time-dependent variables (Table 2; HR = 4.74, 95% CI = 1.59–13.11, P = 0.005). The follow-up and risk estimates data for univariate and multivariable models across the study groups are shown in Table 2. MH obese participants had a comparable risk with those who were MA obese when the latter were used as the reference group (HR = 0.67, 95% CI = 0.29–1.23, P = 0.37). In a subanalysis using a permissive definition of MH (less than or equal to one metabolic abnormality of the ATP-III criteria), 20 cases of CAD were among 1813 MH obese participants with similar risk estimates compared to those who were MH NW (HR = 4.55, 95% CI = 2.20–9.47, P < 0.001; detailed results of this subanalysis are available in Supplementary Table S3, see section on supplementary data given at the end of this article).

Figure 2B presents the cumulative CAD incidence among MH participants when FPG, triglyceride and HDL-c levels, and systolic BP were added to the multivariable model. It is evident that excessive CAD risk persisted among MH obese participants compared to those with NW (HR = 3.08, 95% CI = 1.10–8.68, P = 0.033). Of note, among participants with metabolic syndrome at baseline (presence of at least three ATP-III criteria, Fig. 2C), obesity did not confer an excessive risk during study follow-up (HR = 0.96, 95% CI = 0.41–2.29, P = 0.93).

Discussion

This analysis of 31,684 young men with 209,971 person-years of follow-up demonstrates that among young men, obesity is associated with an increased risk for CAD, independent of the cluster of metabolic abnormalities. MH obese participants constituted 1.9% in our cohort but had approximately threefold higher adjusted risk for CAD compared to those with NW–MH after careful adjustment to other risk factors (Fig. 2).
Several points should be considered when comparing our findings to previous studies. To our best knowledge, the current study is the first to use a strict definition of metabolic healthiness with CAD incidence as an outcome, whereas most studies allowed one (10, 19, 20, 21) or even two metabolic abnormalities (8, 9) in categorizing MH. The inclusion of various cardiovascular risk factors within a population that is labeled as MH as the reference group may potentially lead to a classification bias, resulting in a falsely elevated risk attributed to the MH group. In addition, as opposed to previous studies, classical risk factors for coronary atherosclerosis such as family history of CAD (7, 9, 10, 19, 20, 22, 23) and LDL-c (6, 7, 10, 22, 23) were also included in our multivariable models, and metabolic risk factors were treated as continuous variables within risk factor groups.

The age of study participants may be an important source of ambiguity for the CAD risk among the MH obese. The participants in our study were mostly in their late 20s or early 30s, compared with other studies that included mostly participants in their sixth decade of life (9, 10, 11, 19, 20, 24), or spanned an age range at enrollment of greater than or equal to three decades (20, 23). It is possible that middle-aged individuals who were overweight and obese for many years without developing any metabolic abnormalities confer a lower risk for incident CAD as compared to young adults in whom obesity sustained for a shorter interval. In support, Bobbioni-Harsch et al. (25) and Bell et al. (26) have used similar metabolic definitions to ours and showed that the MH obese are at risk for future metabolic abnormalities even after two decades from initial assessment. Moreover, BMI at late adolescence (27), even independent from that at young adulthood (1), has been shown to affect future adjusted CAD risk, pointing the critical role of obesity at young ages in the development of atherosclerotic plaque. This is further supported by the observation that the effect of obesity was more pronounced among those with MH than those with metabolic syndrome (Fig. 2). Finally, given the relatively young age of our cohort and the proactive screening approach to CAD, it is possible that first-degree relatives of subjects reporting no family history for CAD may still develop CAD in the future.

The clinical significance of our finding should be also discussed in the context of the trend in cardiovascular mortality and recent recommendations of the U.S. Preventive Services Task Force (USPSTF) (28). As opposed to the trend in older age groups, death from cardiovascular causes among young adults remained stable or even increased in recent years (12). Recently, the USPSTF recommended referring

### Table 2: Hazard ratio for developing CAD across BMI and metabolic health status.

<table>
<thead>
<tr>
<th></th>
<th>Normal weight</th>
<th></th>
<th>Overweight</th>
<th></th>
<th>Obese</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MH</td>
<td>MA</td>
<td>MH</td>
<td>MA</td>
<td>MH</td>
<td>MA</td>
</tr>
<tr>
<td>n</td>
<td>8536</td>
<td>6792</td>
<td>3946</td>
<td>8209</td>
<td>599</td>
<td>3422</td>
</tr>
<tr>
<td>New cases of CAD</td>
<td>13</td>
<td>33</td>
<td>12</td>
<td>73</td>
<td>6</td>
<td>61</td>
</tr>
<tr>
<td>Mean follow-up (years)</td>
<td>6.54±4.33</td>
<td>6.66±4.32</td>
<td>6.73±4.09</td>
<td>6.70±4.09</td>
<td>6.58±4.00</td>
<td>6.49±3.95</td>
</tr>
<tr>
<td>Cumulative follow-up (person-years)</td>
<td>55 833</td>
<td>46 448</td>
<td>26 553</td>
<td>54 979</td>
<td>3940</td>
<td>22 218</td>
</tr>
<tr>
<td>Rate (1/1000 person-years)</td>
<td>0.23</td>
<td>0.71</td>
<td>0.45</td>
<td>1.32</td>
<td>1.00</td>
<td>2.74</td>
</tr>
<tr>
<td>Model 1: age-adjusted HR 1 (Ref)</td>
<td>2.41</td>
<td>1.57</td>
<td>3.62</td>
<td>4.93</td>
<td>7.20</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>1.26–4.58</td>
<td>0.72–3.44</td>
<td>2.00–6.56</td>
<td>1.87–10.01</td>
<td>3.93–13.17</td>
<td></td>
</tr>
<tr>
<td>Model 2: age, family history of CAD, LDL-cholesterol, WBC count, smoking status, and physical activity HR 1 (Ref)</td>
<td>1.81</td>
<td>1.57</td>
<td>3.27</td>
<td>4.93</td>
<td>7.20</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>0.84–3.94</td>
<td>0.77–4.49</td>
<td>1.42–5.86</td>
<td>1.69–11.24</td>
<td>2.57–9.25</td>
<td></td>
</tr>
<tr>
<td>Model 3: age, family history of CAD, LDL-cholesterol, WBC count, smoking status (tdv), physical activity (tdv), and BMI (tdv) HR 1 (Ref)</td>
<td>2.01</td>
<td>1.42</td>
<td>2.65</td>
<td>4.74</td>
<td>5.16</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>1.03–3.93</td>
<td>0.61–3.31</td>
<td>1.36–5.17</td>
<td>1.59–13.11</td>
<td>2.26–11.79</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
<td>0.419</td>
<td>0.004</td>
<td>0.005</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>
| tdv, time-dependent variable.
adults aged 18 or older who are overweight or obese to intensive behavioral counseling interventions only in the presence of additional CAD risk factors (28). Our results suggest that similar to type 2 diabetes mellitus (29), MH obesity, even in the absence of other risk factors, confers higher risk for CAD in young men, thereby raising the possibility that obesity alone should be considered as a criterion for such counseling.

This study has several limitations. First, the MELANY cohort may be considered representative of a unique group of healthy young men. Nevertheless, the characteristics of the population are strikingly similar to other cohorts that included young men from various developed countries (30, 31, 32) with a similar prevalence of MH obesity to that used here: 2.6% (26) vs 1.9%. Second, measurements of visceral adiposity (33, 34), such as waist circumference, were not obtained in this study, thereby limiting our ability to assess the prevalence of MH obesity by other definitions and to characterize the role of specific adipose tissue compartments that may link increased BMI with increased CAD risk. Third, the number of CAD cases in our cohort is relatively small given the young age of our participants and is without long-term follow-up that adjust for the stability of the metabolic phenotype (26). Fourth, objective indexes of fitness data were unavailable to us, thereby limiting an accurate contribution of physical fitness in our models. Of note, adjustment for fitness data only partly explained the risk difference reported between MH obese and metabolically unhealthy obese subgroups (35). Finally, we included only men in this study, thereby the generalization of our results to women was limited. The strengths of this study include the standardized and direct (rather than reported) measurements of height and weight (36), strict follow-up, and careful adjustment to other CAD risk factors.

To conclude, we found that obesity confers an increased risk for CAD at any BMI status, including young obese men with no other recognizable CAD risk factors. This finding emphasizes the importance of obesity among young adults in CAD risk stratification, independent of the presence of other risk factors.

Supplementary data
This is linked to the online version of the paper at http://dx.doi.org/10.1530/EJE-15-0284.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement
G Twig, H C Gerstein, study concept and design; D Tzur, data acquisition; G Twig and E Derazne, statistical analyses; G Twig and A Tirosh, interpretation of data; G Twig, A Tirosh, D Ben-Ami Shor, A Afek, and H C Gerstein, drafting of the manuscript; and A Aafek, D Ben-Ami Shor, A Tirosh, E Derazne, and H C Gerstein, critical revision of the manuscript. G Twig had full access to all of the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis.

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